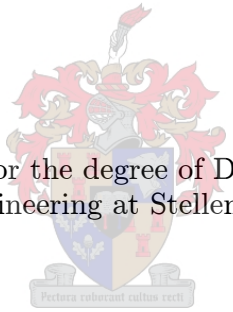
Selecting incentive interventions to encourage pharmaceutical research and development for neglected diseases: A decision-support framework

by

Nicola Hanekom



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Supervisor: Dr Louzanne Bam
Co-supervisor: Dr Imke Hanlu de Kock
Co-supervisor: Prof Nico Vandaele

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Declaration

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Abstract

Neglected diseases are diseases for which adequate drug treatment is lacking or not commonly available to sufferers of the disease. The diseases mostly affect people living in developing countries with more than one billion people globally affected by some of the 'most neglected diseases', known as neglected tropical diseases. Central to understanding the phenomenon of neglected diseases is the concept of market attractiveness, which refers to perceived market potential. As the multinational drug industry is highly competitive, it delivers drugs based on economic market forces. From the perspective of both public- and private investors, the market for neglected diseases is not sufficiently attractive to attain the necessary resources to effectively address such diseases.

Noteworthy effort has been devoted to encouraging pharmaceutical organizations, non-profit organizations, and governments to engage in the research and development (R&D) for neglected diseases. Incentive interventions are a method used to promote these research efforts. Incentives aim to mitigate the challenges of completing drug R&D, by providing some kind of benefit or reward. A significant number of incentive interventions has been proposed and/or implemented for improving neglected disease research. Given the number of incentive strategies and types that exist, difficulty occurs in selecting an incentive intervention that is appropriate for encouraging R&D for the specific pharmaceutical landscape, the stakeholders that are involved, and the health care system context.

This research proposes a decision-support framework that intends to assist any governmental, private or public entity aiming to encourage investment in the R&D of drugs for a disease that is currently experiencing neglect, with the selection of an appropriate incentive intervention. This is done by investigating literature on the goals and outcomes of health care systems, completing a pharmaceutical R&D market analysis, systematically reviewing literature on diseases that are perceived as being neglected and or attractive to pharmaceutical organizations, and investigating existing incentive interventions.

The decision-support framework outcome provides a shortlisted set of recommended solutions (incentivising interventions) based on (i) the current pharmaceutical research and development system being addressed; (ii) the needs, abilities, and limitations of the enabling organization or body; the (iii) needs and objectives of the innovating organizations and the end-users (both the consumers and the procurers of drugs); and (iv) the abilities of the incentivizing interventions to address the priority improvement areas of the scenario under investigation.

Through a verification and validation process involving subject matter experts and the application of three retrospective case studies, the decision-support framework is deemed a comprehensive and valuable contribution to assist in the selection of an appropriate set of incentive-based interventions. The framework thus contributes towards effective and efficient resource allocation in the context of the global neglected diseases R&D sphere.

Opsomming

Verwaarloosde siektes is siektes waarvoor voldoende farmaseutiese-behandeling ontbreek of nie algemeen beskikbaar is aan lyers van die siekte nie. Hoofsaaklik mense wat in ontwikkelende lande woon word deur hierdie siektes geraak, met meer as een miljard mense wat wêreldwyd geraak word deur sommige van die 'mees verwaarloosde siektes', bekend as verwaarloosde tropiese siektes. Die konsep van aantreklikheid van die mark, wat verwys na die waargenome markpotensiaal, is 'n kernbegrip om die verskynsel van verwaarloosde siektes te verstaan. Gegewe dat die multinasionale farmaseutiesebedryf uiters mededingend is, lewer dit medisyne op grond van ekonomiese markkragte. Vanuit openbare-sektor- sowel as privaat-sektor beleggers se perspektief, is die mark vir verwaarloosde siektes nie voldoende aantreklik om die nodige hulpbronne te verkry om hierdie siektes aan te spreek nie.

Beduidende pogings is aangewend om farmaseutiese organisasies, organisasies sonder winsoogmerk en regerings aan te moedig om deel te neem aan die navorsing en ontwikkeling (N&O) van medikasie vir verwaarloosde siektes. Aansporingsintervensies is 'n metode wat gebruik word om hierdie navorsingspogings te bevorder. Aansporings poog om die uitdagings wat met N&O gepaardgaan te verlig deur 'n voordeel of beloning aan te bied. 'n Beduidende aantal aansporingsintervensies is voorgestel en/of geïmplementeer om navorsing oor verwaarloosde siektes te verbeter. Gegewe die aantal aansporingstrategieë wat bestaan, is dit moeilik om 'n aansporingsintervensie te identifiseer wat gepas is vir: 'n spesifieke farmaseutiese landskap; die betrokkenes; en die gesondheidsorgsisteem-konteks.

Hierdie navorsing stel 'n besluitsteunraamwerk voor, wat bedoel is om enige regerings-, privaat- of openbare entiteit te help met die die keuse van 'n gepaste aansporingsintervensie om sodoende belegging in die N&O van medisyne aan te moedig vir 'n siekte wat tans verwaarloos is. Dit word gedoen deur literatuur te ondersoek aangaande doelstellings en uitkomste van gesondheidsorgstelsels, 'n farmaseutiese N&O-marksanaliese te voltooi, 'n stelselmatige oorsig oor literatuur aangaande siektes wat beskou word as verwaarloos en/of aantreklik vir farmaseutiese organisasies voor te lê, asook bestaande aansporingsintervensies te ondersoek.

Die uitkoms van die besluitsteunraamwerk is 'n kortlys met aanbevole oplossings (aansporende intervensies). Die kortlys word bepaal na gelang van (i) die eienskappe farmaseutiese N&O-stelsel wat aangespreek word; (ii) die behoeftes, vermoëns en beperkings van die instaatstellende organisasie of liggaam; en (iii) die vermoëns van die aansporende intervensies om die prioriteitsareas van die scenario wat ondersoek word, aan te spreek.

Na gelang van 'n verifiërings- en valideringsproses wat vakkundiges betrek, word die besluitsteunraamwerk beskou as 'n omvattende en waardevolle bydrae tot die identifisering van gepasde aansporingsintervensies ter bevordering van 'n verhoging in die hulpbronne wat wêreldwyd aan N&O van medikasie vir verwaarloosde siektes gewy word.

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"I will not be shaken, for He is right beside me."
Psalm 16

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Nomenclature

Abbreviations

BL	Background logic
CLIC	Combined list of intervention criteria
CSR	Corporate social responsibility
DALYs	Disability adjusted life years
EP-score	Enabler profile-score
FDA	Food and Drug Administration
LMIC	Low-income or lower -middle income country
ND	Neglected disease
NCD	Non-communicable disease
NTD	Neglected tropical disease
MSF	Medecins Sans Frontieres
OOP	Out-of-pocket
PDP	Product-development partnership
PPP	Public-private partnership
SME	Subject matter expert
RO	Research objective
ROI	Return on investment
RQ	Research question
R&D	Research and development
WHO	World Health Organization

Symbols

i	Combined list of intervention criteria
j	Incentive intervention type
k	Enabler criteria
m	Rating of incentive intervention (enabler profile)
n	Enabler profile priority rating of criterion
x	Rating of incentive intervention (criteria matrix)
y	Criteria matrix priority rating of the criterion

CHAPTER 1

Introduction

This chapter describes the research by providing a concise contextualisation of the problem. The aim and objectives of the research are subsequently defined. The limitations and the scope of the research are discussed. Finally, the expected research outcome and contribution are investigated.

1.1. Background

Pharmaceutical research and development (R&D) is a highly competitive multinational industry that aims to produce innovative solutions to address global health problems. A key challenge faced by this industry, is the significant variation in the R&D resources dedicated to different diseases and pharmaceutical research fields. This variation leads to some diseases receiving funding that appears to be disproportionally high when one considers the burden of disease, whilst other diseases remain neglected.

1.1.1. Research and development of pharmaceuticals

R&D refers to the process followed from the discovery of a drug to market authorization. It includes all research conducted and review processes completed up to the commercial introduction of the new drug.

The development of pharmaceutical drugs is an iterative, time consuming and costly process. Several factors influence the process, including, amongst others: (i) theoretical biology; (ii) the appropriate use of animal assays to determine a compound's biological activity in the body; and (iii) optimising the chemical compounds with medicinal chemistry (PhRMA, 2015). The cost of R&D for each successful new drug was estimated to be $2.6 billion in 2016, as opposed to $1 billion in 2000 (Bujar *et al.*, 2017). Costs include the cost of failures, thus the cost of all the drugs screened, tested and assessed but not necessarily approved. Observers indicate that the development costs of drugs are continuing to rise and become even higher when the cost of research after drug approval is also considered (PhRMA, 2015). Drug development is a lengthy process, lasting up to fifteen years from initial discovery to product launch. The duration of the drug development process can be influenced by various factors, including the testing and analysis of the drug for safety and efficacy.

Drugs require approval from a recognised pharmaceutical regulatory agency, authorising the drug to be launched provided that it adheres to the applicable international guidelines and standards (Bujar *et al.*, 2017). A well-known regulatory agency is the Food and Drug Administration (FDA), the federal agency of the United States Department of Health and Human Services, responsible

for ensuring that organisations in the US, and a number of other countries, adhere to regulatory frameworks (FDA, 2021). When a drug is FDA approved, it is an indication that the potential risk of the drug is outweighed by its benefits, thus making it, legally, safe to use (FDA, 2021).

To discover and develop a new drug, researchers must understand the basic causes of a disease in terms of proteins, genes and cells (PhRMA, 2007). These potential factors that can be affected by drugs to diagnose, prevent or treat a disease are called 'targets' (PhRMA, 2007). The validation of the identified targets, discovering the right molecule to interact with the target, and testing for safety and efficacy, are only a few of the tasks to be completed (PhRMA, 2007). As illustrated in Figure 1.1, the drug development process occurs in five distinct phases, namely: (i) drug discovery; (ii) the preclinical phase; (iii) clinical trials; (iv) the review phase[1]; and (v) post-marketing surveillance. Each stage contributes to fine-tuning the drug under development, so that it is in the best possible state for the target disease. An example of the typical ratio of number of compounds (drug candidates) per phase, as well as the average duration of each phase, is illustrated in Figure 1.1.

The primary aims of the review phase in drug R&D are to ensure that: (i) drugs are safe for human consumption; (ii) drugs are effective in treating the disease targeted; (iii) drugs are affordable for users; and (iv) the benefit of the new drug outweighs the potential risk (PhRMA, 2007). The benefit versus risk ratio is determined by a regulatory agency, based on the data collected in the preclinical and clinical findings. The drugs need to meet the safety and efficacy standards set by regulatory bodies. As an example, currently only 12% of candidate drugs (drugs in the R&D process) receive FDA approval (PhRMA, 2016).

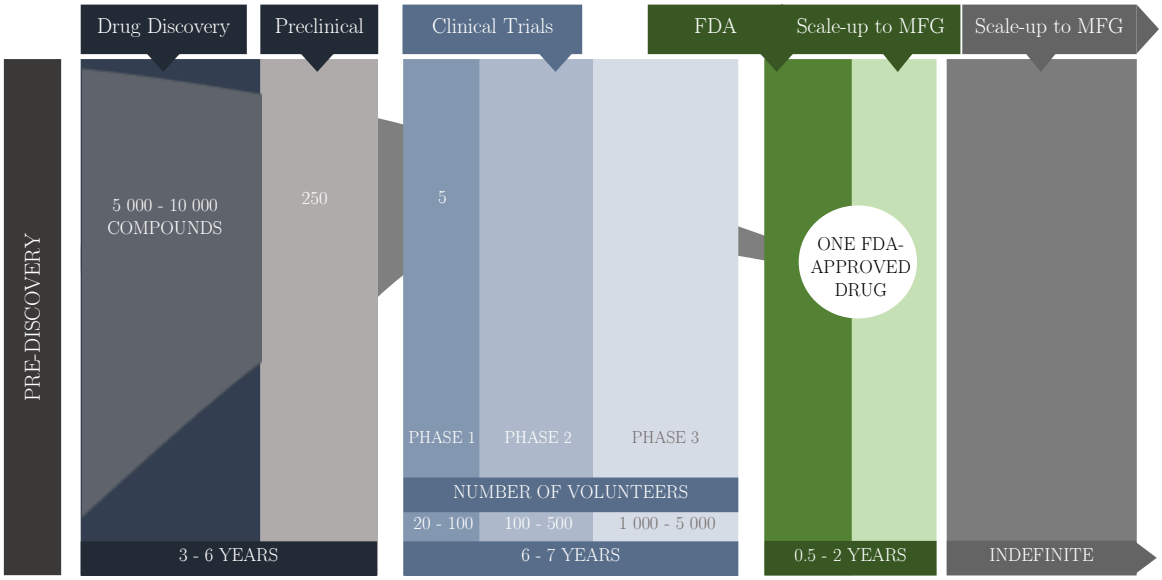


Figure 1.1: Drug R&D process (adapted from: PhRMA (2007)).

[1] This is termed 'FDA review' in Figure 1.1, although the review could also be carried out by another regulatory authority that has the required jurisdiction.

1.1.2. The lack of research and development for certain diseases

The treatment and provision of medication for neglected diseases (NDs) pose a challenge to health care systems on a global level. A disease is considered neglected when there are inadequate treatment options or a lack of treatment options available (MSF, 2001). According to Herrling (2009), NDs in developing countries are difficult to treat due to three potential factors: (i) numerous patients are resistant to the available medication; (ii) the medication causes unbearable side-effects; and/or (iii) there are no drugs available to effectively treat the disease — as a result of possible health system inefficiencies or affordability issues.

The Drugs for Neglected Diseases working group of Médecins Sans Frontières (MSF), state that the development and availability of drugs for NDs should be stimulated in both the public- and private sectors (MSF, 2001), with the WHO conforming the need for R&D and innovation for NTD's (WHO, 2015a). Central to understanding the phenomenon of NDs, is the concept of market attractiveness, which refers to perceived market potential. As the multinational drug industry is highly competitive, it delivers drugs based on economic market forces (Trouiller *et al.*, 2002). From the perspective of both public- and private investors, the market for NDs is not sufficiently attractive to attain the necessary resources to effectively address such diseases.

This lack of resource investment leads to an absence of drugs for the treatment of these diseases, which occur primarily in the developing world (MSF, 2001). According to MSF (2001), the purchasing power of patients with certain NDs is so low that it appears infeasible to alter market forces to stimulate the interest of pharmaceutical organizations. As the aforementioned purchasing power defines research agendas and priorities, this often contributes to a failure to meet the health needs of the poor.

There are a number of prominent examples of how the market forces, briefly described above, influence the actions of pharmaceutical organizations, three examples are provided below.

i. AstraZeneca announced in January 2014 that it withdrew all funding and resources from early-stage R&D of malaria, neglected tropical diseases and tuberculosis whilst the company would continue to focus their efforts on other diseases including cancer, diabetes and high blood pressure (MSF, 2014). These three are diseases that have a high prevalence in higher income countries;
ii. Pfizer stopped R&D relating to all anti-infective drugs in 2012 (MSF, 2014); and
iii. Bayer stated that it did not develop a cancer treating drug *Nexavar* for the Indian market, but rather developed the drug for the Western market, who "can afford it" (MSF, 2014).

1.1.3. Investigating neglected- and neglected tropical diseases

NDs are diseases for which adequate drug treatment is lacking or not commonly available to sufferers of the disease (Dimitri, 2012). Not only is the market potential of the diseases viewed as insufficient to attract the required private sector investment, but government response is also inadequate (MSF, 2001). Many NDs lead to death or decreased quality of life due to treatment being inappropriate or unavailable (Dimitri, 2012). NDs primarily, though not exclusively, affect vulnerable people living in developing countries (Cohen *et al.*, 2010).

According to MSF (2001), diseases with no drugs available for treatment are considered 'most neglected'. The 'most neglected' category of diseases typically includes tropical diseases, with the term neglected tropical diseases (NTDs) often referring to the most NDs globally (Aerts *et al.*, 2017). NTD's are a set of 20 diverse diseases with the singular communality, being their impact on impoverished communities (WHO, 2020a). NTDs are communicable diseases that affected an estimated 2.7 billion people in 2017 with 70% of NTD occurrence reported to be in low-income or lower middle-income countries (LMICs) (Holt *et al.*, 2012; Aerts *et al.*, 2017). The people that are most vulnerable to NTDs live in highly populated areas and these individuals are frequently burdened with more than one infection or parasite (WHO, 2012). It must be noted that the term 'tropical' points to where NTDs originate, with the diseases not restricted to a specific climate zone (Aagaard-Hansen and Chaignat, 2010).

People affected by NTDs live primarily in LMICs and in the most under-developed parts of developing countries (Hotez, 2013; WHO, 2020a). In many cases, infections are caused or amplified by unsafe water, undesirable living conditions and poor sanitation occurring typically in rural areas, urban slums or war-zone areas (WHO, 2012). As can be deduced from the aforementioned, NTD populations lack a strong political voice and have a low profile and status in public health priorities, with children being the most vulnerable and suffering the highest mortality and morbidity caused by NTDs.

Various terminologies are used interchangeably to describe NDs and NTDs. Figure 1.2 aims to facilitate an understanding of how the terms that are commonly in use within the context of ND and NTDs relate to one another.

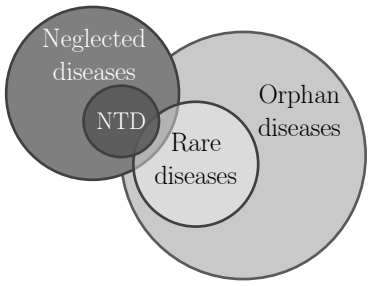


Figure 1.2: Neglected disease terminology.

Saviano *et al.* (2019) differentiate between NDs, NTDs, rare diseases and orphan diseases. Rare diseases are defined as conditions that affect fewer than 200 000 people globally (NIH, 2017). NDs include all NTDs, and some NTDs are classified as both rare and neglected (Saviano *et al.*, 2019). A rare disease becomes an orphan disease when the disease lacks a sufficiently large market to gain the necessary interest to discover treatments (Saviano *et al.*, 2019). NDs do not have the necessary rarity nor lack of market size to qualify as orphan diseases, but rather link to orphan diseases on the grounds of the lack of economic interest necessary to encourage R&D (Saviano *et al.*, 2019). Orphan diseases are defined differently in different regions, for example: in Europe it is defined as a condition that affects less than 180 000 patients; while in the US it is defined as a condition that affects a population of less than 200 000 patients (Saviano *et al.*, 2019).

This study focuses on NDs, therefore including all NTDs, some rare and some orphan diseases. Consequently, the terms 'ND' and 'NTD' are included in the scope of this research, with 'orphan' and 'rare diseases' terms omitted. The rationale behind focussing specifically on NDs, is that this set of diseases share one common characteristic, namely the lack of economic interest necessary to encourage R&D (Saviano *et al.*, 2019).

A list published by both the WHO (2012) and MSF (2001) recognizes the following diseases as NTDs: Dengue; rabies; blinding trachoma; Buruli ulcer; endemic treponema (yaws); leprosy; Chagas disease; human African trypanosomiasis (sleeping sickness); leishmaniasis; cysticercosis; dracunculiasis (guinea-worm disease); echinococcosis; foodborne trematode infections; lymphatic filariasis; onchocerciasis (river blindness); schistosomiasis (bilharziasis); soil-transmitted helminthiases (intestinal worms). NDs include all the aforementioned, as well as, amongst others, tuberculosis, HIV/AIDS and malaria.

1.1.3.1. Quantification of neglected tropical diseases

The effect of NDs can be measured in a variety of ways, including in terms of: the disease burden; mortality and morbidity; disability adjusted life years (DALYs); the effect of the diseases on the economy, including the effect on the potential workforce; and government expenditure on the mitigation of the disease. A study in 2015 determined that, globally, an estimated 56 228 941 deaths occurred, of which 10 522 529 (18.7%) occurred in Africa (Kirigia and Mburugu, 2017). Of the deaths in Africa, 52.2% were attributed to communicable, maternal and nutritional conditions; 37.9% to non-communicable diseases; and 9.9% to injuries (Kirigia and Mburugu, 2017). NTDs were estimated to be responsible for 206 155 deaths, of which 32.9% occurred on the African continent (Kirigia and Mburugu, 2017). This gives an indication of how disproportionately NTDs affect the continent.

The burden of a disease is commonly measured by the WHO as the number of DALYs attributable to the disease, either per country or globally (Lichtenberg, 2005). According to a study completed in 2010, 27 million DALYs globally could be attributed to NTDs, whilst a 2014 study put this number at 47.9 million (Molyneux *et al.*, 2017). The comorbidity of certain diseases, forming part of the NTD list, are not included in the DALYs calculations, as it is excluded in the global burden of disease metrics (Molyneux *et al.*, 2017). The comorbidity not included comprises DALYs as a result of ailments such as permanent blindness, certain skin diseases, or as a result of disability and deformity that leads to long term psychological, social and economic disadvantages. If the aforementioned were taken into account, this would significantly raise the DALYs burden attributed to NTDs (Molyneux *et al.*, 2017) .

Another mechanism to measure the effect of NDs, is to measure the value of the human lives lost. This can be done by making use of the human capital approach, also known as the lost output approach (Kirigia *et al.*, 2015). The lost output approach measures the value lost in the country as a result of premature deaths resulting from ND deaths and is the sum of all potential non-health gross domestic product losses (consumption expenditures, investment and all other components of the gross domestic product on which people have a direct influence) for the entire country (Kirigia and Mburugu, 2017). As an example of the application of the lost output approach to quantifying NDs, Kirigia and Mburugu's 2017 application of this approach to quantifying the burden of NTDs in Africa is briefly discussed. Each country's (53 African

countries) value of human lives lost were calculated. The results indicate that 67 860 deaths due to communicable, maternal, perinatal and nutritional conditions resulted from 16 NTDs (Kirigia and Mburugu, 2017). The 67 860 NTD deaths led to $5 112 471 607 loss in human life value, which is 0.1% of the Africa's gross domestic product value, as in 2015. The productivity losses for NTDs in Africa are lower than the $5.53 billion for maternal mortality and $50.4 billion for tuberculosis deaths in Africa, but is higher than the $1.69 billion loss for diabetes in Africa (Kirigia and Mburugu, 2017).

1.1.3.2. Treatment and health care of neglected diseases

The treatment and provision of medication for NDs is a global health issue (Herrling, 2009). Herrling (2009) states that NDs in developing countries are known to be difficult to treat at the given moment because of the following three possible attributes: (i) numerous patients are resistant to the available medication; (ii) the medication causes unbearable side-effects; and/or (iii) some diseases have no drugs available to effectively treat the disease. The shortage of available medicine for NDs is a well-known phenomenon in the health care industry.

According to the MSF's Drugs for Neglected Diseases Working Group, many other reasons exist for the state of certain diseases and the unavailability of medicine to treat the affected people (MSF, 2001). The Drugs for Neglected Diseases Working Group states that the development of drugs for NDs should be stimulated in both the private and public sectors (MSF, 2001). The absence of pharmaceuticals for diseases, mostly occurring in the developing world, is attributed to numerous factors and is the result of a complex network of decisions made by all stakeholders involved.

1.1.3.3. Incentivising R&D for neglected diseases

A variety of incentive interventions exists to encourage R&D for diseases. Examples of incentives include: (i) mechanisms providing upfront funding with the aim of enabling smaller pharmaceutical organizations to afford R&D that would not otherwise be possible; (ii) mechanisms offering no financial assistance but providing a guaranteed number of drug sales at an agreed fixed price; and (iii) prize-money in the case of compound discovery.

Incentive interventions are established through a range of stakeholders, including: (i) governments; (ii) private institutions; and (iii) philanthropic organizations. The selection of a suitable incentive intervention depends on a variety of factors including: the prevalence of the disease targeted; the available budget of the enabler; as well as the timing at which the funding is made available to the innovating organizations. Consequently, difficulty occurs in selecting an incentive intervention that is appropriate for encouraging and supporting R&D for the specific pharmaceutical landscape as it related to NDs, and the stakeholders that are involved, within the constraints faced by the enabling organization that intends to initiate the incentive.

1.1.4. The health care system as a complex adaptive system

For the purpose of this research, a health system is defined as a system consisting of all the organizations, institutions, resources and people whose primary purpose is to improve health (WHO, 2010a). Where the system provides preventative, curative, promotive and rehabilitative interventions through a range of public and private institutions and organizations (WHO, 2010a).

A fundamental perspective that underpins this research can be deduced from the aforementioned, namely, that the health system can be viewed as a complex adaptive system. Viewing the system as a complex adaptive system, indicates that the stakeholders of the system collectively act as agents of the system and that the structure of the stakeholders cannot be portrayed in a hierarchical manner, but rather as an interconnected network (Rouse, 2008). In proposing this view of the health system, Rouse assumes that each agent serves both their own interests, as well as the interests of their customers, by aiming to provide high quality products and services. All the stakeholders have conflicting interests, consequently even if all agents have good intentions in delivering their product or service, the value of the health care system is lower than what it could potentially be, with certain outcomes being compromised or certain costs being excessive (Rouse, 2008).

1.2. Defining the research

This research takes a set of relevant factors into account to assist in selecting incentive interventions that are more likely to be effective in increasing the research resources allocated to diseases that are not currently viewed as attractive in the pharmaceutical market.

1.2.1. Research question

There is inadequate resource allocation by the pharmaceutical research industry to sufficiently perform drug R&D for all diseases. The relative level of investment in diseases is not always proportional to the burden caused by the disease. Thus, some diseases experience neglect, with no drugs available and no or few drugs in R&D. Furthermore, efforts to incentivize investment of the necessary resources for the development of drugs for these diseases, have not been sufficiently successful to eliminate the phenomenon of NDs, which occurs mostly in developing countries. A large variety of incentive mechanisms that can be employed to encourage R&D of drugs for NDs are available, however, identifying intervention(s) that are appropriate for a specific instance is challenging, due to the large number of relevant factors that need to be considered simultaneously.

1.2.2. Research aim

The aim of this research is to develop a decision-support framework to be used by the (i) governance authorities, a (ii) private, (iii) public or (iv) philanthropic institution, called the enabler, with the aim of increasing the interest of pharmaceutical R&D stakeholders, to develop drugs for a specific disease or set of diseases. The decision-support framework should consider (i) the current state of the pharmaceutical R&D system in the specific scenario, and (ii) the abilities and limitations of the enabler, the pharmaceutical R&D innovator and the end-product consumer, in providing a solution. The decision-support framework should address major influencing factors, identified in research, that inhibit the advancement of drugs through the R&D pipeline. This should be done by considering the drivers of market attractiveness. As output, the framework should provide a shortlist of incentive interventions that are likely to overcome the biggest inhibitors of the scenario considered.

1.2.3. Research objectives

In order to facilitate the attainment of the research aim, a number of research objectives (RO) and sub-objectives have been defined.

RO.1 Identify, and review, components of the complex healthcare system that affect the state of the health and pharmaceutical R&D sphere. The sub-objectives defined for RO.1 include:

RO.1.1 Establish the taxonomy of entities involved, together with the goals and objectives of the overarching healthcare system.

RO.1.2 Evaluate the influence that the economic status of countries has on the treatment and mitigation of diseases.

RO.2 Investigate the pharmaceutical R&D pipeline with specific focus on factors influencing the advancement of drugs through the pipeline, trends that accompany it, and its relationship with the burden of disease.

RO.3 Comprehend the phenomenon of market attractiveness in the pharmaceutical R&D industry. The sub-objectives defined for RO.3 include:

RO.3.1 Consider and apply an appropriate market analysis method to investigate the pharmaceutical R&D market to recognize properties that enhance and reduce the attractiveness of drug R&D.

RO.3.2 Systematically investigate literature on attractive and NDs to establish disease-specific characteristics that respectively enhance and reduce the attractiveness of drug R&D.

RO.4 Gain an understanding of existing incentive intervention strategies, incentive types and incentive instances to encourage the R&D of drugs for NDs. The sub-objectives defined for RO.4 include:

RO.4.1 Complete a systematic literature review to identify incentive intervention instances, suggested or previously implemented, to encourage drug R&D and the investment of resources for neglected R&D.

RO.4.2 Inductively determine a list of existing incentive types to encourage drug R&D. Also investigate the advantages and disadvantages of the respective types.

RO.4.3 Identify context-non-specific criteria for ensuring the successful operation and implementation of incentive intervention instances.

RO.4.4 Analyse stakeholder objectives and internal capabilities for implementing potential incentive interventions and completing R&D for ND.

RO.5 Derive requirement specifications (defined as per Table 1.1), that the decision-support framework should incorporate and adhere to.

RO.6 Develop a decision-support framework to suggest feasible incentive types for encouraging pharmaceutical R&D for NDs. Evaluate the framework's credibility and efficacy through verification and validation. The sub-objectives identified for RO.6 include:

RO.6.1 Construct a framework that provides the means to incorporate context-specific and context-non-specific criteria for establishing an incentive intervention type to stimulate R&D for neglected disease drugs in a specific scenario.

RO.6.2 Verify the design of the framework through comparing to the requirement specifications, and by consulting subject matter experts (SMEs). Analyse and evaluate verification output data to identify omissions of the framework and concepts to incorporate.
RO.6.3 Refine the design of the decision-support framework by incorporating the suggestions made by SMEs during the verification interviews.
RO.6.4 Validate the decision-support framework by interviewing SMEs. Establish the feasibility, efficacy and applicability in the real-world. Apply the decision-support framework to three case studies to provide a detailed demonstration of the framework operation, resulting in empirical data to add to the body of knowledge.
RO.6.5 Investigate opportunities for future work and further development of the decision-support framework.

1.3. Research scope

Given the ambitious topic of this research as well as the broad scope applicable to this study; the research developed as the understanding of the topic matured. Consequently, each step of this research was determined by what was found in literature, as opposed to confining the scope before a thorough study of literature was conducted. This allowed the study to be led by a developing understanding of the research field, and not by a pre-defined set of arguments. Figure 1.3 depicts how the concept of a literature scope funnel was applied in this research.

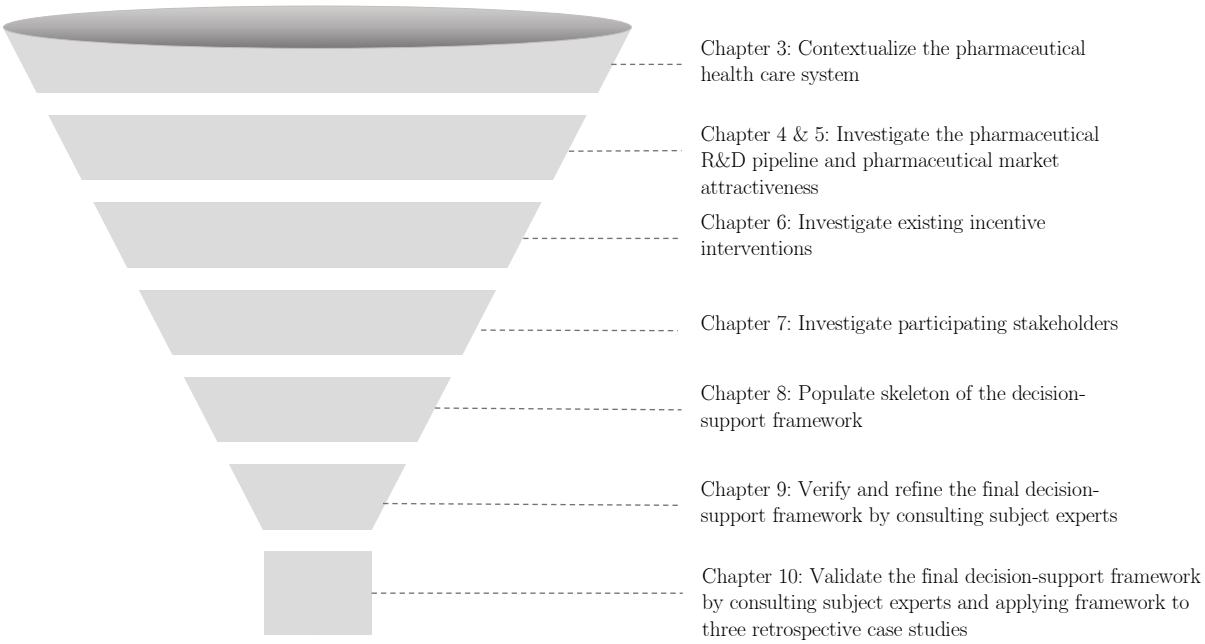


Figure 1.3: Literature scope funnel.

A number of scope limitations were also defined at the outset of the research, namely:

i. Although acknowledged as a critical part of disease intervention in a given population, the diagnostics, development of diagnostic technology and incentive interventions for the development of diagnostic methods, are not considered as part of this research. This is because diagnostic R&D involves different processes than that of drug R&D.

ii. This research primarily focuses on the R&D process, and the R&D pipeline of drugs. Though topics such as access to medicines, and the distribution of drugs, are considered as part of the contextualization of the research, direct efforts to improve these aspects fall outside the scope of the research.
iii. Though the importance of vaccine interventions to mitigate and eliminate NDs is acknowledged, this research does, however, not include an investigation of vaccine R&D. The motivation for this delimitation is being that vaccine R&D is a complex process that differs in nature from drug R&D.

1.4. Knowledge gap

The knowledge gap aimed to be addressed in this research is to construct a framework that will provide decision-making guidance for finding an appropriate incentive intervention to ultimately increase the attractiveness of performing drug R&D for a specific ND or set of NDs. The prospects of this study are that the framework will be used to improve the R&D pipelines for diseases lacking market attractiveness. This framework should be practical to utilize and implement.

A search in literature was conducted to identify whether similar research outcomes have been published. The structured search was done in the following literature databases: (i) Scopus database[2]; (ii) Web of Science database[3]; and (iii) PubMed[4]. The objective of the structured literature search was to answer the following research question (RQ):

RQ: Does a decision-support framework/model/tool/roadmap exist that facilitates the selection of appropriate incentive interventions for the R&D of drugs for NDs based on characteristics of the pharmaceutical R&D environment, the disease being targeted, and the stakeholders of the incentive/R&D process?

Keywords for the search were derived from the research question and arranged in a logical manner. A search was completed with the search line: ("R&D" OR research) W/5[5] ("neglected disease" OR "ND" OR "NTD") W/5 (incentive*).

The search, using the keywords mentioned above, gave an output of eight (Scopus), 11 (Web of Science), and 25 (PubMed) documents. Of the total number of documents (44), six duplications in the three sets of document outputs were identified. 23 of the remaining 38 documents were irrelevant. Five of the 44 documents are reviews of one publication, the original publication was included, and the reviews excluded. Thus, a total of ten potentially relevant documents were uncovered. A brief summary of each of the ten documents is given in Table 1.1.

[2] Scopus is the database of Elsevier, and the world's largest abstract and citation database of peer-reviewed literature. Scopus provides global interdisciplinary and scientific information across all research fields. (Naci *et al.*, 2015).
[3] Web of Science, a multidisciplinary, global citation database (Web of Science Group, 2019).
[4] PubMed, a search engine accessing primarily Medline database on life sciences and biomedical topics (PubMed, 2019).
[5] Proximity operator, finding documents where the preceding concept is within 5 words of the following. This was replaced by 'AND' for the search in PubMed, as the database does not allow the use of proximity operators.

Table 1.1: Applicability of the relevant systematic literature review output documents.

	Title of relevant document	Summary of publication	Reference	Criteria A	B	C	D
1.	Strong medicine: Creating incentives for pharmaceutical research on neglected diseases	Proposes specific incentive interventions to stimulate private R&D for particularly HIV/AIDS, tuberculosis and malaria using economic perspectives. The focus is on vaccine intervention.	Kremer and Glennerster (2005)	✓	✓		
2.	The "priority review vouchers" for neglected pharmaceutical innovation and their impact on pharmaceutical patent	Investigates priority review vouchers, and the potential impact on pharmaceutical patents.	Sanchez (2014)	✓			
3.	Globalization in medical research	Investigates, the ethical problems emerging from increased clinical trial studies.	Ehni and Wiesing (2018)	✓			
4.	Spurring new research for neglected diseases	Investigates the benefits of providing tax credit to encourage organizations to perform, specifically, pre-clinical research on ND.	Anderson (2009)	✓			
5.	Increasing R&D incentives for neglected diseases: Lessons from the Orphan drug act	Suggests the design of interventions focused on government, that will alter the economic incentives, from a policy perspective.	Grabowski (2005)	✓	✓		
6.	R&D incentives for neglected diseases	An analysis of the three major incentive strategies, an investigation of advantages and disadvantages, and suggestion of a solution.	Dimitri (2012)	✓	✓		
7.	Choosing the right incentive strategy for research and development in neglected diseases	Compares current 'end-to-end' incentive proposals to 'pay-as-you-go' proposals and lists drawbacks of both incentive strategies.	Maurer *et al.* (2004)	✓	✓		
8.	Optimal use of donor funding to incentivize vaccine research and development for neglected diseases: An analysis of different R&D incentive mechanisms	Investigates different incentive interventions, and weighs the different approaches against one another	Koh Jun (2012)	✓			
9.	The economics of priority review vouchers	A review of the strengths of priority review vouchers.	Dimitri (2010)	✓			
10.	Towards a science of global health delivery: A social-anthropological framework to improve the effectiveness of NTD interventions.	A socio-anthropological approach to improve the implementation of interventions to control NTD.	(Bardosh, 2018)	✓			

Criteria legend:
[A] Review an incentive/multiple incentive interventions for ND
[B] Provide a solution/suggestion for ND R&D in general
[C] Provide a means to evaluate a scenario specific R&D environment
[D] Provide decision-support

1.5. Conclusion: Introduction

This chapter investigates problem background, followed by defining the research question, aim and objectives. The scope of this research is described with the out-of-scope research areas of the study highlighted. Lastly, the expected outcome and contribution to the ND body of knowledge is investigated.

CHAPTER 2

Research methodology

The objective of this chapter is to highlight the methodology employed to conduct this research. The philosophical perspective that is adopted throughout this research, followed by the research strategy and research approach employed in this research. Lastly, the research methods applied per research objective are described together with the document structure.

2.1. Philosophical perspective employed in this research

Research philosophy refers to the system of beliefs and assumptions employed in the development of knowledge (Saunders *et al.*, 2009). Different research philosophies, therefore, differ with respect to their fundamental assumptions regarding what knowledge is (Saunders *et al.*, 2009), and the means to know and learn (Schuh and Barab, 2007). This underlying set of assumptions (whether tacit or explicit) consequently drives the decisions made for the research.

According to Saunders *et al.* (2009), three main types of research assumptions exist, namely: (i) ontological assumptions (concerns assumptions about the nature of the world and reality); (ii) epistemological assumptions (concerns assumptions about knowledge); and (iii) axiological assumptions (concerns the role of values and ethics within the research process). Different research philosophies can therefore be distinguished by the differences in their ontological, epistemological, and axiological assumptions. The types of assumptions made can further be distinguished based on where these lie on a continuum with the two extremes being objectivism (argues that social reality is external to people) and subjectivism (argues that social reality is made from the perceptions and consequent actions of social actors).

There are many branches in research philosophy (Schuh and Barab, 2007), with this research considering the five research philosophies defined by Saunders *et al.* (2009), namely: (i) positivism; (ii) critical realism (also called critical theory); (iii) interpretivism (also called constructivism); (iv) postmodernism; and (v) pragmatism. Table 2.1 describes each of the aforementioned research philosophies with respect to its: (i) principal orientation; (ii) suggested research approach; (iii) research strategy; (iv) ontological assumption; (v) epistemological assumption; and (vi) axiological assumption.

As indicated in Table 2.1, both the positivism and critical realism philosophies have an objective philosophical perspective, with interpretivism and postmodernism, categorized as having a subjective philosophical perspective. In contrast, pragmatism can be both subjective and objective.

Positivism and interpretivism philosophies represent two extremes, with the former usually being employed in the physical and natural sciences, with law-like generalizations made from the quantitative research completed (scientific); and the latter typically being employed in research in order to understand the world through the lens of peoples' perspectives, primarily through qualitative methods (humanistic) (Saunders *et al.*, 2009). Critical realism explains the phenomena that we see and experience in terms of underlying structures of reality that shape the observable events (Bhaskar, 2013). Where postmodernism seeks to question the ways of thinking that are generally accepted and deconstructs data to expose instabilities and absences within it (Saunders *et al.*, 2009).

Table 2.1: Philosophical perspectives (based on text from (Saunders *et al.*, 2009)).

	Principal orientation	Research approach	Research strategy	Ontology	Epistemology	Axiology
Positivism	Researcher maintains objective view and develops a hypothesis that is extensively tested	Deductive[6] approach	Quantitative methods	Real, external, and independent with one true reality	Scientific with observable and measurable facts	Researcher is detached and neutral (Objective)
Critical realism	Reality is moulded by history focusing on critique of oppositions. Researcher acknowledges bias by world view, though tries to minimise bias and errors	Abductive[7] approach	Quantitative or qualitative methods	External and independent	Knowledge historically situated and transient	Researcher as objective as possible but acknowledges bias by world views. (Objective)
Interpretivism	Researcher is subjective, and assumes that the investigator and the object of inquiry is inevitably linked	Inductive[8] approach	Qualitative methods	Complex, multiple meanings, interpretations, and realities	Focus on narratives, stories, perceptions, and interpretations	Researcher part of what is researched. (Subjective)
Postmodernism	Researcher seek to question the accepted ways of thinking and to deconstruct data to expose instabilities	Inductive or deductive approach	Qualitative methods	Nominal and complex with some interpretations and realities dominated by others	What counts as 'truth' and 'knowledge' is decided by dominant ideologies	Researcher and research embedded in power relations. (Subjective)
Pragmatism	Recognize that there are many different ways of interpreting the world, and that a single point of view cannot give the entire picture in the case of multiple realities.	Inductive or deductive, following the research problem question	Range of methods: mixed, multiple, qualitative, quantitative	'Reality' is the practical consequence of ideas	Focus on problems, practices and relevance	Research initiated and sustained by researcher's doubts and beliefs. (Objective or subjective)

Lastly, pragmatism recognizes that the world can be interpreted in a variety of ways, and that no single point of view can give the entire picture as there can be multiple realities. Another way to describe pragmatism is that it is not built on assumptions about the nature of knowledge, but rather focused on solving practical problems in the real-world (Maarouf, 2019). This approach

[6] The deductive approach starts with a hypothesis or rule that is tested with data, and if found to be true leads to conclusion (Dudovskiy, 2018).

[7] Abductive approach is an exploratory data analysis to understand a new phenomenon or suggest a new theory, also a combination of deductive and inductive research approaches (Mitchell, 2018).

[8] Inductive research occurs when a series of observations leads to a general conclusion that might be true (Dudovskiy, 2018).

integrates the use of multiple research methods (Saunders *et al.*, 2009; Dudovskiy, 2018), and according to Saunders *et al.* (2009) pragmatic research starts with a problem and aims to contribute practical solutions that will inform future practice.

The pragmatic philosophical perspective is adopted in this research. The pragmatic perspective leads the researcher to address the research problem with a combination of quantitative and qualitative research methods. The researcher also acknowledges that the problem which is the topic of this research can be interpreted and addressed in various ways, and that the solutions suggested, though grounded through a structured research strategy and approach, are not the only available means to address this problem but rather a single point of view of the problem sphere. This research aims to contribute a practical solution to the problem of selecting incentive interventions for neglected diseases and aims to inform future practice.

2.2. Research strategy

The research employed is non-empirical, thus, relying on mostly qualitative research methods including structured literature reviews, and existing data on incentives in the pharmaceutical R&D industry, to acquire the needed data. Consequently, the research is based on secondary data. Though the majority of the research presented in this dissertation is qualitative, a small quantitative component is also incorporated. Thus, a mixed-methods approach was followed. This research falls in the theory and model building research design, as defined by Mouton (2001), depicted in Figure 2.1.

According to the purpose of the study, the research can be classified as applied research (aimed to find a solution to a real-world problem), rather than fundamental research (which is primarily theoretical, with the aim of expanding knowledge on a specific theoretical phenomenon) (Dudovskiy, 2019). This links to the pragmatic philosophical perspective adopted in this research.

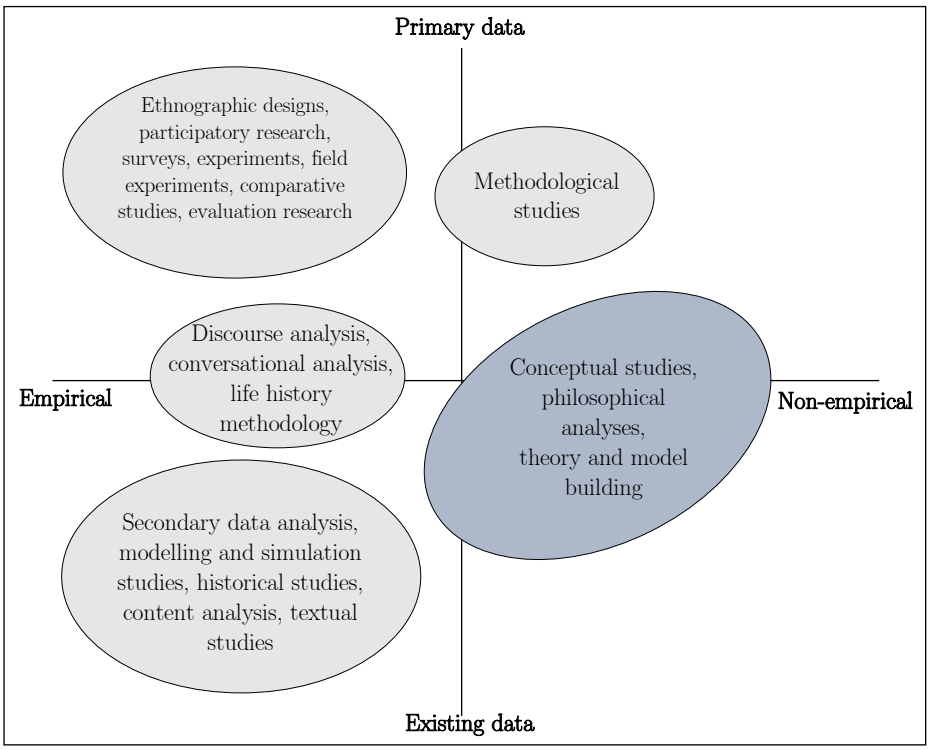


Figure 2.1: Research designs mapped into four dimensions (reproduced from Mouton (2001)).

2.3. Research approach

The overarching research approach followed to complete the study, is based on the 'design research cycle' introduced by Takeda *et al.* (1990). The former led to the research being categorized into five phases, namely: (i) awareness; (ii) suggestion; (iii) development; (iv) evaluation; and (v) conclusion. Takeda *et al.* (1990) describe each of the five phases as follows:

i. Awareness – grasping an understanding of the problem. The problem is defined, the scope is demarcated and the need for the solution is articulated.
ii. Suggestion – existing knowledge and theories are investigated. The problem is contextualized, and possible solutions or concepts are suggested to be incorporated.
iii. Development – the proposed solution is designed and developed. The key concepts are constructed into a solution by using various insights and knowledge gained in the awareness and suggestion phases. More than one development cycle can exist, with a new problem identified becoming a new design cycle within the development phase.
iv. Evaluation – the developed solution is evaluated and tested. Quantitative or qualitative techniques can be implemented to measure the performance of the developed solution.
v. Conclusion – the results of the designed solution are presented. The contribution of the designed solution to the body of knowledge is described.

The design research cycle approach is selected, as it proposes a structured approach to investigate the problem, evaluate literature, develop a solution and evaluate the solution feasibility. The five phases of Takeda *et al.* (1990) provide appropriate guidance to develop a solution that is grounded in literature. The approach includes a design iteration which allows for solution refinements after verification of the initial solution is completed. It is acknowledged, however, that the Takeda *et al.* (1990) design research cycle approach, is not the only approach that is appropriate or applicable to this research, with other approaches, such as the systems engineering approach (Defense Aquisition University Press, 2001) and building of a conceptual framework (Jabareen, 2009), also having been considered.

The development phase of the research incorporated the use of a requirement specification. The approach to compiling the requirement specification is discussed in more detail in Section 2.3.1. Various types of research products, such as conceptual frameworks, decision-making frameworks, models, logic models, and roadmaps exist. The motivation for the classification of the research product to be developed in this research is discussed in Section 2.3.2. Finally, the validation approach that is incorporated in this research is briefly introduced in Section 2.3.3. A comprehensive discussion of the verification and validation methodology is provided in Chapter 9 and 10.

2.3.1. Design requirement categories

Van Aaken *et al.* (2007) propose the business problem solution methodology to design a solution. This methodology provides an outline for completing a business-problem, by solving it in a strategic manner. The aim of this method is to create a design-focused, theory-based solution to the problem at hand. The method, therefore, utilizes theory in a comprehensive (systematic review of literature), critical (judge and value limitations of existing literature), and creative (aim to build on existing theory) manner (van Aaken *et al.*, 2007). Consequently, this business problem solution methodology is incorporated into this research, in the suggestion phase of the Takeda *et al.* (1990) design research cycle approach.

According to van Aaken *et al.* (2007), requirement specifications serve as a checklist that prevents design specifications from being overlooked. The requirement specifications, therefore, enable the researcher to have a holistic overview of the design process, as well as of all the characteristics involved in the process. Van Aaken *et al.* (2007) identify five types of requirement specifications, as defined in Table 2.2.

All five specification types are used in this research, where the specifications for the framework are identified throughout the research. In order to keep a record of which specifications are defined; each chapter concludes with a summary of the specifications identified, including a brief description of each. The framework development is guided by the specifications, as described in Chapter 8.

Table 2.2: Requirement specification categories (based on Van Aaken *et al.* (2007)).

Specification type	Definition
Functional requirements (F)	These are core specifications that the object to be designed needs to adhere to. Also viewed as performance demands of the developed design. Important that these functional requirements are not seen as primary input, but rather as part of the initial design process.
User requirements (U)	These are requirement specifications from the viewpoint of the user. The designed object must fulfil a certain function for the user.
Boundary conditions (B)	These are requirements that are to be met unconditionally. These might refer to aspects such as legal requirements; business policies; and company cultures which the design must fit into.
Design restrictions (D)	Design restrictions define the feasible solution space and might include time or budget limitations.
Attention points (A)	These are desirable and relevant requirements of the designed solution; however, these requirements are neither binding nor restrictive.

2.3.2. Classification of the research product delivered

Various research products can be categorized under the theory and model building research design. The aforementioned research products include frameworks, models, tools, roadmaps and decision-support systems. Table 2.3 lists and defines prominent research products, classified under the model building research design followed in this research.

Table 2.3: Investigation of prominent research products.

Research product	Description and definition	Source
Decision-support system	Mostly computer-based information systems designed to assist users to select one of the many alternative solutions to the problem.	Sauter (2002); Tripathi (2011)
Decision-support framework	A decision-support framework is a crucial step for understanding a complex system. A conceptual framework that defines the decision-support system, without being a computer-based information system.	Sauter (2002)
Framework	Frameworks define a structure or system for the realization of a defined result or goal. A framework is more comprehensive than a model but less comprehensive than a method. A framework can comprise of more than one model or tool.	Verbrugge (2017)
Conceptual framework	A structure formulated to best describe or explain a phenomenon. A depiction of the explanation of the problem, providing an integrated overview, and describing main relationships between concepts.	Dickson *et al.* (2018)
Theoretical framework	Framework that is based on existing theory, sometimes referred to as a 'blueprint'. Serves as foundation on which research can be constructed.	Dickson *et al.* (2018)
Models	The presentation of an existing state, future state, or situation often in a simplified, schematic form. Most models are decision-support tools. With all models being tools, but not all tools being classified as models.	Brenner (2016); Verbrugge (2017)
Logic models	The thinking behind a program design is explained through the definition of inputs, outputs and outcomes, showing how specific activities lead to desired results.	Compass (2015)
Roadmap	Roadmaps are high-level plans, defining the major steps planned for achieving strategic objectives.	ProductPlan (2019)
Tool	Tools are a means to an end. Tools are instruments used to go from specified goals and constraints to an optimal decision. Tools have predefined inputs and deliver pre-defined outputs.	Brenner (2016)
Decision-making tools	Techniques used to make decisions, with pre-defined inputs and outputs.	Brenner (2016)

The output of this research is classified as a decision-support framework, comprising of various decision-making tools (such as decision-matrices). The decision-support framework is further operationalized into a user-friendly computer-based framework, therefore qualifying the research output to be classified as a decision-support-system. The only difference between the decision-support framework and the operationalized version of the framework, is that all the equations and incorporation of the input data required for the decision-support framework is automated, with no fundamental difference between the two research products. The operationalized framework, though being automated, is not a complex information system, and is consequently still referred to in this research as a decision-support framework.

2.3.3. Evaluation approach

The evaluation of the developed research products includes the verification and validation of such research products. As mentioned previously, a comprehensive discussion of the verification and validation methodology, is provided in Chapter 9 and 10. Thus the approach is summarised here.

Verification and validation are completed in separate phases in this research. The verification phase aims to establish that the initial design is accurate, with any framework gaps and/or inadequacies being identified during the verification process. Verification is completed in two stages, namely: (i) internal design requirement verification, where the requirement specifications identified throughout the document are evaluated; and (ii) external SME verification, where one-on-one interviews with subject matter experts, seek to verify the developed framework.

The external phase of verification is conducted in two phases. The first phase of external verification was conducted on a preliminary version of the decision-support framework, excluding certain components of the final version, and the second phase of external verification is conducted on the final version of the decision-support framework. The first phase of external verification provided deeper insights into SME perceptions of the framework as well as provided fundamental understandings that aided in the further development and refinement of the decision-support framework.

Framework refinement follows the verification phase. Omissions and inadequacies of the framework, identified during the two verification stages, are addressed where applicable. The outcome of the framework refinement phase is the final decision-support framework.

The validation of the framework seeks to quantify whether the framework is fit for its intended purpose. The validation is completed by, firstly, performing one-on-one subject matter interviews. The interviews provide the opportunity to engage with leading SMEs in the fields of (i) NDs; (ii) pharmaceutical R&D; and/or (iii) incentive interventions.

The second means to validate the developed decision-support framework is through applying the decision-support framework to three retrospective case studies. The retrospective case studies are evaluated, with the aim of testing the ability of the decision-support framework to suggest a set of incentive interventions for a specific case.

2.4. Research methods and document structure

The overarching research approach followed, as mentioned previously, is the five phases of Takeda *et al.'s* (1990) design research cycle. The document structure as well as the methodology followed to achieve each of the research objectives, is summarized in Table 2.4. This information is mapped to Takeda *et al.'s* (1990) research phases, given in the column on the left.

Table 2.4: Research methodology and document structure

	RO.	Research objective	Chapter	Methodology
Awareness	0	Define the problem and approach	Chapter 1, 2	Comprehend the problem through investigating the problem background, and defining the aim, objectives and research question. Establish research methodology, including philosophical perspective, research strategy as well as the scope of the research.
Suggestion	1.0	Review aspects of the health care system	Chapter 3	Contextualize the problem background, by investigating relevant underpinnings of the health care system.
	2.0	Investigate pharmaceutical R&D pipeline	Chapter 4	Complete systematic literature reviews to determine factors that influence the advancement of drugs through the R&D pipeline, and trends in the pipeline.
			Chapter 4	Quantitatively analyze the relationship between drugs in the R&D pipeline and burden of disease, with a regression analysis.
	3.0	Identify properties that enhance, or reduce attractiveness of drug R&D	Chapter 5	Complete a market analysis of the pharmaceutical R&D industry. Complete both the external-, and internal analysis components.
			Chapter 5	Complete a systematic literature review, investigating disease-specific characteristics that enhance, and reduce attractiveness, from the perspective of the market.
	4.1	Identify existing incentive instances	Chapter 6	Complete a systematic literature review to identify a (non-exhaustive) list of existing incentive instances.
	4.2	Determine existing incentive types	Chapter 6	Inductively deduce the complete set of incentive types to encourage R&D for NDs, based on the results of the aforementioned systematic literature review findings.
	5.0	Derive requirement specifications	Chapter 3, 4, 5 & 6	Derive requirement specifications that the decision-support framework should incorporate, based on the research completed.
Development	6.1	Develop decision-support framework	Chapter 8	Incorporate requirement specifications to develop a decision-support framework that: (i) satisfies the functional requirements; (ii) incorporates the perspective of stakeholders, as defined in the user requirements; (iii) complies with the design-restrictions; (iv) adheres to the boundary conditions; and (v) includes all attention points.
	6.3	Refine framework	Chapter 9	Incorporate suggestions of SMEs into design of the decision-support framework, where applicable.
Evaluate	6.2	Verify the decision-support framework	Chapter 9	Verify the requirement specifications and verify the design of the framework through SME interviews.
	6.3	Validate the decision-support framework	Chapter 10	Determine efficacy, applicability in the real-world, and novelty of the research through SME interviews and the application of three case studies.
Conclude	6.5	Conclude research	Chapter 11	Conclude the research by reflecting on the research completed, discussing research limitations, and investigating potential future work.

2.5. Conclusion: Research methodology

This chapter investigates the philosophical perspective adopted in this research, relating to the research structure and approach followed to complete the research and develop the suggested decision-support framework. Lastly, the methods employed to achieve the research outcomes and document structure are described.

CHAPTER 3

Contextualization: Health care system

In this chapter, the health care system, to provide context into the complex pharmaceutical environment in which R&D for drugs is performed, is investigated. A high-level overview of the taxonomy of care levels, and a breakdown of health system components, relating to the neglected disease sphere, is presented. The desired outcomes of an improved neglected pipeline are demarcated and the goals and objectives to accomplish it are defined. Lastly, the health care system is analysed to determine objectives as well as goals of the system.

3.1. Views of the health care system

To understand the functioning of the health care system, it is important to firstly investigate the stakeholders involved in providing care. This is done by investigating the levels of care, as depicted by the World Health Organization (WHO) in the 'six levels of a health care system'. Secondly, the WHO Health Systems Framework is analyzed to determine what the key elements of a health system are, and how the operation of these elements aid in delivering the desired drug interventions to the consumers (patients). The objectives and goals of all health systems, with specific reference to the neglected disease health system, are thirdly, defined. These are established from the four objectives set out by the WHO Health Systems Framework.

Health care systems are investigated to grasp the holistic purpose that the outcomes of the health system should fulfil. The outcomes are discussed by means of the four sub-outcome categories, as defined by the WHO Health Systems Framework. The complexity of the health care system is an aspect that, although difficult to quantify, should be given due consideration when reflecting on the operations of the various functions and stakeholders within the health system.

3.1.1. Health care level of care

According to the WHO (2010), the taxonomy of care levels in the health system, also described as the 'levels of the health care system', serves as a method of unraveling the complexity of the health care system. The levels-of-care view of the health system is a usual mechanism to frame an analysis of the system. For the purpose of this research, the levels of care are used as reference to identify which stakeholders form part of the pharmaceutical drug R&D process, in order to pinpoint the required problem areas to address, and to improve the state of the pharmaceutical

drug R&D process for specifically NDs. Rardin's (2007) depiction of the six levels of care of the health care system is reproduced in Figure 3.1.

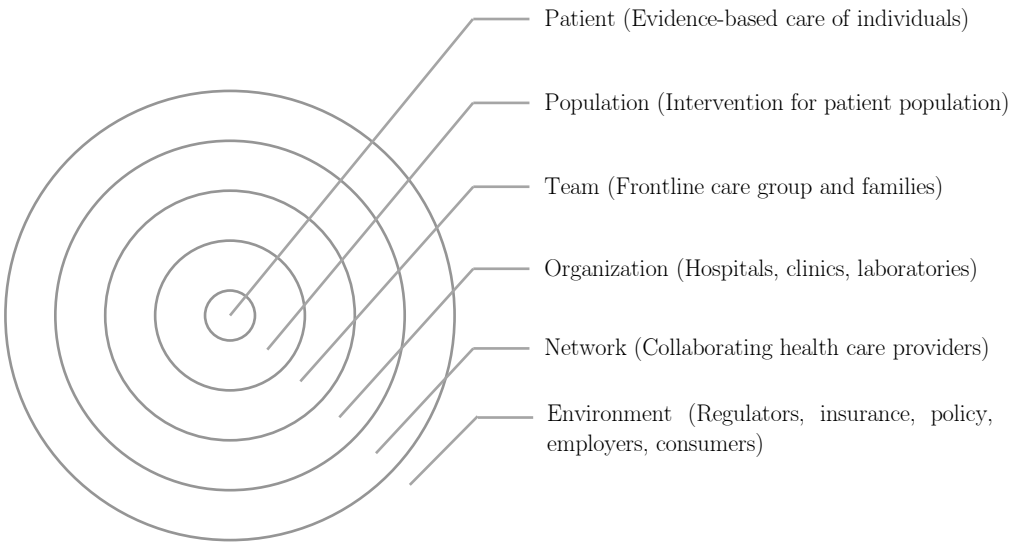


Figure 3.1: Six levels of care of the health care system (reproduced from Rardin (2007)).

As depicted in the levels-of-care view, the main entities that form part of the pharmaceutical R&D process include: (i) the patient, or consumer, of the drug (whose needs should be the core of health care delivery); (ii) the population, used to identify and motivate the neglected state of diseases; (iii) the organizations, of whom the laboratories (organizations that innovate and perform R&D) are considered a major stakeholder for the development and delivery of medicines to satisfy consumer needs; (iv) network, representing the complex collaborating relationships between all the stakeholders of the R&D of drugs; and (v) the environment, where governments, regulation, policy and third party organizations play a role in stimulating or responding to the needs of the core (consumers). The only stakeholder not considered in this research is the teams' level of care, as it is primarily concerned with the practical aspects of delivering frontline care.

3.1.2. The WHO Health Systems Framework

The Health Systems Framework developed by the WHO, shown in Figure 3.2, is a means by which the health care system and its components can be described. Each health system building block (depicted in the column to the left in Figure 3.2) contributes to the strengthening and state of the health care system in a different way (WHO, 2010a), while the framework defined four overall goals/objectives of a health care system (depicted in the column to the right). According to the framework, the system building blocks impact the achievement of the overall goals/objectives via its impact on four mediating outcomes (depicted in the middle of the figure). The aim of this section is not to provide a detailed explanation of the building blocks, outcomes/objectives, and mediating outcomes of the WHO framework presented in Figure 3.2, but rather to focus on the relevance of each of the elements to this research. The building blocks are discussed in Section 3.1.3 and the goals/objectives are discussed in Section 3.1.4. The

mediating outcomes are discussed in Section 3.4, following preceding discussion of health care systems in LMICs, financing mechanisms, and NDs.

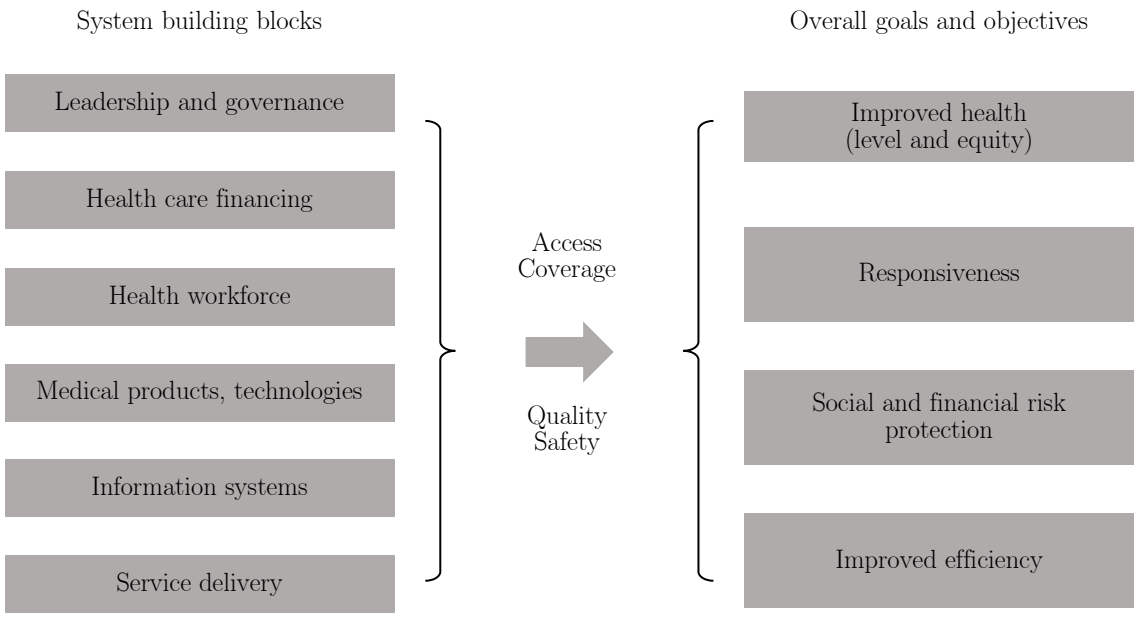


Figure 3.2: WHO Health Systems Framework (reproduced from WHO (2010)).

Though this health care systems framework provides a useful means for obtaining a high-level overview of prominent aspects of the health care system, some relevant aspects are omitted. For example, the framework does not consider actions which influence people's behavior, and does not address underlying social and economic determinants of health, such as gender inequities and education (WHO, 2010a). A second omission of the framework that is particularly salient, given the fundamental assumption of the health care system as a complex adaptive system in this research, is that the framework does not address the complex interactions of the different building blocks.

3.1.3. System building blocks of the WHO Health System Framework

Factors that contribute to diseases becoming neglected can be determined by considering the potential role of each of the system building blocks in contributing to this outcome. As part of the WHO Health Systems Framework, 'core indicators' are identified that can be used to measure each of the building blocks and the state thereof. Data sources and methods of collection, are also identified (WHO, 2010a). Table 3.1 depicts the meaning of each building block as an interpretation of the building blocks in the context of this research.

Table 3.1: The WHO Health Systems Framework building blocks and relevance to this study.

	Description and meaning of the building block	Relevance to this research
i	**Leadership and governance** ensure that a strategic policy framework exist, and that regulation thereof is taking place. With accountability being a major aspect in this building block, stakeholders need to accept responsibility for the following: a. Delegating and understanding the application of services; b. Financing the necessary resources to deliver health service; c. Performance of the supply of the health service; d. Receiving information to monitor system performance; and e. Enforcing sanctions or rewards, based system performance.	A strategic policy framework that assigns responsibility for actions such as "financing the necessary resources to deliver health service" and "enforcing… rewards-based system performance" relates strongly to the ability to incentivize pharmaceutical R&D for NDs.
ii	**Health financing** is the "mobilization, accumulation and allocation" of money to provide services and products to satisfy the health needs of people (WHO, 2010a). For a health system to have satisfactory health financing, it is required that there are enough funds to finance the service delivery of health care. It is also necessary that the individuals have financial risk protection with regard to becoming ill.	The availability of funds is essential to enabling incentive mechanisms for pharmaceutical R&D for NDs.
iii	**Health workforce** can be defined as "all people engaged in actions whose primary intent is to enhance health" (WHO, 2010). The knowledge, skills, motivation and deployment of the people who performs the health services all contributes to the ability of the country to adequately perform the health service (WHO, 2010).	Given the broad definition of the health workforce employed here, it is clear that the actions of individuals who determine health-related policies and budgets, will have a significant impact on both the means to incentivize R&D and on how attractive the market is, given regulatory details, etc.
iv	**Medical products and technologies** include all the drugs, vaccines, diagnostic tests, equipment and tools used to diagnose, prevent and treat diseases. This is the means and the functional components used to effectively reduce the occurrence of diseases.	The ultimate aim of pharmaceutical R&D for NDs is to ensure that viable drugs to treat these diseases are developed and ultimately reach the market.
v	**Health information systems** has four key functions: a. Data generation; b. Compilation; c. Analysis and synthesis; and d. Communication and use. This component plays a major role in health care decision-making. The health information system collects data from the involved stakeholders and converts data into relevant and high-quality information that can be used in decision-making related to health care (WHO, 2010).	Accurate data on the prevalence of NDs could strengthen the market attractiveness of R&D on the disease, by, for example, providing an estimate of the expected demand for the medication that private sector partners have confidence in.
vi	**Service delivery** is the complete process of providing a health service to citizens, and the complex network behind it. According to the WHO (2010) good service delivery includes eight key characteristics. These characteristics are the following: a. **Comprehensiveness:** Refers to the range of services provided and its appropriateness to the population group.	The availability of quality drugs, at prices that are affordable has a strong link to various aspects of service delivery, including: comprehensiveness and coverage (if treatment for a ND is not available, this inhibits the ability to offer comprehensive health

Table 3.1 continue on next page

Table 3.1 continued from previous page

b. **Accessibility:** The health service provided should always be accessible to all. No barriers should exist which prohibits the ability of individuals to access the services provided. c. **Coverage:** All the people in a population group should be covered by the service provided. d. **Continuity:** Every individual should have access to health care without any interruptions in the accessibility of the service. e. **Quality:** Health service should be of a high quality, thus effective, safe, patient-need centered and should be provided on time. f. **Person-centered:** The service should not be solely focused around the disease, but rather on the individuals. g. **Coordination:** The service delivery networks of the local area should be organized properly across all types of actors, types and levels of care as well as for agility of service supply. h. **Accountability and efficiency:** The service should be managed in such a way to minimize waste of resources. The management should also take accountability for the performance and outcomes of the services provided.	care/coverage to a population affected by the ND); accessibility (affordability of pharmaceuticals links strongly to the ability to access care); quality (the quality of available drugs has an impact on this aspect of service delivery).

The building blocks are essential in creating an effective health system that provides timely, affordable and high-quality services to all individuals who need them (Rauscher *et al.*, 2018). All six building blocks are valued to be applicable in addressing the neglected disease problem. It is furthermore prominent in Table 3.1 that financing of the health system is the enabling building block required to implement, facilitate and sustain all the building blocks to function in its desired state. This substantiates that the health financing building block is the most relevant to the research.

3.1.4. Objectives and goals of the WHO Health System Framework

Four overall goals/objectives that each health care system should strive toward are identified in the WHO Health Systems Framework. The relevance of these four goals/objectives, to the topic of this research, is briefly summarised in Table 3.2.

3.2. Health care systems in LMICs

Following the overview of the building blocks as well as the overarching goals/objectives of health care systems, this section contains a high-level discussion of the state of health care systems in LMICs. The income category of countries may have a large influence on the ability of citizens to afford the drugs necessary to treat a disease (Trouiller *et al.*, 2002), consequently, the income-categories of countries, as estimated by the World Bank, are discussed in Section 3.2.1. The health expenditures of the public sector for these income-categories, and the impact of a lack of disease mitigation in LMICs, are discussed in Sections 3.2.2 and 3.2.3 respectively. Finally, the willingness of both the private and public sectors to invest in the R&D of medicines for NDs is discussed in Section 3.2.4.

Table 3.2: Objectives and goals of the health system and relevance to this study

Goals/objectives of health system	Relevance to this research
i. **Improved health** and health equity of populations.	This study aims to contribute towards the improved health of neglected populations by providing a means to incentivize R&D for ND drugs. Contributing to this field will advance health equity amongst population groups from specifically under-developed environments.
ii. **Responsiveness of the health system.** Being adequate services provided in the right quantity, when intervention is needed.	A contribution towards the current global health system's adequacy to address NDs is intended by incorporating the various stakeholders into the R&D of neglected drugs. This may have an indirect impact on the responsiveness of health systems by improving the R&D pipeline for NDs.
iii. **Social and financial risk protection** for both patients and entities involved in health services. Entities should be protected against risks involved regarding health provision and acceptance.	This research aims to promote the social and financial risk protection of the consumers (neglected population) by investigating the increased provision of high-quality drugs with affordable drug pricing for NDs. By improving the state of the R&D pipeline, attention should also be directed to the innovating organizations undergoing financial risks by performing R&D. It is envisioned that this risk could be reduced by encouraging enabling entities to share in the financial risks involved.
iv. **Improved efficiency** of available resources. Services should be adequately available and accurate.	The efficiency of a health system can be enhanced by promoting an improved ND drug R&D pipeline. Improved efficiency is investigated in more detail in Chapter 3.

3.2.1. The affordability of health care in LMICs

LMICs are countries where the gross national income per capita falls below $4 035. Table 3.3 indicates the income level categories of countries, as established by the World Bank in July 2018.

Table 3.3: Country classification based on gross national income per capita in 2017 (data source: World Bank (2018)).

	Country classification	Gross national income per capita
1.	Low-income	$995 or less
2.	Lower middle-income	$996 - $3 895
3.	Upper middle-income	$3 896 - $12 054
4.	High-income countries	$12 055 or more

As per the classification in Table 3.3, the individuals of most LMICs countries have limited resources to use for all basic needs, including out-of-pocket (OOP) payments for essential medicines (Niëns and Brouwer, 2013). The populations of these countries can often not afford the necessary medicines, thus, they either go without taking the prescribed drugs, or go into debt to afford the drugs in addition to other basic needs (Niëns and Brouwer, 2013).

3.2.2. Expenditure for the improvement of health conditions in LMICs

On average an estimated $20 (in 2014) is spent on health per capita in LMICs, in contrast to $947 of some high-income countries (Luchetti, 2014). The estimated amount spent per capita in

sub-Saharan Africa is less than the average low-income countries', and amounts to less than $6 per annum, including drug expenditures (Trouiller *et al.*, 2002). A target set out to enable the most disadvantaged countries to lessen the health burden in their countries, is a spend of $44 – $60 per capita, which would ensure that the poorest populations have access to the most essential health services and medicines (Trouiller *et al.*, 2002). It is clear from the aforementioned, that the expenditure per capita for high-income countries is substantially higher than for LMICs. Population groups from LMICs are often left to pay for the required treatments themselves, which is unaffordable and not feasible given their circumstances. Options for aid in the payment for medicines exist but the equity of these systems are often not reliable (WHO, 2000).

It should, however, be noted that it is not only expenditure on medicine that is required to alleviate many of the diseases in the LMICs. The WHO estimated that in developing countries, diseases associated with poor living conditions and poverty accounts for up to 45% of the disease burden (Luchetti, 2014). Poor living conditions refer to the circumstances of people and how it affects their well-being, and often implies that the living standards of the population has a negative impact on their lives. Examples include aspects such as, the lack of education, malnutrition, poor sanitation and no access to safe drinking water. All the aforementioned are conditions that can be improved by governmental initiatives but will require large capital investments in both the short- and long term (Luchetti, 2014).

3.2.3. The main consequences of the lack of diseases mitigation in LMICs

Various stakeholders are affected by the wellbeing of a population. The consequence of a high disease burden of a community stretches throughout all levels of the society, and has the potential to have a large economic, political and a social impact on the country (WHO, 2020a). The individuals in LMICs affected by NDs are often the ones who suffer the most (Stolk *et al.*, 2016). For an average individual from an LMIC, falling sick reduces their ability to work which leads to a decrease in their income (WHO, 2003). The WHO (2003) also mentions the possibility of the cycle of poverty and ill health as a danger for poor families who are suffering from diseases that are not treatable or are not treated well. The cycle refers to poverty preventing an individual from treating their disease, which in turn causes housing circumstances to deteriorate (even) further, creating the potential for more diseases in the family.

3.2.4. The investment of countries in health care

The amount of funding invested in the health care of different countries varies. The funding for health care of LMICs is typically limited, and the required policies and management of the health system are not acceptable (Global Forum for Health Research, 2004). In high-income countries, effort must be made to allocate health funding more appropriately, by taking both national and international health issues into account (Global Forum for Health Research, 2004).

Although the private pharmaceutical sector is playing an increasingly important role in the funding of R&D of medicines for diseases, the need of improved drugs for these diseases still exists. Therefore, private organizations must be encouraged to invest in the R&D of drugs for NDs. Numerous methods exist to incentivize, amongst other, private organisations to invest in the R&D

of NDs. Chapter 6 investigates existing incentive methods, and the potential that they hold to improve the current state of the drug pipeline for these diseases.

In simplistic terms: the pharmaceutical industry reasons that the benefit of financing R&D for diseases that, experience has proven, leads to higher financial returns, weighs more heavily than the potential return on producing drugs for NDs, given the uncertainty and risks associated with these (Trouiller *et al.*, 2002). Consequently, the responsibility of funding R&D for NDs falls primarily to the public sector. In support of the aforementioned statement, the WHO (2020b) states that in 2016 74 % of worldwide health care investment was financed by governments (i.e. public funded), 18.6 % was out-of-pocket expenditure, 7.2 % was private insurance and 0.2 % was donors. It should also be considered that public funding greatly depends on political factors (Universal Health Coverage Partnership *et al.*, 2016).

Politicians tend to focus more on responding to their constituencies, whom are generally situated in industrialized areas (MSF, 2001). The disease profile in rural areas is, however, often different from that in industrialized areas which in effect leaves a gap in the drug delivery system (MSF, 2001). In response to the latter, private foundations and donors are exerting a great amount of effort on NDs, but should not and cannot take the responsibility from the public sector who is the main stakeholder responsible for the health of their nation (MSF, 2001). Linking to public sector responsibility, is the consideration of sustainability in mitigating and addressing NDs in the long term. With the likelihood of sustainable funding increasing when public stakeholders own the responsibility.

3.3. Relevant health financing concepts

In LMICs, medicines represent the largest OOP expenditure (WHO, 2000). In developing countries, 50 - 90% of medicine used in a family is paid OOP (WHO, 2000). In contrast, in high-income countries, two-thirds of medicine is paid through government funding or social insurance programmes (WHO, 2000).

User fee schemes are becoming a well-known concept but should not be seen by governments as a long-term solution to the problem of financing medicine for the poor. User fee schemes are known to worsen equity of poor populations (WHO, 2000). This does not, however, mean that user fee schemes are bad in all circumstances, rather these should be used as a supporting mechanism of providing health care finances, in collaboration with government programmes (WHO, 2000).

Social and universal health coverage is a goal to strive towards as it provides equity, solidarity and affordability for all (WHO, 2000). The sustainable development goals are desired targets set out by the WHO to improve universal health. Sustainable development goals Target 3.8 is a goal for all countries to achieve universal health coverage. Universal health coverage means "ensuring that all people receive the essential health services they need without being exposed to financial hardship as a result" (WHO, 2018e).

3.4. Outcomes of health care for neglected diseases

According to MSF (2001), people in developing countries represent 80% of the world population but are only responsible for 20% of worldwide drug sales annually. Various reasons exist as to why the medicine sales for developing countries are so much lower than for developed countries. Reasons may include the lack of availability of medicines in developing countries, where availability refers to whether the medication is: (i) affordable for patients suffering from NTDs; (ii) physically accessible within reasonable distance from patients' homes; and (iii) of good quality. In some instances, no medication to effectively treat the disease is available.

As discussed in Section 3.1.2, the WHO Health Systems Framework defined four mediating outcomes through which the health system building blocks can impact the achievement of the goals/objectives of the health care system. As depicted in Figure 2.2, these mediating outcomes are: (i) access; (ii) coverage; (iii) quality; and (iv) safety. The meaning of these four outcomes, in the context of NDs specifically, is discussed in the remainder of this section.

3.4.1. Access of the health care system

It is necessary to comprehend the access barriers of medicine and health care for certain diseases in any given population to establish whether the health system is accessible. Access has various dimensions, defined by Jackson (2018) as: (i) availability; (ii) accessibility; (iii) affordability; (iv) appropriateness; and (v) acceptability. These five dimensions of accessibility of any product or service in a community can be established by answering certain questions and determining where in the system the most significant barriers exists (Jackson, 2010). The questions for each aspect, as defined by Jackson (2018), are summarized in the diagram in Figure 3.3.

In an attempt to improve access to drugs for diseases that have a significant global health impact, the WHO constructed an 'essential medicines' list. Essential medicines are described as medicines that "satisfy the propriety health care needs of the population". The medicines on this list are selected by considering relevance to public health, available proof of safety and efficacy as well as reasonable cost effectiveness (WHO, 2018c). Some, but not all, NTD treatments are part of this list. According to Luchetti (2014), the lack of access to drugs indicated a failure of public health policy, and the responsibility for the extent of the problem lies with governments (Luchetti, 2014). When governments add large tariffs and taxes on medicines, this further decreases access (Luchetti, 2014).

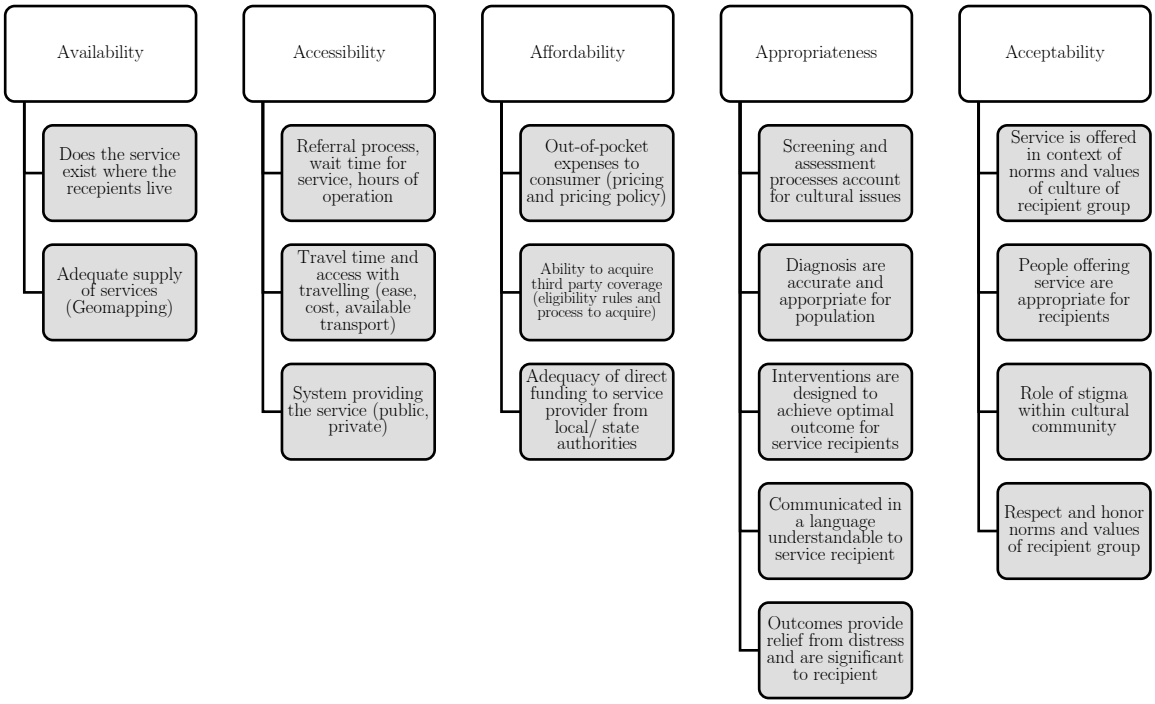


Figure 3.3: Question matrix for assessing the impact and effectiveness of a product or service in a population group (based on text from Jackson (2018)).

3.4.2. Coverage of the health care system

According to van Olmen *et al.* (2010) access and coverage are related terms. Access refers to the number of people that can use a health service, where coverage describes the proportion of the target population that benefit from a specific intervention (van Olmen *et al.*, 2010). One way identified by van Olmen *et al.* (2010) to measure coverage is to assess the ratio of health services available in relation to the size of the target community or population.

The state of the neglected disease environment is an indication of the extent of health interventions coverage over LMICs and population groups suffering from these NTDs. Coverage for LMIC populations would imply that a 100% proportion of the people affected by NDs would benefit from the interventions launched to mitigate them.

3.4.3. Quality of care of the health care system

The quality of care of a health system greatly depends on the perspective of the stakeholder (van Olmen *et al.*, 2010). According to van Olmen *et al.* (2010) the quality of care should enable and empower the patients to master their own health situation and to better cope with their health circumstances, and should comprise of the following characteristics: (i) effectiveness; (ii) efficiency; (iii) safety; (iv) patient-centredness; (v) comprehensive care; and (vi) should stretch beyond visits to health facilities. Quality is an indication of the acceptability of care, which is found to also be a dimension of access.

As mentioned in Section 3.4.1, the quality of ND drugs, are often not acceptable. It is consequently important that the interventions implemented as part of this research realizes high quality drugs.

3.4.4. Safety of the health care system

Safety in the health system primarily refers to the safety of drugs. All drugs have side effects, but the consequences and severity of effects vary from minor to extreme (Alshammari, 2016). Minor side effects include mild itches, or headaches; where as more severe symptoms might lead to damage to vital organs or even death in extreme cases (Alshammari, 2016). Most side effects are previously established and mentioned in the leaflets of the medicine, there are however some side effects not indicated or even established, known as adverse drug reactions.

Before a drug can be marketed, it needs to go through extensive evaluations and regulatory reviews to establish quality, safety and efficacy standards (MSF, 2001), as discussed in Chapter 1. Drug safety refers to when drugs have a near-zero risk to any side effects or adverse drug reactions. Cost is, however, a major contributor to the extent of measures taken to ensure the safety of a drug. In drug markets with a high return on investment (ROI), cost is not a major issue, but this is not always the case for neglected disease R&D (MSF, 2001). For NDs, cost is a major problem and the risk-to-benefit ratio for quality, efficacy and safety of drugs should be considered while taking the gross public health failure in to account of many individuals not having any treatment available and accessible at all (MSF, 2001).

The more strict the drug guidelines for medicines to be approved, the higher the costs of development, and the higher the barriers for drug development in developing countries, especially for small-and medium sized organizations (MSF, 2001). Even though cost might be higher, there should be no tolerance for medicine that does not comply with the basic rules and standards set out for drugs to be safe for use. According to Dorlo *et al.* (2012) medicine of substandard (poor quality and not safe or effective) is a bigger problem in LMICs, than in higher-income countries. The aforementioned, stems from the lack of recourses, negligence and fraud which is often the case in lower-income countries (as investigated in Section 3.2).

3.5. Requirement specifications

The requirement specifications, as mentioned in Section 2.3.1, serve as part of the research approach in the formulation of the research product. The requirement specifications ensure that all design specifications are incorporated (van Aaken *et al.*,2007).

The requirement specifications derived from this chapter are indicated shown in Table 3.4. As mentioned in Chapter 2, the requirement specifications serve as the foundation for developing the decision-support framework, in Chapter 8.

Table 3.4: Requirement specifications, as derived from Chapter 3.

Reference		Requirement definition	Section
Functional requirements	F.1	The developed framework should provide a means to outweigh the risks and uncertainty of the R&D operation of innovating a drug with the benefits of the provided solution (or set of solutions).	3.1.4
User requirements	U.1	The framework should select an incentive intervention that considers the patient and population as core drivers for the incentive.	3.1.1
	U.2	The framework should provide a solution, or set of solutions, that will incorporate the outcomes and goals, as set by the WHO health care framework, namely: -Improve access; -Improve coverage; -Improve quality of services delivered; -Ensure safety; -Improve overall health (burden of disease); -Be responsive; -Provide social and financial risk protection; and -Improve efficiency of mitigating the disease.	3.1.4, 3.4
Design restrictions: No design restrictions are derived from this chapter.			
Boundary conditions	B.1	The framework should promote the needs of all stakeholders and consider the role of each stakeholder to ultimately provide a solution that will positively influence the patient, as well as other stakeholders involved.	3.1.1
Attention points	A.1	The framework should be grounded on improving, or addressing, all six building blocks of the health care system, as described by the WHO health care systems framework, namely: -Leadership and governance; -Health care financing; -Health workforce; -Medical products, technologies; -Information systems; and -Service delivery.	3.1.3

In this chapter, one functional requirement, two user requirements, one boundary condition, and one attention point were identified. No design restrictions were identified in this chapter.

3.6. Conclusion: Health care system

The health care system is a complex system existing of a large number of stakeholders, that work on different levels to provide health care to population groups. Desired outcomes of the health

care system are discussed, and performance measures to measure the system against are established. The four primary outcomes of a health care system are for the system to be: (i) accessible; (ii) to cover everyone; (iii) be of high quality; and (iv) be safe. A major influencer of the ability of the health care system of a country to satisfy the needs of the population is found to be the income classification of countries. Where the health expenditure per capita for LMICs is significantly lower than for higher income countries, which might in turn lead to insufficient health care.

NDs is a serious problem in especially LMIC settings, with all four the WHO Health Systems Framework outcomes being unmet in the current disease environment. Although this research does not aim to primarily achieve the four outcomes, these will be addressed to a certain extent in the solution space of this research.

The following chapter will investigate the pharmaceutical drug R&D pipeline environment and identify elements in the pharmaceutical sphere that influence the state of the pipeline for specifically NDs.

CHAPTER 4

Pharmaceutical R&D pipeline

The primary objective of this chapter is to investigate the pharmaceutical R&D pipeline. The chapter starts with a systematic literature review that seeks to identify: (i) factors that have a direct influence on the drug R&D process, thus affecting the state of the drug pipeline; and (ii) trends in the development of drugs over the past 10 years. Following this, characteristics of a number of drugs in the global R&D pipeline are investigated. Lastly, the relationship between the burden of disease and the number of drugs in the R&D pipeline is evaluated for a selected set of diseases.

A significant portion of the text in Sections 4.1 - 4.5 has been reproduced from two conference articles that were published as part of this research. The copyright agreement for both publications provides for use of the text in a dissertation. The text in Section 4.1 has been reproduced from a conference article with following citation: Hanekom, N., Bam, L., de Kock, I.H. (2018). "Towards a more efficient and effective pipeline of tuberculosis medication: the value of identifying trends and influencing factors." In *SAIIE29 Proceedings, 24th – 26th of October 2018, Spier, Stellenbosch, South Africa* (pp. 391–404).

The text in Sections 4.2 - 4.5 has mostly been reproduced from a conference article with the following citation: Hanekom, N., Bam, L., de Kock, I.H. (2019). "What makes diseases and drug research and development attractive for the pharmaceutical industry." Accepted for publication in: Proceedings of the *25th ICE/IEEE International Technology Management Conference, 17th - 19th of June 2019, Sophia Antipolis, Nice, France.* © 2019 IEEE.

4.1. The pharmaceutical R&D pipeline

The drug pipeline refers to the set of drugs that a pharmaceutical company, or the entire pharmaceutical industry, have in the discovery or R&D phases at a given point in time (Surowiecki, 2004). The drug pipeline encompasses the R&D activity taking place, thus serving as a form of reference to the extent of interest, investment and resource allocation in a specific drug or disease (Segen's Medical Dictionary, 2012). In the pharmaceutical industry, the drug pipeline includes all the processes from initial drug discovery to the introduction of the product for public consumption (Surowiecki, 2004). However, the drug pipeline does not end when the drug development process has been completed and the drug approved for launch; ongoing research and data collection form part of post-approval studies (PhRMA, 2016). These studies are conducted for as long as the product is used by patients and include the examination of the drug

and its effects on drug users; these insights can also be used to expand treatment options in future drug development (PhRMA, 2016).

The pharmaceutical pipeline is under significant pressure when the substantial number of events, processes, stakeholders, circumstances and regulations influencing the outcome are considered. Advances in science, technology and management practices in drug development have been made over the past 60 years; yet the number of new drugs approved, per billion US dollars spent on drug development, has decreased about 80-fold (Scannell *et al.*, 2012). The impact of time and cost challenges on the drug industry are well known. Another contributor to the loss of efficiency in the drug pipeline is the 'curse of attrition' (Bunnage, 2011). This refers to the considerable number of drugs being rejected in clinical trial phases, as the drug progresses through the compulsory trials and processes (Bunnage, 2011). The low success rate of compound development is further impaired by the amount of funds lost once a drug is rejected at such an advanced stage of development (Bunnage, 2011). The pharmaceutical industry strives to decrease the number of drug compounds exiting the R&D system without being approved, thereby minimising lost investment costs, research effort and time.

4.1.1. Systematic literature review: R&D pipeline

Numerous research studies have been aimed at pinpointing factors that contribute to the loss of efficiency in the pharmaceutical R&D process (Naci *et al.*, 2015). The value of identifying these factors lies within the opportunity to potentially address the identified factors in the R&D process, thus limiting the negative effect that these might have on the pharmaceutical pipeline. This study aims to identify the factors that have a direct influence on the drug R&D process, thus affecting the state of the drug pipeline. A systematic literature review has been used to determine such factors.

4.1.1.1. Systematic literature review method: R&D pipeline

The literature review search was done in the Scopus literature database. The objective was to establish the factors that lead to a lack of efficiency in the pharmaceutical drug pipeline. Answering the following two research questions (RQs) will contribute to addressing the primary objective of the study effectively.

RQ 1: What factors influence the overall drug pipeline of the pharmaceutical industry?
RQ 2: What trends can be identified in the development of drugs over the past 10 years?

Keywords for the search were derived from the two research questions and arranged in a logical manner. A search was completed with the search line: ("clinical trial" OR ((pharmaceutical OR drug*) W/5 ("R&D" OR pipeline OR development)) W/5 (factor* OR challenge* OR influence* OR improve* OR affect*)).

4.1.1.2. Systematic literature review results: R&D pipeline

The search, using the keywords mentioned above, gave an output of 16 309 possibly relevant documents. The document set was further limited by type to journal sources only, excluding 1 017 articles. The document type was limited to articles, leading to 8 623 articles in total. The publication date was limited to a range from 2008 to 2017, resulting in a total of 5 504 documents.

Finally, all articles written in languages other than English were excluded, resulting in set of 5 099 documents.

In order to reduce the number of documents in the document pool further, it was decided to use the top 200 cited documents from the set of 5 099. To correct for the bias inherent in only selecting the top cited documents, all documents published from 2015 to 2017 were also included in the document pool. This resulted in a document pool of 200 (top cited) + 2 049 (published 2015-2017). Eleven documents were duplicates in the two sets, which gave a total of 2 238 preliminary, relevant documents.

The titles of all 2 238 documents were scanned for relevancy to the two research questions. Consequently 147 documents were deemed relevant. The abstracts of these 147 documents were reviewed and resulted in the final selection of 97 documents with information relevant to both RQ1 and RQ2. The abstracts of these documents were analysed from two perspectives. Firstly, the abstracts were reviewed to establish factors that are relevant to RQ1 (see Section 4.1.2). Secondly, the abstracts were reviewed to identify trends that correspond with RQ2 (see Section 4.1.3). *ATLAS.ti*[9] was used to assist in evaluating the literature.

4.1.2. Factors that influence pharmaceutical R&D pipelines

The preliminary identification of influencing factors was conducted by investigating the abstracts of the 97 documents and identifying factors that correlate with RQ 1. In total, 37 factors were identified. The range of occurrence varied from a single occurrence to 13 occurrences across the 97 articles. Table 4.1 shows the most prominent factors present in the articles included in the dataset. Refer to Appendix A for the complete list of 37 factors identified.

The top four factors found to influence the pharmaceutical pipeline occurred in 10% or more of the document pool selected for this systematic review. All four factors are briefly discussed below.

1. Policy and regulatory challenges refer to any challenge encountered in ensuring, establishing or completing the regulations laid out by the regulatory drug agencies of the pharmaceutical industry. These challenges might exist because of national or international policies and are often influenced or enforced by government.
2. Clinical trial set-up refers to the way in which the clinical trials are organised, planned or arranged. The set-up determines how the activities of the trial phases will operate and what each step will entail.
3. Participants of clinical trials refers to the patients on whom tests are being conducted. Participants usually volunteer for clinical trials and might be provided with some sort of incentive to participate.
4. The complexity of clinical trials refers to the difficulty of completing and performing the actions required for the trials. It refers to the operational challenges experienced in carrying out the necessary protocols in all aspects of the clinical trials.

[9] ATLAS.ti is a computer program, used primarily for qualitative research and qualitative data analysis (ATLAS.ti, 2019).

Table 4.1: The top ten occurring influencing factors from analysis of the document pool.

	Influencing factor	References	Occurrence
1.	Policy & regulatory issues	(Eichler *et al.*, 2008; Califf and Sugarman, 2015; Payne *et al.*, 2015; J. Wechsler, 2015; Tsourounis *et al.,* 2015; Mesut *et al.*, 2015; Cardot *et al.*, 2016; Tsukamoto *et al.*, 2016; Kondal *et al.*, 2016; Nugent *et al.*, 2016; Vischer *et al.*, 2017; Cheng and Xie, 2017; Gallini, 2017)	13
2.	Set-up of clinical trials; randomisation in trials; and trial methodology	(Ratain and Sargent, 2009; Bates *et al.*, 2015; Clifton *et al.*, 2015; Ricotti *et al.*, 2015; Zhou *et al.*, 2015; Jill Wechsler, 2015; Mesut *et al.*, 2015; Gupta *et al.*, 2016; Moatti *et al.*, 2016; Harrington *et al.*, 2017; Mayo *et al.*, 2017; Phadnis *et al.*, 2017)	12
3.	Participant recruitment and retention; enrolment & minority representation; and little clinical trial awareness	(Gul and Ali, 2010; Brown *et al.*, 2015; Jennings *et al.*, 2015; Thacker *et al.*, 2016; Hammer *et al.*, 2016; Bose *et al.*, 2017; Condon *et al.*, 2017; Kurt *et al.*, 2017; Logan *et al.*, 2017; Mahmoodabad *et al.*, 2017; Parker *et al.*, 2017)	11
4.	Complexity of trials; deal with multiple endpoints; better operational framework; clinical trial activation difficulty	(Clifton *et al.*, 2015; Jill Wechsler, 2015; Martinez *et al.*, 2016; Newman *et al.*, 2016; Nugent *et al.*, 2016; Tsukamoto *et al.*, 2016; Kellar *et al.*, 2017; Phadnis *et al.*, 2017; Snapinn, 2017; Vischer *et al.*, 2017)	10
5.	Clinical trial risk	(Eichler *et al.*, 2008; Kent *et al.*, 2010; Schneeweiss *et al.*, 2011; Zhou *et al.*, 2015; Sewell *et al.*, 2016; Thakor *et al.*, 2017; Yousefi *et al.*, 2017)	7
6.	Lack of transparency; accountability; and accessibility of clinical trial information	(Tsourounis *et al.,* 2015; Shaw and Ross, 2015; Viergever and Li, 2015; Campa *et al.*, 2016; Kondal *et al.*, 2016; Li *et al.*, 2016; Šolić *et al.*, 2017)	7
7.	Quality of clinical trial; improved use of innovative clinical trial tools; quality of pre-clinical trials	(DHHS, 2016; Newman *et al.*, 2016; Tsukamoto *et al.*, 2016; Harrington *et al.*, 2017; Lee *et al.*, 2017; Shapley *et al.*, 2017)	7
8.	Physician participation; relationships between stakeholders; collaboration	(Tsourounis *et al.,* 2015; Mathur *et al.*, 2015; Shapiro *et al.*, 2015; Campa *et al.*, 2016; Tsukamoto *et al.*, 2016; Gallini, 2017)	6
9.	Lack of capacity and funding; lack of return on investment	(Bates *et al.*, 2015; Payne *et al.*, 2015; Ho *et al.*, 2016; Mirsaidi, 2016; Vischer *et al.*, 2017)	5
10.	Ethical obstacles and issues	(Califf and Sugarman, 2015; Kagan *et al.*, 2016; Li *et al.*, 2016; Tsukamoto *et al.*, 2016; Salas, 2017)	5

4.1.3. Pharmaceutical pipeline trends

Trends in the pharmaceutical pipeline indicate either a general direction in the development of the pipeline or changes to the pipeline. Of the 97 abstracts reviewed, eight mentioned 'trends' in the pharmaceutical drug pipeline. Table 4.2 indicates the four applicable trends that occurred in the systematic search.

Table 4.2: Trends identified from the structured literature review.

	Pharmaceutical pipeline trend	References	Occurrence
1.	Challenges in clinical trial registration	(Viergever and Li, 2015)	1
2.	Cost drivers and costs of clinical trials	(Sertkaya *et al.*, 2016)	1
3.	Investment capital and returns of pharmaceutical sector	(Thakor *et al.*, 2017)	1
4.	R&D productivity	(Lendrem *et al.*, 2015)	1

Four trends in drug R&D and pipelines are identified and investigated in this section, namely: (i) R&D productivity; (ii) investment capital and returns in the pharmaceutical sector; (iii) clinical trial registration; and (iv) the cost of clinical trials.

4.1.3.1. R&D productivity

The productivity of pharmaceutical R&D can be measured by various methods. According to Lendrem *et al.* (2015) productivity is measured by evaluating the number of new therapeutic drugs per billion dollars R&D spent per annum; Schulze *et al.* (2014) evaluated the number of peak sales values of drugs for new therapeutic drugs instead. The method of measurement used by Lendrem *et al.* (2015) includes the effect of inflation-adjusted R&D costs.

Based on the aforementioned productivity evaluation, Lendrem *et al.* (2015) conclude that escalating R&D costs is a dominant feature that influenced the productivity of R&D during the study period (1990 to 2013). Hammer and Champy (1993) propose that the rise in operating costs might be as a result of a change in focus during the 1990's towards maximising the development speed of drugs. The cycle times of successful molecules were halved from 1990 to 2001, but this led to a pronounced increase in development costs, ultimately affecting the entire drug development process. When inflation is considered, the productivity of R&D decreased steeply over Lendrem *et al.'s* (2015) study period (1990 to 2013). The increase in the inflation-adjusted R&D costs offers an explanation for the marked decline in overall R&D productivity (Lendrem *et al.*, 2015).

4.1.3.2. Investment capital and returns in the pharmaceutical sector

The investment capital in this sector has decreased over time in response to many factors. These factors include preclinical scientific breakthroughs (Cortright *et al.*, 2014), clinical trial data, regulatory oversight, health care policies, pricing, technology and other economic changes related to drug discovery and development (Thakor *et al.*, 2017). According to Thakor *et al.* (2017), the most direct driver of capital flow in and out of the industry is the performance of pharmaceutical investments, thus providing attractive returns on the investments made. Some sources state, however, that not all pharmaceutical organizations are struggling to realise returns, and that health care venture capital outperformed all other venture sectors over the past decades (Thakor *et al.*, 2017).

The annual returns of the pharmaceutical sector for the period 1980 to 2015 exceeded that of the stock market by 3%. The pharmaceutical portfolio also outperformed the market portfolio, where $1 invested in pharmaceutical organizations in 1980 would be worth $114, compared with $44 if invested in the market at the same time (Thakor *et al.*, 2017). Each investment holds a certain amount of risk and volatilities in returns (Thakor *et al.*, 2017). The Sharpe ratio, a measure of an investment's return per unit of total risk, for the pharmaceutical sector was higher than that of the average market (Thakor *et al.*, 2017). The high Sharpe ratio indicates that the risk-adjusted returns of the pharmaceutical sector were better than the average market for the period 1980 to 2015 (Thakor *et al.*, 2017).

4.1.3.3. Clinical trial registration

The registration of clinical trials is necessary to increase their ethical and scientific value (Viergever and Li, 2015). More than half of clinical trials are never published and are reported selectively, resulting in a waste of resources and decision-making based on biased evidence, such as exclusive groups of patients used to participate in trials (Viergever and Li, 2015). According to Viergever and Li (2015), the number of registered clinical trials increased substantially between 2004 and 2013, from 3 297 to 23 384. Table 4.3 depicts the number of clinical trials registered, based on the income group of the country where the trial was registered.

Table 4.3: Clinical trial registrations based on income groups (adapted from Viergever and Li (2015)).

Country income groups	Number of trials registered in 2005-2013	Percentage of all clinical trials registered in 2005–2013
High-income countries	143 137	82.5
Upper middle-income countries	24 937	14.4
Lower middle-income countries	8 229	4.7
Low-income countries	1 433	0.8
Not specified	6 319	3.6

It is evident from the information presented in Table 4.3 that high-income countries have the highest number of registered trials, representing 82.5% of all the clinical trials registered globally. In comparison, only 0.8% of the total number of clinical trials registered are conducted in low-income countries. The registration of clinical trials has improved transparency in pharmaceutical research by increasing access to information across the globe (Viergever and Li, 2015), though, challenges still exist (WHO, 2017). These include: (i) the quality of data available; (ii) the accessibility of all clinical trial data; and (iii) data searchability and data aggregation (Viergever and Li, 2015).

4.1.3.4. The cost of clinical trials

The cost of each clinical trial completed is influenced by a range of factors. The factors identified in Section 4.1.2, amongst other things, affect the cost of the trial. Sertkaya *et al.* (2016) evaluated all direct cost components and constructed a list. Their study established that the average cost of a phase 1 study ranges from $1.4 million to $6.6 million. Estimated phase 2 costs range from $7 million to $19.6 million, whereas phase 3 costs range from $11.5 million to $52.9 million, on average. The top three cost drivers were clinical procedure costs (15-22%), administrative staff costs (11-29%), and site monitoring costs (9-14%). It is important to note that the aforementioned

findings are based on trials funded by pharmaceutical and biotechnological organisations and not governments, academic institutions or other organisations (Sertkaya *et al.*, 2016).

4.1.4. Discussion of results

The identified influencing factors (Table 4.1) and trends (Table 4.2) can be evaluated based on the effect that they have on one another, and on how certain factors influence the trends within the pipeline.

The productivity of drug R&D is a result of several factors, including the cost of R&D. Policies and regulations (influencing factor 1) potentially reduce the number of NTD drugs introduced into the market. This implies that the process of eliminating unsafe and ineffective compounds from the pipeline results in reduced risk for potential drug users. The complexity and difficulty of trials (factor 4) mean that more time is required to conduct accurate studies. The quality of the trials also plays a role in the time it takes to complete the necessary procedures and whether it is necessary to repeat the study because of inadequate, inaccurate or insufficient data. The recruitment and retention of participants (factor 3) in the drug development process has a direct effect on the length of a study. It might take longer than planned to recruit all the participants necessary for the study, or the participants might be unable to complete the study, making the study unacceptable to regulatory authorities.

The amount of investment capital and the returns of the pharmaceutical industry relies on the amount of risk (factor 5) involved in the drug development process. For each disease this risk differs. Clinical trial registration requires organisations to be transparent (factor 7) about the procedures of the clinical trials and the trial outcome and information. Lastly, the cost of clinical trials is affected by almost all aspects of the drug development process. The longer the process, the higher the cost of drug development. The attrition of drug compounds during the R&D process also plays a major role in the cost – funds are lost when compounds pursued for many years fail to qualify as safe and effective drugs. In summary, the status quo of the pharmaceutical pipeline, including the trends that are present in the pipeline (Table 4.2), is dependent on all the factors mentioned in Table 4.1.

4.1.5. Burden of disease

The 'burden of disease' concept is salient when considering resource equity within health care. To evaluate the significance of disease and disability of a population in a region or of the global population is necessary. Also, it is essential to grasp what threat which diseases pose to the population and the extent of the risk involved (Influenza, 2016).

Numerous definitions of the concept of 'burden of disease' exist, and the meaning greatly depends on context of use. For the purpose of this research, burden of disease can be described as the 'human and economic cost', which results from illness and health conditions (Influenza, 2016). There are two main approaches used to quantify the burden of disease, as a public health measure.

The 'biomedical' approach is the most common. It involves assessing the impact of disease and the disability on persons from the onset of the disease to the final outcome, namely sickness (disability), recovery or death (Influenza, 2016). The biomedical approach also involves investigating the possibility of medical interventions to alter the course of disease and future disability (Influenza, 2016). Aspects that are important to understanding the biomedical burden of disease, include: (i) morbidity; (ii) mortality; (iii) trends in morbidity and mortality; and (iv) risk attribution. The second approach to understanding burden of disease is to view it from an economic perspective (Influenza, 2016). The measures that this approach focuses on are both direct- and indirect costs.

An umbrella term typically used to estimate the burden of disease is health-adjusted-life-years, classified as a biomedical approach (Influenza, 2016). Common approaches to measure the health-adjusted-life-years are: (i) DALYs; (ii) Quality-adjusted life years; (iii) Disability-adjusted life expectancy; and (iv) Healthy life years. The most widely used of the four approaches is the DALYs measure (WHO, 2002). DALYs estimates the difference between the current condition of public health compared to the ideal health expectancies. DALYs is a combined measure that gives an approximation of the time lived with disability together with time lost due to premature mortality (WHO, 2002).

The DALYs is based on the assumption that time is the most appropriate gauge to measure burden of disease; thus, the greater the time lived with the disease or time lost due to premature death, the greater the burden of disease. One of the most prominent advantages of using DALYs as burden of disease measure, is that diseases that causes premature death, and little disability, can be compared to diseases that causes disability but are not likely to lead to death. For this research, the DALYs measurement was used to quantify the global burden of disease.

4.2. Investigation of the number of drugs in the R&D pipeline

In order to probe the variance in the resources dedicated to pharmaceutical R&D for different diseases, the number of drugs in the R&D process is considered. It is acknowledged that the total R&D spend would be the preferred metric to utilize and that the number of drugs in the R&D pipeline for a disease will not necessarily correlate to the resources that have been dedicated to R&D for the specific disease. As granular pharmaceutical R&D spending data is not publicly available however, the number of drugs in the R&D process is considered a sufficiently accurate metric to utilize in the analysis.

Data from the Access to Medicine Foundation's (2018) Access to Medicine Index were utilized. The index indicates the areas in which pharmaceutical organizations are currently focusing their efforts to improve access to medicines. The number of medicines in R&D, by 20 of the world's largest research-based pharmaceutical organizations (in 2018) were considered (Access to medicine foundation, 2018). The size of the 20 pharmaceutical organizations is based on factors including market capitalization, relevance, product portfolios and pipelines. The top ten diseases with the largest number of drugs in R&D by the 20 pharmaceutical organizations combined, are listed in Table 4.4. The R&D pipeline presented in Table 3.4, includes all medicines from clinical trial phases I – IV, as well as recent market approvals, and excludes non-medicines such as vaccines and diagnostic tools.

The Access to Medicine Index reported on 65 diseases, for which a total of 729 drugs are currently in the R&D pipeline. The 65 diseases are categorized in 4 disease categories namely: (i) communicable diseases (12.4%); (ii) non-communicable diseases (85.3%); (iii) NTDs (1.9%); and (iv) maternal and neonatal health conditions (0.4%). From Table 4.4 it is evident that the amount of R&D currently devoted to cancer, is substantially higher than for any other disease.

Table 4.4: Top diseases with the highest number of drugs in R&D (data source: Access to medicine foundation (2018)).

	Disease	Number of drugs
1.	Cancer	442
2.	Diabetes mellitus	61
3.	Asthma	31
4.	HIV/AIDS	24
5.	Lower respiratory infections	21
6.	Kidney diseases	16
7.	Ischemic heart disease	15
8.	Chronic obstructive pulmonary disease	14
9.	Malaria	13
10.	Hepatitis B and C	13

Cancer accounts for more than 60% of drugs in R&D in 2018. Whereas the disease with the second highest number of drugs in R&D is diabetes mellitus with more than 8% of the total amount of drugs in R&D being attributed to it. Asthma has the third highest number of drugs in R&D, at 4% of the total amount of drugs in the pipeline. It is also evident that of the top ten diseases for which medicines are in development, three are infectious diseases that occur primarily in developing countries.

It is important to recognize that the number of drugs allocated per disease is not necessarily indicative of the attractiveness of the disease but might be subject to other factors. The relationship between the number of drugs in the R&D pipeline and the burden of disease are explored in Sections 4.3.

4.3. Relationship between drugs in R&D and disease burden

As discussed in Section 4.2, burden of disease is a useful metric to utilize when attempting to determine whether the resources allocated to pharmaceutical R&D for various diseases are equitable. For the purpose of this research, the number of drugs in R&D for 20 of the largest research-based pharmaceutical organizations is compared to the burden of disease. The burden of disease for this research is recognized by evaluating the DALYs. Where DALYs is a combined measure that gives an approximation of the time lived with disability together with the time lost due to premature mortality (WHO, 2002).

A statistical analysis was completed to establish whether there is a significant linear relationship between the global burden of disease (DALYs) and the number of medicines in R&D for the disease (refer to Appendix B for the complete analysis). Figure 4.1 depicts the output of the statistical analysis completed.

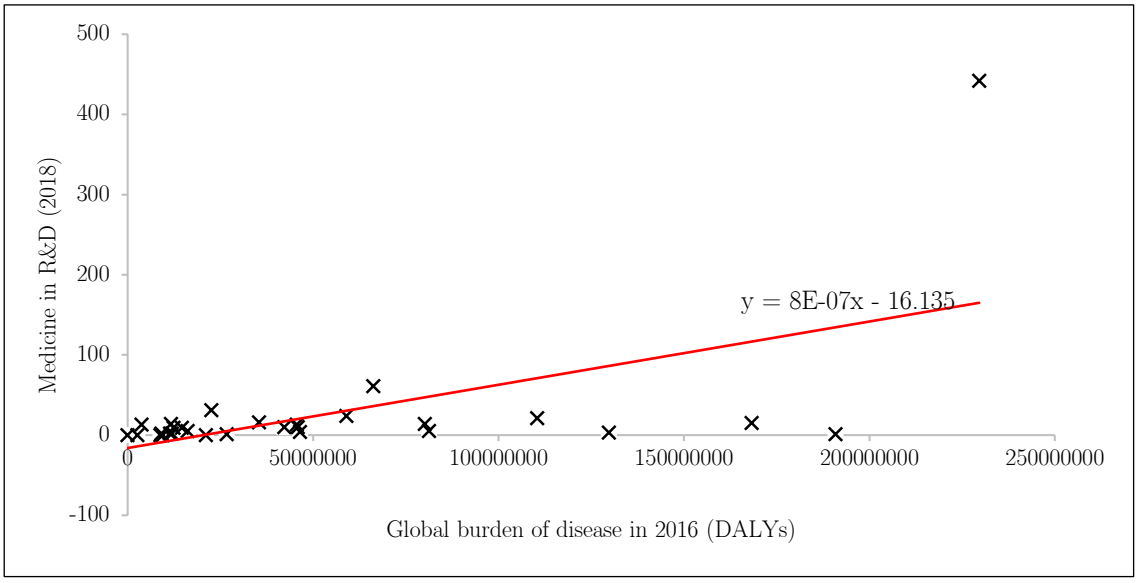


Figure 4.1: Number of drugs in R&D versus global burden of disease.

When the outlier observation was excluded from the data set, the correlation between the number of drugs in R&D and the burden of disease, indicated by the correlation coefficient ($r = 0.1660$), was not statistically significant. Thus, if cancer is not taken into account, there is no evidence of a relationship between the number of drugs in the R&D pipeline and the global burden of disease.

4.4. Relationship between funding allocated and corporate social responsibility

Corporate social responsibility (CSR) is defined as "the overall contribution of businesses to sustainable development", or as the European Commission defines it "the responsibility of enterprises for their impacts on society" (Droppert and Bennett, 2015). Droppert and Bennett (2015) investigated the number of large pharmaceutical organizations that are engaging in CSR to improve global health. Their study found an increase in efforts of pharmaceutical organizations to align their strategies towards CSR. It was found that differing views of CSR exist, with some organizations viewing it as philanthropic activities compared to others seeing it as activities worth pursuing to generate social and economic value for the organization (Droppert and Bennett, 2015).

Motivations for engaging in CSR efforts include increasing the access to medicines in LMICs, as a means to improve global health; as well as the reputational benefit for the respondents, which might be linked to competitive advantage (Droppert and Bennett, 2015). Droppert and Bennett's study established that multinational organizations are allocating diverse CSR efforts to influence the health of LMICs. The aforementioned leads to the conclusion that CSR can potentially contribute to the amount of research efforts that are performed for NDs.

4.5. Requirement specifications

The requirement specifications identified in Chapter 4, are depicted in Table 4.5.

Table 4.5: Requirement specifications, as derived from Chapter 4.

Reference		Requirement definition	Section
Functional requirements	F.2	The developed framework must incorporate the occurrence of the major challenges, relevant to the scenario, that influences the R&D pipeline. Some of the top challenges include: (i) policy & regulatory issues; (ii) set-up of clinical trials; (iii) participant recruitment and retention; (iv) complexity of trials; and (v) clinical trial risk. Refer to Appendix A for the 37 factors that influence the R&D pipeline.	4.1.2
	F.3	The framework must provide a solution set with the potential to advance the four pharmaceutical R&D pipeline trends namely: (i) improve R&D productivity; (ii) improve investment capital and ROI of the sector; (iii) increase the number of clinical trials registered; and (iv) decrease or provide means to cover the costs of clinical trials.	4.1.3
User requirements	U.3	The proposed solution must provide a means to alleviate the burden of disease of the consumer.	4.1.5, 4.3
Design restrictions: No design restrictions are derived from this chapter.			
Boundary conditions: No boundary restrictions are derived from this chapter.			
Attention points: No attention points are derived from this chapter.			

As shown in the table, only two functional requirements and one user requirement specification that are relevant to the design of the framework solution that is to be developed, were identified in this chapter.

4.6. Conclusion: Pharmaceutical R&D pipeline

This chapter investigated the pharmaceutical R&D pipeline to determine influencing factors that respectively enhance and reduce market attractiveness of drug R&D. The burden of disease concept was defined and an investigation of the number of drugs in the global pharmaceutical R&D pipeline was conducted. It was established that the number of drugs in R&D for a disease is not influenced by the burden of that disease, and that CSR might influence the amount of funding allocated to pharmaceutical R&D.

CHAPTER 5

Market attractiveness

Certain research fields or diseases attract more interest from the pharmaceutical industry than others. This chapter aims to identify the characteristics that distinguish 'attractive' research fields or diseases from the perspective of the pharmaceutical R&D industry.

The chapter starts with an introduction to the concept of market attractiveness, as well as an overview of macro-, and micro-level determinants of attractive markets. Two approaches are followed in this chapter to determine characteristics that make a pharmaceutical market either attractive or unattractive. The first approach is to perform a market analysis and the second approach is by means of structured literature reviews.

In terms of the first approach, various market analysis methods are investigated, and an appropriate method for use in this research is selected. This is presented in Section 5.2. In Section 5.3, the selected method is applied to the pharmaceutical market to perform the market analysis. In terms of the second approach, two structured literature reviews are conducted, one focusing on factors that cause diseases to be/become neglected and the other focusing on factors that cause diseases to attract pharmaceutical R&D investment. These structured literature analyses are presented in Sections 5.4 and 5.5 respectively. Lastly, the sets of factors and criteria that influence market attractiveness, identified in Sections 5.3, 5.4, and 5.5 are compared and synthesized in Section 5.6.

A significant portion of the text in Sections 5.4 and 5.5 has been reproduced from a conference article that were published as part of this research. The citation is: Hanekom, N., Bam, L., de Kock, I.H. (2019). "What makes diseases and drug research and development attractive for the pharmaceutical industry." Accepted for publication in: Proceedings of the *25th ICE/IEEE International Technology Management Conference, 17th - 19th of June 2019, Sophia Antipolis, Nice, France.*

5.1. The meaning of market attractiveness

The meaning of market attractiveness as well as the characteristics that influence the amount of interest of potential investors in a given market are investigated in this section.

5.1.1. What does it mean for a market to be attractive?

A market is defined by the Cambridge dictionary to be the "business or trade in a particular product, including financial products". Every market is unique in its structure and has different economic fundamentals that play a role in how profitable the industry appears or realises to be

(Porter, 2014). The performance of a market can be measured through various metrics, some of the most popular performance metrics include (IGI Global, 2018): (i) sales revenue; (ii) market share; (iii) profitability; (iv) competitive advantage; (v) customer satisfaction; and (vi) customer loyalty.

Markets occur in various settings and are established to compete on various levels. Examples of the levels of markets that exist include (S. Riley, 2015): (i) local markets, focusing on households within a country; (ii) regional markets, focus on communities falling in a certain region; (iii) national markets, focus on delivering value to all the citizens of a country; and (iv) international markets, is where different foreign exchange takes place globally.

The measurement of market performance aids in managerial decisions (e.g. budget and resource allocation) (Darmon *et al.*, 2013). Performance indicators, also known as key performance indicators, serve as a reference to quantify and compare performance over time. Key performance indicators can be both financial or non-financial and assesses, for a specific market or sector, the functionality of the business operations and progress against the stated strategies (Elwin and Hirst, 2007). When the key performance indicators of a market, business or sector improves, it is usually assumed that the specific entity improved its current state with reference to a former state measured at a point in its history.

When an entity improves the state of its key performance indicators, it can be assumed that its potential to generate a high return on investment has also improved. The concept of market attractiveness is related to the positive performance of markets. The attractiveness of a market is a reflection of the likelihood that one can benefit from investing in the market (Urbšienė *et al.*, 2014). Thus, the greater the perceived potential of a market to generate a substantial ROI, the greater that market's attractiveness (Urbšienė *et al.*, 2014).

According to Spohn (2004), business portfolio planning techniques were the first to mention the term market attractiveness. The business portfolio planning techniques, for example the Boston Consulting Group matrix, suggests that organizations should invest in markets that have certain attractive characteristics (Spohn, 2004). Spohn also states that market attractiveness includes "all the characteristics that affect organisational success of a collective group of organisations within one market".

5.1.2. Properties of an attractive market

Firm-level determinants, macro-level determinants, and the market structure all influence the attractiveness of a market. These determinants of market attractiveness are briefly discussed in this section, followed by a short reflection on the relevance of these factors to the pharmaceutical drug R&D market.

5.1.2.1. Firm level determinants of attractive markets

Tóth and Zemčík (2006) identified determinants that attract foreign investors to invest in organizations, including characteristics within the organization or market, as well as in the external environment. The authors propose that the following six firm-level factors play a role in determining attractiveness from an investor's perspective: (i) profitability; (ii) risk; (iii)

organization size; (iv) ownership concentration; (v) market share; and (vi) other factors. These six firm-level factors are briefly considered in the remainder of this section.

Profitability can be measured in various ways, including the accounting rate of return , calculated as the average net income to the shareholders' equity book value; and the Book-to-Market ratio, calculated as the book value of the equity divided by the market value of equity at the end of the fiscal year (Tóth and Zemčík, 2006). Risk is a complex factor, and the level of risk that people or organizations are willing to accept differs. Typically, higher risks are associated with higher rates of return, thus an investor may be willing accept a certain level of risk, given that it is compensated for in the price.

Tóth and Zemčík (2006) observe that the larger the firm or market, the more likely it is to attract foreign investors' attention and funds. The concept of ownership concentration refers to the phenomenon where foreign investors are likely to target organizations in order to obtain a controlling share of the company, in the case where the company requires significant investment in terms of opportunity costs (Tóth and Zemčík, 2006). The market share factor refers to a strategy where foreign investors purchase a domestic firm in its entirety as a mechanism to get access to a specific local market. Local organizations with higher market shares are usually preferred (Tóth and Zemčík, 2006). Other factors that may attract foreign investors into a market include staff costs per sales and value-added sales (Tóth and Zemčík, 2006). The staff costs per sales come into play for developed countries that are interested in investing in emerging economies, whereas value added sales arise in markets or organizations that require a very skilled labor force (Tóth and Zemčík, 2006).

5.1.2.2. Macro level determinants of attractive markets

A number of macro-level determinants of market attractiveness that have been identified in literature will be briefly discussed in the remainder of this section, namely: (i) investor sentiment; (ii) the corporate income tax system; (iii) and labor costs in the market.

Investor sentiment refers to people's opinions, emotions, views of, or attitude towards something (Reinstein and Churyk, 2004). Market sentiment summarizes the investor sentiments and creates a sum of the expectations for a market as a whole (Reinstein and Churyk, 2004). Analyses of the impact that investor sentiment has on the stock market from the perspective of behavioral finance, have found that stock values and fundamental financial analysis are not always correlated (Reinstein and Churyk, 2004). Reinstein and Churyk (2004) developed a generic depiction of an investor's decision-making process, reproduced in Figure 5.1. According to Reinstein and Churyk (2004), the inclusion of investor sentiment in stock valuation will not aid to predict crashes of financial markets but it will provide a means by which stock portfolios can be analyzed. Reinstein and Churyk (2004) formulate the following argument: The more favorable the global investment climate or sentiment, the higher foreign investor ownership will be.

Other macro-level determinants that influence the attractiveness of a market from the perspective of foreign investors include the corporate income tax system and labor costs in the market (Reinstein and Churyk, 2004). It is reasoned that investors may be more interested in buying

shares or investing in domestic enterprises if this could lead to savings in labor costs or reduce the corporate income tax liability (Reinstein and Churyk, 2004).

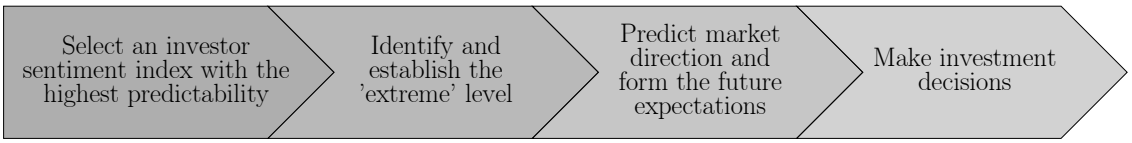


Figure 5.1: Investors decision-making process (reproduced from Reinstein and Churyk (2004)).

5.1.2.3. Market structures

Scarchuk (2013) define four basic types of market structures, namely: (i) perfect competition; (ii) monopolistic competition; (iii) oligopoly; and (iv) pure monopoly. As depicted in Table 5.1, these four types of market structures cover the continuum from no market power to total market power and the characteristics that can be used to distinguish between these market structure types include: the number of sellers in the market; the type of product that is sold; and the barriers to enter the market.

Table 5.1: The four market structures and the market power of each (reproduced from TDMU (2018)).

	Degree of Market Power			
	0%	. . .		100%
Characteristics	Perfect Competition	Monopolistic Competition	Oligopoly	Pure Monopoly
Number of Sellers	Many	Many	Few, dominant	One
Individual firm's market share	Tiny	Small	Large	100%
Type of product	Homogeneous	Differentiated	Homogeneous or differentiated	Homogeneous by definition
Barriers to entry	None	None	Substantial	Complete
Buyer information	Perfect	Slightly imperfect	Perfect or imperfect	Perfect or imperfect

Market power refers to an organization's ability to manipulate the price of an item in the marketplace, by manipulating the level of supply and, or demand, thus it refers to the level of influence an organization has within its industry. The higher the market power, the higher the organization's ability to control its profit margin and its ability to increase the barriers for new market entrants (Kenton, 2018).

5.1.2.4. Properties relevant to this study

In terms of the pharmaceutical R&D market, several of the aforementioned attractiveness determinants are applicable. Profitability in the pharmaceutical industry is a major driver, as in any other industry. The expensive R&D process of drugs leads to pharmaceutical organizations seeking opportunities that can increase their revenues. This industry also accepts a large amount of risk (Kola and Landis, 2004). A considerable number of resources is required to advance a drug from compound discovery to marketing authorization. On average, only one in 5 000 compounds are approved in a time span of 12 to 15 years (PhRMA, 2016).

The market structure in the pharmaceutical industry is mostly oligopolistic (Browning and Zupan, 2014). This is largely attributed to the fact that a small number of large organizations dominate the pharmaceutical market[10]. It can therefore be concluded that the degree of power of the large organizations in the pharmaceutical industry is relatively high. Though the industry is not viewed as a pure monopoly, it has a large number of similar attributes that might affect the consumers, other competitors and stakeholders of the industry negatively, when they do not conform to the demands of large pharmaceutical organizations. One of these attributes, is the high barriers to entry for small and/or new pharmaceutical organizations into the drug R&D sphere. A more comprehensive investigation on the relationship between pharmaceutical organizations and consumers, as well as among R&D competitors is presented in Section 5.3.1.2.

The decision-making process of the pharmaceutical market is complex. However, forecasted future global health needs do impact drug development, especially for government-funded R&D projects (MSF, 2001). The structure of the market and the degree of market power will be analyzed in more detail in Section 5.3.

5.2. Methods to quantify market attractiveness

The primary purpose of a market analysis is to establish the attractiveness of a market, as well as identify the opportunities for and threats to an organization and how these relate to strengths and weaknesses in the sector (Wierzchowiecka, 2014). The following sections depicts the decision-making process followed to select a market analysis technique to use in this research.

5.2.1. Comparison of market analysis methods

Seven methods to analyze markets were identified and considered for use in this research. The primary aim of each of the seven methods, as well as the steps involved to complete the analyses are listed in Table 5.2. A more detailed description of each market analysis method is included in Appendix C.

From the information presented in Table 5.2, four distinct aims of the market analysis methods can be distinguished:

- Methods no. 2 and no. 5, both seek to analyze the market from both an external and an internal perspective. Method no. 4, has a similar aim, though the primary focus is exclusively on external factors influencing the market;
- Methods no. 1 and no. 3, on the other hand, both aim to quantify the market opportunities that exist;
- Method no. 7 is primarily concerned with evaluating the various interactions in the market as well as the scope of activities; and
- Method no. 6 focuses on drivers for profitability, where profitability within a market or industry is found in Section 5.1.2.1 to be one of the primary factors that impact market attractiveness.

[10]For the purpose of this research, large pharmaceutical organizations are defined as those organizations with a revenue that typically exceeds $1 billion per annum. This threshold was selected as the largest 100 pharmaceutical organizations all exceed this threshold (Novasecta, 2018).

Table 5.2: Market analyses method primary aim and process steps comparison.

	Analysis method	Primary aim	Process steps
1.	Market opportunity analysis framework	Evaluate market opportunities	Demand analysis Segmentation analysis Industry analysis Competitor analysis Channel analysis
2.	Aaker's strategic market analysis	Analyse market on both external as well as internal levels	External analysis: Customers Competitors Market Environment Internal analysis: Performance Determinants of strategic options
3.	Woodruff and Gardial's market analysis method	Evaluate opportunity that exists in a market	Environmental and impact Analysis Market definition analysis Customer, competitor and supplier analysis Market demand forecasting Evaluation of market opportunity
4.	SWITCH-ON's market analysis framework	Establish external conditions that influences a market	Market definition Market intelligence Market segmentation Market analysis
5.	The 5C analysis	Understand external environment and internal capabilities	Company Customers Competitors Collaborators Climate
6.	Michael Porter's five forces model	Holistic way to look at industry to understand drivers for profitability	Threat of new entrants Bargaining power of buyers Bargaining power of suppliers Threat of substitute products Rivalry among existing competitors
7.	Michael Porter's value chain model	Scope and interaction of the market or organization's activities	Identify primary activities Identify support activities Establish interactions

The process steps of the seven methods, as summarized in Table 5.2 do not refer to steps that need to be performed sequentially, but rather to the complete set of analyses that need to be performed as part of each method. These process steps can be organized into eight categories, based on the aspects of the market that are evaluated as part of each method. Table 5.3 indicates the similarities of the market analysis methods (rows) by indicating the aspects of the market evaluated (columns) by each method. The primary findings, derived from Table 5.3, are as follow:

- Methods no. 2 and no. 3 analyze seven of the eight market aspects, with the demand analysis and uncertainty analysis omitted;
- Method no. 2 is the only method that includes an uncertainty analysis; and
- Method no. 7 evaluates the least number of aspects, with only two of the seven analyzed.

Table 5.3: Corresponding analysis aspects of the market analysis methods.

	Market aspects evaluated in market analysis							
	Competitor analysis	Customer analysis & segmentation	Demand analysis	Environment & industry analysis	Internal, channel & opportunity analysis	Market and definition	Supplier analysis	Uncertainty analysis
1. Market opportunity analysis framework	x	x	x	x	x			
2. Aaker's strategic market analysis	x	x		x	x	x	x	x
3. Woodruff and Gardial's market analysis method	x	x	x	x	x	x	x	
4. SWITCH-ON's market analysis framework		x			x	x		
5. The 5C analysis	x	x		x	x		x	
6. Michael Porter's five forces model	x	x					x	
7. Michael Porter's value chain model				x	x			

An analysis of the seven market analysis methods is necessary to determine the appropriateness of each for use in this study. The expectation of completing this market analysis on the pharmaceutical R&D market, is to observe the market from several perspectives, considering a wide range of factors that potentially influence the attractiveness of the market.

To establish which market analysis method to use, or whether a hybrid between two or more methods should be used, six relevant metrics and the aim of the market analysis for this study are identified. These six metrics evaluate the ability of the market analysis method to satisfy each of these criteria:

A. Establish market attractiveness: Based on the properties of market attractiveness discussed in Section 5.1.2, the method should clearly establish the state of the market and its attractiveness to investors.
B. Identifies opportunities and threats within the market: The method should be capable of analyzing the market to identify internal as well as external factors enhancing or restraining the market advancement, based on various levels of the market environment.
C. Evaluates the external market environment: The method should have the capability to view the industry from a systems perspective in order to determine macro-level environmental factors and how these influence the attractiveness of the market.
D. Analyze the internal market capabilities: The method should be capable of determining the value of the resources and abilities of an organization within a market.
E. Measure the (current and future) market: The method should provide a mechanism for documenting the current state of the market and forecasting the prospective state of the market.

F. Establish the degree of market power of stakeholders: The method should determine the type of market structure. The market power of the organizations within the market to manipulate the price of the items, as well as the level of influence it has within the industry, should be established.

The seven methods are rated on a binary scale, based on research performed on each of the methods as well as on discretion used to evaluate each method with regard to the information to hand, on its ability to comply with each of the six criteria identified. Table 5.4 shows the comparison of market analysis methods. A total score out of six is determined for each of the methods, based on the sum of the binary one's allocated to the method when it has the ability to satisfy the criterion.

Table 5.4: Market analysis method comparison and evaluation.

Market analysis methods	Criteria						
	A	B	C	D	E	F	SUM
1. Market opportunity analysis framework	1	1	1	0	1	1	5
2. Aaker's structured market analysis	1	1	1	1	1	1	6
3. Woodruff and Gardial's market analysis method	1	1	1	1	1	1	6
4. SWITCH-ON's market analysis framework	1	1	1	1	0	1	5
5. The 5C analysis	0	1	1	1	0	1	4
6. Michael Porter's five forces model	1	0	1	1	0	1	4
7. Michael Porter's value chain model	0	0	1	1	1	0	3

The top score is six out of six, achieved by both method no. 2 (Aaker's structured market analysis) and method no. 3 (Woodruff and Gardial's market analysis method). The two runner-up methods, namely no. 1 and 4, scored a five out of six. It should, however, be noted that all four of the aforementioned methods make use of the Porter's five forces model. Thus, the market analysis methods already include a hybrid of methods.

As per the information presented in Table 5.4, both Woodruff and Gardial's as well as Aaker's market analysis methods comprise an equal number of process steps and can therefore be assumed to require a similar effort to implement. Aaker's structured market analysis method was selected to complete the pharmaceutical market analyses.

5.3. Aaker's analysis of the pharmaceutical R&D market

The pharmaceutical industry is described by Bradfielda and El-Sayedb (2009), to be a high performance and highly profitable industry. The industry comprises of a variety of organizations such as generic drug manufacturers, researchers as well as a small dominating group of large multi-national organizations.

The Aaker market analysis, completed in this section, investigates the pharmaceutical R&D market by means of an external analysis (Section 5.3.1) and an internal analysis (Section 5.3.2). Followed by identification of determinants that improve and reduce the R&D market attractiveness (Section 5.3.3). The level of analysis is global; thus, the global pharmaceutical market is considered. In line with this perspective, the customers in this level of analysis are countries, whilst the internal analysis focuses primarily on the capabilities and other properties of the most dominant players in the global pharmaceutical market, namely the large pharmaceutical organizations[11], though properties of smaller organizations are also given some consideration.

5.3.1. External analysis

The external analysis considers factors that are external to the business or organization that affect the strategy. To complete an external analysis, it is important to define the scope of analysis to establish the level of detail (Aaker, 2013). In order to limit the scope of the work, not all of the potential aspects that can be subjected to an external analysis, as per Aaker's model, are considered. Instead, to provide an overview of the pharmaceutical R&D market, the external analysis is restricted to the following four aspects: (i) customer analysis; (ii) competitor analysis; (iii) market and submarket analysis; and (iv) environmental and strategic uncertainty analysis. The analysis of each of the four aspects is presented in the sections that follow.

5.3.1.1. Customer analysis

The first aspect of Aaker's (2013) external analysis that is implemented, is a customer analysis. Customer analysis entails understanding three aspects, namely (Aaker, 2013): (i) customer segments; (ii) customer motivations; and (iii) the unmet needs of customers that might exist. The pharmaceutical market operates on both a business-to-business and a business-to-government basis. A business-to-government can be viewed as a derivative of the more general business-to-business marketing (Nemat, 2011). The level of analysis selected for this study, is the country-level. This level of analysis is considered appropriate as, the largest procurers of pharmaceutical products are public rather than private institutions. Three categories of customer segments are defined, namely low-, middle-, and high-income countries

(i) Customer segments

Customer segmentation refers to the process of dividing the market (of both existing and potential customers) into segments, based on shared characteristics. The (potential) customer base of the pharmaceutical industry includes both private and public entities, from the entire global market. As mentioned previously, public organizations are the largest procurers of pharmaceutical products and customers are therefore defined as countries, for the purpose of this study.

[11] As defined in Section 5.1.2.3, large pharmaceutical organizations are defined, for the purpose of this research, as those organizations with a revenue that typically exceeds $1 billion per annum.

It is proposed that in the context of public pharmaceutical procurement, the available budget per individual is considered to be the most salient distinguishing characteristic between customers. Consequently, it is proposed that customer segmentation is implemented based on the socio-economic status of countries (based on gross national income per capita, identified in Table 3.3).

An example of a customer segmentation analysis of one low-income (Malawi) and one high-income (USA) country, is presented in Appendix D. The customer segmentation analysis indicates that the health expenditure per person varies significantly for low-, and high-income countries. For the case of Malawi versus the USA, the total expenditure on health per person differed significantly, with the estimated 2014 expenditure being $93 (Malawi), and $9 523 (USA) respectively.

Another difference is that the low-income country case (i.e. Malawi) has a significantly lower urban population density, with less than 20% of the population living in urban areas, as opposed to 83,7% for the high-income case (i.e. the USA). Another prominent difference between the low-, and high-income cases, is the number of physicians per 1 000 population, with Malawi having a significantly lower ratio (0.018) than the USA (29.2). There is also a difference in the average life expectancy, though it is important to note that the USA has a relatively low life-expectancy for a high-income country (Chen *et al.*, 2017), thus the difference in terms of life expectancy between low- and high-income countries on aggregate, is likely more pronounced than the difference between these two cases specifically. The difference in aggregate life expectancy between low- and high-income countries, may be attributable to inadequate public health care or inaccessibility of the existing health facilities.

(ii) Customer motivation

Customer motivation refers to the motivation of each customer to take part in or to make use of the research or medicine output from the pharmaceutical R&D market (Aaker, 2013). In line with the level-of-analysis employed, the motivations of each of the three customer segments are summarized in Table 5.5.

Table 5.5: Customer motivation per segment (sourced from UNITAID (2016)).

Segment	Motivation
Low-income countries	Affordable and high-quality medicine, often buy generic drugs
Middle-income countries	Affordable and high-quality medicine often buy quality-assured generic drugs
High-income countries	Affordable and of high-quality medicine, buys fewer generic drugs

(iii) Unmet customer needs

By considering unmet customer needs, one can identify opportunity gaps where the fulfillment of the need may lead to an increase in demand for products and/or services, which in turn may enable the market to grow in size or revenue. Various process steps can be followed to identify the unmet customer needs. For this research, some prominent unmet needs for each customer segment were identified by reviewing literature, these are listed in Table 5.6.

Table 5.6: Unmet customer needs per segment.

Segment	Unmet customer needs	Source
Low-income countries	1. Excessive treatment costs	(OECD, 2009; Sowa *et al.*, 2014)
	2. Lengthy waiting times for medicines and care	(OECD, 2009)
	3. Distance to health care facilities too far to reach	(OECD, 2009)
	4. Prevalence of corruption in health care	(Sowa *et al.*, 2014)
Middle-income countries	1. Excessive treatment costs	(OECD, 2009)
	2. Within-country inequalities, related to socio-economic status	(Sowa *et al.*, 2014)
High-income countries	1. Excessive OOP treatment costs	(OECD, 2009)
	2. Socio-economic status inequalities	(Hoebel *et al.*, 2017)

Prominent challenges in low-income countries include corruption and a lack of adequate health services. Treatment costs, including OOP payments, are a challenge that occurs in all three customer segments. In the case of higher-income countries, a combination of inequality and a lack of universal health coverage may result in a situation where excessive OOP costs makes treatments inaccessible to patients (even though sufficient health service infrastructure and drugs are available).

5.3.1.2. Competitor analysis

The second aspect of Aaker's (2013) external analysis that is implemented, is a competitor analysis. A competitor analysis starts with identifying the current and potential competitors (Aaker, 2013). In line with the global level of analysis employed in this research, the competitors are defined in a generic sense as pharmaceutical organizations. The analysis focuses primarily on large pharmaceutical organizations, as these dominate the market (refer to Section 5.1.2.4), though the impact of smaller pharmaceutical organizations is also briefly considered.

For this research the competitors were analyzed by making use of Porter's five forces model, the analysis is summarized in Figure 5.2.

As shown in the figure, the pharmaceutical drug R&D market is associated with low industry profits in three of the five market forces, namely:

- Threat of new entrants – Low. There are strong and durable barriers to enter the pharmaceutical market, with smaller pharmaceutical organizations not posing a significant threat to large pharmaceutical organizations;
- Threat of substitutes – High. Generic versions of drugs are legal after patent expiry, and the possibility exists for novel drugs to substitute existing treatments; and
- Rivalry between existing players – High. There is intense rivalry between existing pharmaceutical organizations with competition for intellectual property (IP) rights and the possibility of similarities between drug R&D.

As shown in Figure 5.2, the pharmaceutical drug R&D market associates with high industry profits in two of the five forces, namely:

- Bargaining power of customer – Low. The IP protection of drugs allows innovator organizations to dictate prices for the duration of the patent window, patients have limited political voice to influence pricing; and

- Bargaining power of suppliers – Low. The raw materials for drug R&D are widely available.

The pharmaceutical R&D market is known as a high profit industry. This is primarily the case for large pharmaceutical organizations based on their large safety-net to recoup lost R&D costs, their technological expertise advantage, and the weak bargaining powers of the customers. Smaller pharmaceutical organizations typically do not have the financial resources to recoup unsuccessful R&D costs. With smaller organizations' technology and expertise, financial resources and infrastructure being limited. This consequently leads to the pharmaceutical market being considerably profitable for large organizations and less profitable for smaller organizations.

Porter's five forces	Description of force
Bargaining power of customers	· Low bargaining power of buyers. · The patient has a low bargaining power in terms of drug price but can choose between brands. The prescriber of the drug is not allowed to profit from the sale of drugs. The entity buying the drug can influence price by buying in bulk (Chu *et al.*, 2015). · Pharmaceutical innovators determine pricing (in patent window).
Bargaining power of suppliers	· Low bargaining power of suppliers. · Raw materials for pharmaceutical R&D are commodity products in the chemical industry and are available from various sources (Whiteside, 2016).
Rivalry between existing players	· The intellectual property of pharmaceutical R&D results in strong competition (Hoen, 2009). · Any new drug launched in the market is analysed for the possibility of being similar to an existing product (Whiteside, 2016).
Threat of substitutes	· Range from moderate to high (Desai, 2017). · A novel drug has the potential to recoup all R&D costs, if it is the first to the market to cure a major disease, however the opposite is true for a drug not being novel (Whiteside, 2016). · Generic versions are legal after patent expiry.
Threat of new entrants	· Low to moderate threat (Desai, 2017). · Start-up pharmaceutical companies is common but poses no significant threat to large pharmaceutical organizations. · Small pharmaceutical organizations are frequently sold to large pharmaceutical organizations (Whiteside, 2016).

Figure 5.2: Porter's five forces analysis.

5.3.1.3. Market and submarket analysis

The third aspect of Aaker's (2013) external analysis that is implemented, is a market and submarket analysis. The market analysis builds on the customer and competitor analyses and leads to understanding the strategic dynamics and structures of the market and submarkets (Aaker, 2013). According to Aaker (2013) a market analysis considers the perceived degree to which the pharmaceutical R&D market satisfies each of the seven dimensions. The analysis of the seven dimensions is presented in Table 5.7.

Table 5.7: Pharmaceutical submarket analysis (based on Aaker (2013)).

	Dimension	Elaboration on pharmaceutical drug R&D
1.	Submarkets	Existing examples of new submarkets for the pharmaceutical R&D industry, includes: (i) providing drugs or treatments at lower price; (ii) providing medicine to patients never treated before; (iii) conduct R&D in only a specific disease or treatment type; (iv) provide drugs or research outputs that satisfies the unmet needs of patients; or (v) leverage a new technology to treat a disease or health issue.
2.	Size and growth	The total global pharmaceutical R&D spending was $149.8 billion (2015), estimated to grow 4% annually (IFPMA, 2017).
3.	Profitability	The five forces analysis completed indicated that the pharmaceutical industry corresponds more to an industry with low profits, than to industries with high profits. However, large pharmaceutical organizations with significant infrastructure and resources are more likely to experience high industry profits, as they have a buffer zone for when research outputs are not performing as desired. Pharmaceutical industry profits ranges from less than 0 to 40%, where industry average in 2017 reached 12.5 - 14% (Slovak, 2018).
4.	Cost structure	According to Aaker (2013), Porters Value Chain model is a good method to use to identify the fixed and variable costs associated with an industry. According to A.T. Kearney (2011) the operating cost structure of the pharmaceutical industry of 2009 (in US$ billions) is in total $612 in 2009. Of the total amount, 15% was attributed to R&D; 30% to cost of goods sold; 29% to selling, general and administrative expenses; and 7% to dosage and administration and with an operating margin of 18% of the total amount.
5.	Distribution systems	Pharmaceutical wholesalers, health institutions and hospitals serve as necessary links between the pharmaceutical R&D industry and the patients. Three pharmaceutical distribution models exist, namely: (i) wholesaler model, wholesaler provide logistical efficiency across manufacturers and provide high service level to patients; (ii) limited distribution model, limits wholesaler relationships and optimizes supply chain productivity and integrity; and (iii) direct distribution model, manufacturers distribute directly doing bulk shipments to customers or central distribution warehouses (Jamasoft, 2014).
6.	Trends and developments	Distinguish between real trends that drives growth and differentiate strategies for the good. Trends of pharmaceutical drug R&D, as discussed in Chapter 3.1.3, include: (i) a constant R&D productivity trend; (ii) a decrease in investment capital and returns; (iii) a significant increase in clinical trial registration; and (iv) the cost of clinical trials.
7.	Key success factors	Key success factors for the pharmaceutical R&D market, according to Pefindo (2018), include: (i) good brand recognition; (ii) strong market position; (iii) alliance potential with other global pharmaceutical producers; (iv) focus strategy should be on higher margin products; (v) a variety of products are necessary to generate a wide range of profits; (vi) good business operation management; (vii) important to accurately control cost; (viii) larger players have competitive advantage (stronger bargaining power and economies-of-scale); (ix) should adopt well to the needs of retailers; (x) maintain good business network relationships; (xi) good advertising to target markets; (xii) build and maintain brand loyalty; (xiii) good track record of fulfilling financial obligations; (xiv) should have cash flow protection and liquidity; and (xv) should be financially flexible.

From the analysis completed in Table 5.7, it can be derived that the pharmaceutical industry has a significant number of submarkets and opportunities that exists. The size of the pharmaceutical R&D industry, compared to other industries, is relatively large, with a high growth rate.

For instance, the growth rate of the car & automobile manufacturing industry was 3.4% from 2016 to 2017 (Business Essentials, 2017); which is lower than 4% achieved by the drug R&D industry over the same period (IFPMA, 2017). When comparing the profitability of the pharmaceutical R&D industry to the average over all industries, the pharmaceutical industry outnumbers the industry average considerably (Congress Budget Office, 2006). The distribution systems in the pharmaceutical industry are necessary to provide the required links between the pharmaceutical R&D stakeholders and the patients. Key success factors, that enable the pharmaceutical market to provide effective products and services, include that the industry has a strong market position and that brand recognition for pharmaceuticals is important to increase and maintain sales.

5.3.1.4. Environmental analysis and strategic uncertainty

Aaker (2013) analyses the environment surrounding the market by evaluating the (i) technology; (ii) consumer; and (iii) government/economic trends, followed by (iv) asking general and external analysis questions; and (v) looking at different scenarios. For the external analysis in this study a PESTEL analysis is completed. PESTEL is a broadly used tool to identify macro (external) forces influencing an organization. The acronym denotes political, economic, social, technological, environmental and legal aspects (Holland and Bátiz-Lazo, 2005). The level-of-analysis is the global market within which pharmaceutical organizations operate. The PESTEL analysis presented in Figure 5.3 indicates that the pharmaceutical R&D industry is experiencing a range of pressures from all six perspectives.

Six aspects of the pharmaceutical drug R&D market PESTEL analysis		
Political The government is the most powerful purchaser (WHO, 2015a). The industry is globalized (Kim, 2014). Growing pressure from inter-country pricing disparities and parallel trade (Arfwedson, 2004).	**Economical** Patients have little influence on choice and price of medicine. Large organizations are experts on mass-market products on global scale (PWC, 2009).	**Social** Hoen (2009) argues that innovation is monopoly-based in the pharmaceutical R&D field.
Technology Technology in the pharmaceutical drug R&D field is advancing (Wilson, 2016). Some technological advances (genetic engineering) have led to some of controversy and litigation (Nuffield Council on Bioethics, 2016).	**Environmental** The internet gives patients some access to information about treatments available. "Cradle to grave" manufacturing reduces waste by changing patterns of production and consumption (Sarkar, 2013).	**Legal** Health authority intervention is key to determine length of patent protection (Hoen, 2009). Clinical trial regulation costly. Enforcement of patent protections ('t Hoen, 2009).

Figure 5.3: PESTEL analysis of pharmaceutical drug R&D market.

Of the pressures mentioned in Figure 5.3, the patent protected monopoly, and the regulation standards in place for clinical trials stand out as major environmental pressures experienced by the industry. The political pricing disparities may lead to a future scenario where some governments and health institutions prefer generic drugs over the medicine brands that are

currently commonly used. Such a scenario could lead to the generic drug R&D market to expand immensely on global scale, which in turn can lead to a greater drop in drug profitability, as soon as the IP rights of a highly priced drug expire.

Strategic uncertainties can be derived from the external analysis presented in Figure 5.3, as well as from Bradfielda and El-Sayedb (2009). If a scenario is defined as a strategic uncertainty, this indicates that the specific mentioned event is not predictable, can not necessarily be stopped and might have a significant impact on the pharmaceutical R&D market performance if it were to occur. Aaker (2013) recommends grouping strategic uncertainties into logical themes. For this study, strategic uncertainties for the pharmaceutical R&D market were identified based on the results of the PESTLE analysis, as well as sourced from (Bradfielda and El-Sayedb, 2009). The strategic uncertainties, summarized in Table 5.8, are grouped into the same categories used in the PESTLE analysis. As shown, strategic uncertainties exist in terms of each PESTLE analysis category.

Table 5.8: Strategic uncertainties of pharmaceutical drug R&D market (data source: Bradfielda and El-Sayedb (2009)).

Category	Strategic uncertainty
Political	Inter-country pricing disparities and the effect on global medicine trade and purchases is uncertain, and might cause significant change in the industry.
Economic	The rate of growth or contraction of the global economy is uncertain and can potentially have a significant impact on the industry.
Social	The way society views health care influences public health care policy, regulation as well as demand for health care products.
Technological	There have been some ethical dilemmas regarding new technological advances, such as for human genetic engineering. On balance, however, technological advances are expected to result in innovative and integrative technology for both drug R&D and as a result of R&D.
Environmental	There is increasing pressure as well as regulatory requirements to conduct R&D in an environmentally friendly manner and to develop methods to reduce the footprint of health interventions globally. These pressures/regulatory requirements could potentially require that certain aspects of the R&D process be radically redesigned.
Legal	The legal and ethical regulations and standards for clinical trial executions are tedious and costly, it is uncertain whether this issue will change in the nearby future. In addition, the future of IP protection is questionable with controversy rising in for example genome engineering (Nuffield Council on Bioethics, 2016).

5.3.2. Internal analysis

As discussed in the introduction to Section 5.3, Aaker's (2013) method comprises both an external and an internal analysis. The external analysis was presented in Section 5.3.1, while this section focuses on the internal analysis. The goal of the internal analysis is to identify: organizational strengths and weaknesses; constraints of the operations; and the firm's ability to react to external demands and forces. Aaker (2013) suggests that the following aspects be considered as part of the internal analysis: (i) financial performance measurement; and (ii) the strengths, weaknesses, opportunities and threats that exists within the organization.

As discussed in the introduction to Section 5.3, the level of analysis is global and the internal analysis therefore primarily focuses on the capabilities and other properties of the most dominant

players in the global pharmaceutical market, namely the large pharmaceutical organizations, in a generic sense. Some thought is, however, also given to smaller pharmaceutical organizations. Thus, in contrast to the intended use of Aaker's (2013) method, the internal analysis focuses on a generic representation of an organization. This approach is followed to allow generalized insights on the global pharmaceutical market to be derived from the analysis.

Because pharmaceutical organizations in general, rather than a specific pharmaceutical organization are considered for the internal analysis, the competitor analysis presented in Section 5.3.1.2 also covers the 'financial performance measurement' and 'performance dimensions determination' aspects of the internal analysis. This is briefly discussed in Section 5.3.2.1. An analysis of the generic strengths, weaknesses, opportunities and threats that exist within large pharmaceutical organizations is presented in Section 5.3.2.2.

5.3.2.1. Performance measures

Aaker (2013) recommends that both financial measures of performance, as well as measures that goes beyond financial aspects alone be considered. The financial performance of the pharmaceutical drug R&D industry can be measured by using widely used measures, suggested by Aaker (2013), such as: (i) profitability; (ii) market share and sales; as well as (iii) shareholder value. The non-financial performance measures include a determination of: (i) product and service quality; (ii) brand loyalty; and (iii) industry associations (Aaker, 2013).

As discussed in the introduction, because pharmaceutical organizations in general, rather than a specific pharmaceutical organization are considered, the competitor analysis presented in Section 5.3.1.2 also covers the 'financial performance measurement' and 'performance dimensions determination' aspects of the internal analysis. This analysis utilized Porter's five forces model and included an analysis of primarily the aforementioned financial, and non-financial performance measures.

5.3.2.2. Determinants of strategic options

A widely used method to determine the opportunities, weaknesses, strengths and threats of any entity is the SWOT analysis. For this research, the SWOT analysis is used to evaluate the internal strategic determinants. The analysis, depicted in Figure 5.4, include findings by the indicated sources, as well as insights derived from literature.

The strengths of the pharmaceutical R&D market include the strong sales force that exist, and that is likely to continue to exist in the future. One of the major weaknesses of pharmaceutical organizations is that it relies on regulations to conserve IP, which often does not suffice. The weaknesses illustrate opportunities for improvement. Some of the opportunities that exist for pharmaceutical organizations is the possibility of developing and producing generic drugs at lower costs, which in turn have the potential for higher sales volumes in especially LMICs. Lastly, threats facing pharmaceutical organizations include difficulty in IP law regulation and security.

	Helpful	Harmful
Internal	Strengths · Strong sales force (De Boeck *et al.*, 2008). · Well established marketing and distribution network (Kim, 2014). · High skilled workforce (IFPMA, 2017).	Weaknesses · Dependant on sales of costly medicine. · IP regulations possibly keeps medicine from being widely available (Outterson, 2004). · Coordination between industry and academia lacking.
External	Opportunities · Revenue can grow from acquisitions. · Regulatory approval at higher rates than expected. · Export potential of drugs.	Threats · Competition between organizations (Kim, 2014). · IP expires before R&D cost reaches break-even. · IP protection not secure (Hoen, 2016).

Figure 5.4: SWOT analysis of pharmaceutical R&D market.

5.3.3. Results: Characteristics that influence R&D market attractiveness

Based on Aaker's (2013) external and internal pharmaceutical R&D market analysis completed in Sections 5.4.1 and 5.4.2, derivations can be made in relation to the factors that shape and influence the pharmaceutical R&D market. A summary of factors that improve and reduce market attractiveness is presented in Table 5.9 and Table 5.10, respectively.

In the external analysis, it was recognized that the industry comprises a business-to-business structure, where the pharmaceutical organizations themselves are not directly in contact with the patients (clients) of medicines, but rather are in contact with the clinics or pharmacies (or governments, in the case of business-to-government). The customers of the industry differ depending on certain factors, in this study the difference between different income group countries were investigated. Low-income countries appear to have inadequate financing to afford the necessary medicine for the population.

When evaluating the unmet customer needs per country segment, it is observed that the low-income countries' unmet needs involve problems that results from poor resource availability or from the population living primarily in rural areas. High treatment cost is evident for all the country segments. Porter's five forces model re-establishes that large pharmaceutical organizations are more likely to be profitable than smaller organizations.

IP rights and laws are dominant aspects that both increase and diminish the level of attractiveness of pharmaceutical R&D research completed. The aforementioned statement is based on findings made in the market and submarket analysis, Porters' five forces analysis and the PESTLE analysis. IP laws and regulations are found to protect the novel findings of pharmaceutical innovators, serving as an incentive to innovate. There are, however, cases where IP law regulation is not being enforced, as is seen in the 'Legal' division of the PESTLE analysis.

Table 5.9: Characteristics that improve the pharmaceutical R&D industry attractiveness.

	Market analysis	Determinants improving attractiveness
External analysis	Customer analysis	There might be a willingness to compensate quality for affordability (low-income countries) Products can potentially be sold at a higher cost (high-income countries) Ability to influence price Information on patented drugs can potentially be accessed for free or relatively cheaply (low-income countries)
	Competitor analysis	Suppliers have low bargaining power New market entrants pose no significant risk Novel drugs have the potential to recoup all R&D costs Small pharmaceutical organizations are frequently sold to large organizations
	Market and submarket analysis	Opportunities emerged from possible submarkets The size of the industry is continuously growing Profitability in the pharmaceutical industry is higher than the average across all industries
	Environmental analysis	Globalized industry Technology in pharmaceutical drug R&D is advancing
Internal analysis	Performance measures	Brand loyalty is not easily lost
	Determinants of strategic options	Strong sales force Well-established marketing and distribution network Highly skilled workforce Revenue can grow from acquisitions Potential to export products

The former constitutes a strategic uncertainty for the pharmaceutical drug R&D market. Another strategic uncertainty in the industry is the disparity of pricing between different income groups, or countries which leads to certain population groups struggling to afford medicine that is perceived as reasonably affordable in other socio-economic income groups. The internal analysis considered the industry's ability to react to external forces. Although the most widely used measure used to determine performance was established to be profitability, other measures, indicating non-financial performance, were identified, including factors such as brand loyalty and the quality of what is delivered.

The external and internal analysis corresponds with regard to certain aspects, for instance in the case of IP regulations. As mentioned, IP rules and regulations surface in Porter's five forces analysis, the PESTLE analysis, and are seen to also occur in the SWOT analysis of the internal analysis, surfacing as internal weakness that might potentially be 'harmful'. The SWOT analysis also identifies the IP protection not being secure as an external threat, which directly corresponds with the strategic uncertainty observation in the external analysis and the Porter's five forces threat identification.

Table 5.10: Characteristics that reduce the pharmaceutical R&D industry attractiveness.

	Market analysis	Determinants reducing attractiveness
External analysis	Customer analysis	Low-income countries (buying power might be lower than for higher income) High-income countries (strong competition)
	Competitor analysis	Strong competition among competitors Once the patent expires, generic versions of the product is legal Possibility of being too similar to an existing drug
	Market and submarket Analysis	New organizations struggle to compete with large pharmaceutical organisations High cost of clinical trials
	Environmental analysis	The effect of inter-country pricing disparities is unknown Patent-protected monopoly Market driven by European and North American force Ethical controversy in technological advances Green R&D is encouraged but might increase cost Health authority intervention might be time consuming Clinical trial regulation is costly Legal and ethical regulations for clinical trial executions are time consuming
Internal analysis	Performance measures	If no products are being successfully developed, then R&D costs cannot be recovered
	Determinants of strategic options	A gap between academia and industry Very strong competition between rival organizations IP protection not always secure

Diseases that are attaining significant R&D interest, also known as 'diseases of the developed world', occur in settings known for having the potential to pay higher prices for medicines (MSF, 2014). MSF (2014) states the problem at hand is a situation where pharmaceutical organizations are lacking the necessary incentives to, amongst other things, develop drugs to treat diseases that primarily affect the poor. Pharmaceutical organizations have obligations towards their stakeholders to maximize revenue and achieve high sales. The latter particularly realizes when the drugs developed by the pharmaceutical organizations are intended to treat diseases that affect those with the financial capacity to pay a high price for the drugs they need.

5.4. Neglected diseases and R&D fields analysis

In the following section a structured literature review investigates the elements potentially affecting the interest of pharmaceutical R&D organizations, based on elements that signify NDs.

5.4.1. Investigating diseases and drug R&D for becoming neglected

The problem of NDs stems from within and from sources that might seem to be outside of the health care system. The health care system does however not only refer to all the actors involved in the complete process of providing an adequate service to mitigate a disease. A health system is defined by Milton (1993) to be "the combination of resources, organization, financing and

management that culminate in the delivery of health services to the population." This statement relates back to the assumption made, in Section 1.1.4, that the health system functions is a complex adaptive system.

5.4.1.1. Systematic literature review method

The literature review was completed in Scopus database. The objective of this review was to identify factors that lead to a market not attracting significant investment. To this end, the following two research questions were formulated:

RQ1: What are reasons for, or factors leading to diseases becoming neglected?
RQ2: What factors inhibit pharmaceutical organizations' investment in R&D of NTDs?

Keywords were derived from the research questions, and the following search function was formulated: (("drug*" OR "pharmaceutical" OR "reason* for" OR "cause* of" OR "factor* leading to") AND ("neglected" OR "NTD") W/5 (disease* OR "research and development" OR "R&D")).

5.4.1.2. Systematic literature review results

3448 documents were uncovered using the search function. The document set was further refined to include only articles, conference papers, book chapters, and books items published in English between 2008 and 2018. This reduced the number of documents to 2069. The following three keywords were subsequently excluded from the search: (i) animals; (ii) animal; and (iii) nonhuman. This resulted in 903 relevant documents. Given the size of document set, the set was further limited to only consist of documents that contain one of four keywords namely: (i) neglected disease; (ii) NDs; (iii) neglected tropical disease; and (iv) NTDs. This resulted in 342 documents. The 342 document titles were subsequently examined to establish whether they aligned with the objective of the literature review, as mentioned above. Of the 342 documents, 54 were relevant to RQ1 and/or RQ2.

The abstracts of these 54 documents were reviewed in line with the two research questions and Table 5.11 was constructed with the complete list of 17 factors that have been proposed as limiting the attractiveness of a disease for pharmaceutical R&D investment in literature. *ATLAS.ti* was used to assist in evaluating the literature. The number of occurrences of each factor in the set of literature that was reviewed is also indicated.

The four factors that are mentioned most frequently are briefly discussed:

(1) As mentioned earlier, the majority of people affected by NDs live in the poorest areas, in developing countries, with many living in remote or rural areas, urban slums or warzones (WHO, 2012). ND infections are in many cases caused or amplified by unsafe water, undesirable living conditions and poor sanitation (WHO, 2012). Developed countries offer viable market incentives for R&D through individual purchasing power as well as purchasing through government-run health insurance programs, which is not the case for developing countries.
(2) Incentives aim to encourage new innovations in drug R&D, however for diseases that are classified as NDs, these incentives appear to be outweighed by potential risks. A prominent source of risk is weak purchasing power for diseases that are less common in

developed regions, leading to an inability to recoup the funds invested to achieve market authorization of the new drug.

(3) The expected market- and financial- returns of NDs are low as the developing countries, where these diseases are most prevalent, do not have strong economic buying power. This lack of economic buying power leads to pharmaceutical organizations having little incentive to invest in the R&D of such diseases and drugs (Trouiller *et al.*, 2002). The return on investment for R&D of certain neglected drugs might be lower as a result of the least developed countries being granted exemption from the Trade-Related Aspects of Intellectual Property Rights (TRIPS) patent agreement (UNDP and UNAIDS, 2012).

(4) Weak IP protection and enforcement of international IP rights are a major source of concern to the pharmaceutical innovation industry (Webber and Kremer, 2001).

Table 5.11: Factors leading to diseases becoming neglected.

	Causing factor	References	Occurrence
1.	Occur in developing countries	(Ruminski, 2011; Waters, 2011; Holt, Gillam and Ngondi, 2012; Willyard, 2013; do Espírito Santo, R.D. Machado *et al.*, 2014; Hussaarts *et al.*, 2017; Courtay-Cahen, 2018; Liese and Schubert, 2009; Mahmoud and Zerhouni, 2009; Towse *et al.*, 2012; Mueller-Langer, 2013; Bai *et al.*, 2016; So and Ruiz-Esparza, 2012; Lopez *et al.*, 2014)	15
2.	Lack of financial, economic and industry incentives	(Geraghty, 2009; Fehr, Thürmann and Razum, 2011; Pollastri and Campbell, 2011; Ruminski, 2011; Waters, 2011; Fenwick, 2012; N Dimitri, 2012; Mueller-Langer, 2013; do Espírito Santo, R.D. Machado *et al.*, 2014; Hussaarts *et al.*, 2017; Pund and Joshi, 2017; Kataria *et al.*, 2011; Santana, Lupatini and Leite, 2017)	13
3.	Poor expected market- and financial return on investments	(Musgrove and Hotez, 2009; Chaudhuri, 2010 ; Jakobsen *et al.*, 2011; Pollastri and Campbell, 2011; Ruminski, 2011; Holt *et al.*, 2012; Hussaarts *et al.*, 2017)	7
4.	Patent law & IP protection	(Chaudhuri, 2010; SCHROEDER and SINGER, 2011; Kameda, 2014; Grabowski *et al.*, 2015; Bai *et al.*, 2016)	5
5.	No mass drug administration	(Musgrove and Hotez, 2009; Worrell and Mathieu, 2012; de Oliveira and Lang, 2018)	3
6.	Reluctant to invest big amounts of resources	(Liese and Schubert, 2009; Ruminski, 2011; Willyard, 2013)	3
7.	R&D time consuming and costly	(Pogge and Hollis, 2011; Cohen *et al.*, 2016; Maxmen, 2016)	3
8.	Low priority on health agenda	(Lopez *et al.*, 2014; Bai *et al.*, 2016)	2
9.	Fixed prices	(Kameda, 2014; Grabowski *et al.*, 2015)	2
10.	No regulatory oversight to promote R&D for NTD	(Fehr *et al.*, 2011)	1
11.	Lack of political will	(Fenwick, 2012)	1
12.	Scarce resources	(Lee *et al.*, 2015)	1
13.	Burden not fully characterized	(Lee *et al.*, 2015)	1
14.	Lack of target repurposing	(Pollastri and Campbell, 2011)	1
15.	Disease burden	(Bai *et al.*, 2016)	1
16.	Domestic policy	(Bai *et al.*, 2016)	1
17.	Lack of regulatory exclusivity provisions	(Grabowski *et al.*, 2015)	1

5.5. Attractive disease and R&D fields analysis

Several properties linked to high amounts of funding allocated to certain diseases and research fields have been identified and evaluated in Section 5.1.2. In order to form a complete understanding of the factors that cause pharmaceutical organizations to either invest in R&D for a disease or to decline to do so, the characteristics of diseases where high R&D interest and funding are evident, should also be established.

5.5.1. Systematic literature review method

This literature review search was completed in Scopus database, similar to the literature review completed in Section 5.4. The objective of this review is to identify factors that lead to a market being attractive. The following research question should be answered to contribute effectively to this study:

RQ 1: What factors increase interest and investment in certain diseases or research areas?

Keywords were derived from the research question, and the following search function was established to complete the search with: ((why OR "reasons for" OR "causes of") AND (interest OR invest* OR funding OR finance* OR profit*) W/5 (disease* OR "research and development" OR "R&D) AND pharmaceutical)).

5.5.2. Systematic literature review results

The search uncovered 86 relevant documents. The document set was further refined to include only items published in English between 2008 and 2017, reducing the number of documents to 44. The abstracts of these 44 documents were subsequently examined to establish whether they aligned with the objective of the literature review, as defined above. 14 Relevant documents were identified, and their introduction and conclusion sections were reviewed to identify the factors as described in the RQ. *ATLAS.ti* was used to assist in evaluating the literature.

5.5.3. Factors leading to diseases and research fields to be invested significantly more

The 16 factors, and its sources, identified in the systematic literature review, associated with diseases that are attractive, are depicted in Table 5.12.

The number of occurrences of each factor in the set of literature that was reviewed is also indicated. The frequency of occurrence varied from a single occurrence to occurring eight times across the 14 articles. Of the 16 factors identified, eight occurred more than once.

Table 5.12: Factors leading to increased attractiveness in neglected disease drug R&D.

	Causing factor	References	Occurrence
A.	Profitability and ROI	(Umemura, 2011; Nicholson, 2012; Hill, 2013; Burn *et al.* 2014; El Baghdady and El Baghdady, 2014; Russo and Banda, 2015; Bayazidi, 2016; Dandona *et al.*, 2017)	8
B.	Patents as a result of drug development to gain market exclusivity	(Mccabe *et al.*, 2008; Nicholson, 2012; Hill, 2013; El Baghdady and El Baghdady, 2014; Bayazidi, 2016; Dandona *et al.*, 2017)	6
C.	Uncapped drug prices (competitive drug prices) e.g. Japan restricts drug prices	(Umemura, 2011; Nicholson, 2012; Hill, 2013; El Baghdady and El Baghdady, 2014; Russo and Banda, 2015)	5
D.	Possibility of improving the economic development of a country	(Bastos and Coelho, 2013; Ranade *et al.*, 2013; Burn *et al.*, 2014; Ramaraj and Alpert, 2008)	4
E.	Access to international market or an open market - linked to government policies	(Umemura, 2011; Nicholson, 2012; Russo and Banda, 2015)	3
F.	Certainty of industry protection (apart from patents)	(Hill, 2013; El Baghdady and El Baghdady, 2014)	2
G.	Larger organizations (easier to achieve economies of scale in R&D)	(Umemura, 2011; El Baghdady and El Baghdady, 2014)	2
H.	Promotion and brand loyalty play a big role	(Nicholson, 2012; El Baghdady and El Baghdady, 2014)	2
I.	Funding agencies suggested to align funding to the health needs of the country	(Ramaraj and Alpert, 2008)	1
J.	To steer country to health equality	(Ramaraj and Alpert, 2008)	1
K.	Significant drug sales (forecasted increase in prevalence of disease)	(Bastos and Coelho, 2013)	1
L.	Assessment outcomes of the value of the health produced	(Mccabe *et al.*, 2008)	1
M.	Value-based licensing	(Mccabe *et al.*, 2008)	1
N.	Global Push for certain treatments (e.g. HIV/AIDS)	(Russo and Banda, 2015)	1
O.	TRIPS flexibilities	(Russo and Banda, 2015)	1
P.	Inelastic consumer demand	(El Baghdady and El Baghdady, 2014)	1

The top five factors are briefly discussed:

(A) Profitability is the most sought-after property for any organization, proven by this systematic review to also be the case for the pharmaceutical drug R&D industry. Profitability indicates that the organization is yielding financial gain from its processes.

(B) Patents is a form of IP, where a patent gives the owner exclusive property rights to make, sell, use or import a specific drug, or any invention of the owner, for a given amount of time (usually 20 years) (Lehman, 2003). In the pharmaceutical industry, patents are a major incentive to innovate in pharmaceutical R&D.

(C) Uncapped and competitive drug prices: Regulatory authorities limit the prices charged by pharmaceutical organizations. The most common methods used, involves comparing the price of drugs to the price already paid by other payers, or the price paid for similar

products. Profit controls is another method used that serves as an indirect form of price regulation. Each country has their own set of price regulatory policies, e.g. the US is less price regulated and might have significant variance in the price of the same drug in different areas or for different patient groups (Henry and Searles, 2012). Small pharmaceutical organizations often have weak bargaining power in the negotiation of prices; thus, market power plays a role.

(D) Possibility of improving the economic development of a country: A country is found to allocate significant amounts of effort to certain diseases, when clear evidence exist that the economic development of the country can be improved by mitigation efforts.

(E) Access to international market: Market access involves engaging with all components and different stakeholders of a national and international market. Entry into markets that are well established is sometimes difficult, as in the case for Japanese pharmaceutical organizations. Access to international markets is a bottleneck experienced by many developing country organizations.

5.6. Characteristics that influence R&D attractiveness

This chapter identified a considerable number of factors that influences pharmaceutical market attractiveness. The factors are derived from the market analysis, as well as the two systematic literature reviews completed on attractive diseases and NDs. The aforementioned resulted in four sets of factors in Tables 5.9, 5.10, 5.11 and 5.12. Figure 5.5 summarizes the four sets of factors, grouped into nine categories (mainly based on the WHO health systems framework, discussed in Chapter 3.1.2). The nine categories are briefly discussed.

(i) Disease setting and affected population

The market attractiveness of higher-income countries compared to lower-income countries is more significant, based on the ability of the consumers to pay higher drug prices; but less attractive based on low-income settings offering easier access to IP data and often being willing to accept lower quality products for more affordable prices. The higher the perceived disease burden in a country, the higher the sales opportunity and consequently also the perceived attractiveness, although the ability of the consumers (or procurers) to afford the prices (more possible in high-income settings) influences the ROI possible from the sales, regardless the volume. Low-income settings, therefore, reduce market attractiveness from the perspective of the pharmaceutical organizations, based on their lower potential to pay high treatment prices and often not characterizing the burden fully.

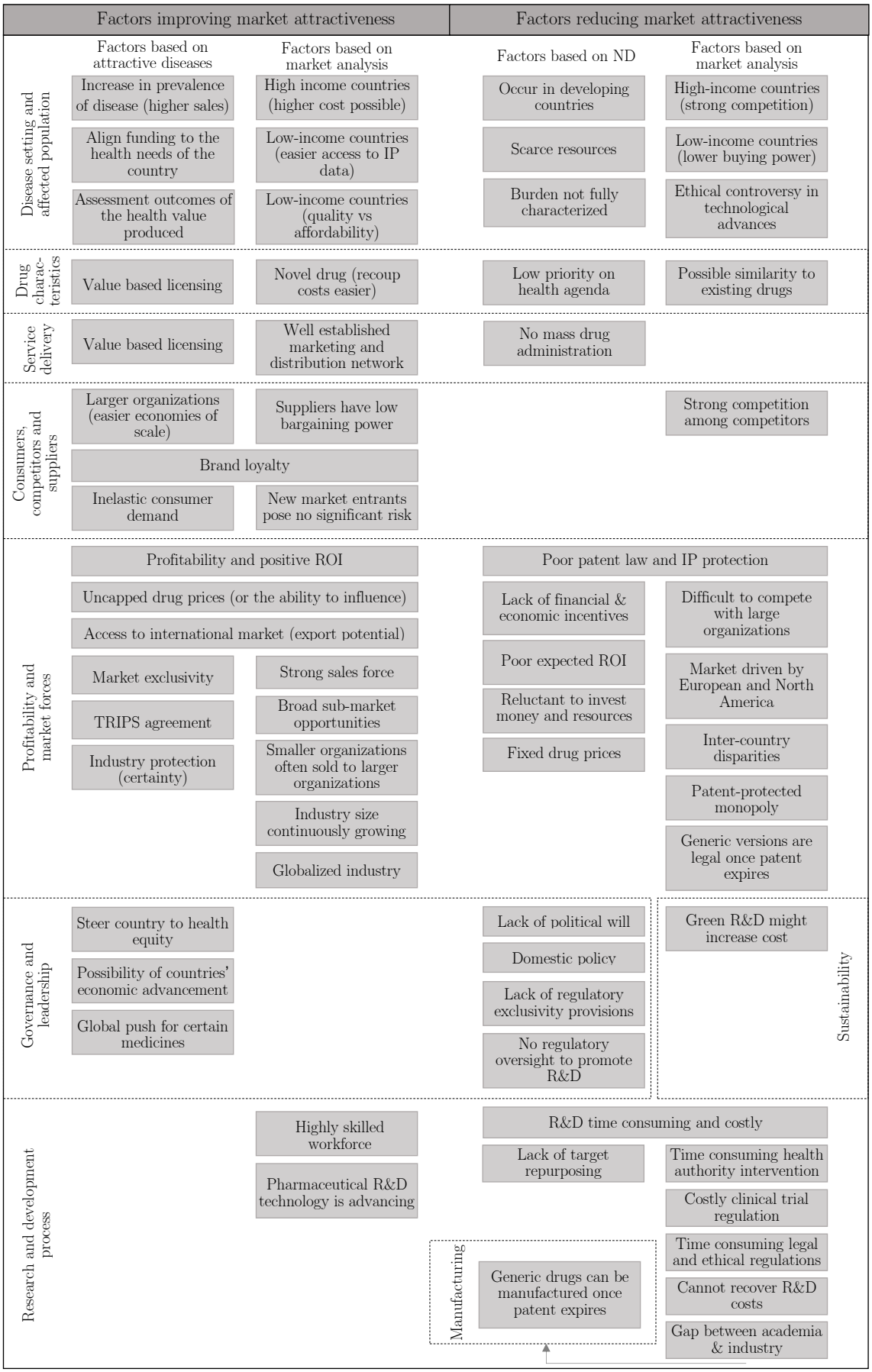


Figure 5.5: Overview of factors identified to influence market attractiveness.

(ii) Drug characteristics

The health value potentially added by a drug to a population or country, improves the market attractiveness of the drug R&D market in the case of high value, as the priority on the health agenda is improved. For the case where the disease is a low priority on the health agenda, and it consequently has less health value potential, market attractiveness is reduced. When developed drugs are similar to existing drugs, market attractiveness is reduced due to not being able to recoup costs based on the innovativeness of the drugs. The opposite is true for novel drugs to the market that have a high potential of recouping R&D costs.

(iii) Service delivery

In settings where well-established marketing and distribution networks exists, service delivery from the procurer to consumers is more reliable. With more reliable service delivery of drugs, the potential of high drug sales and successful distribution increases, consequently improving the market attractiveness. The aforementioned drug distribution improves with increasing efforts to mass drug administrate, where settings with fewer or no mass drug administration are linked to reduced market potential.

(iv) Consumers, competitors and suppliers

The consumers are defined as drug procurers, health facilities and patients; competitors are defined as competing pharmaceutical organizations; and suppliers are defined as the providers of the raw materials required for drug R&D.

Market attractiveness is typically improved by a consumer profile that has inelastic product demand and shows brand loyalty (note that affordability by consumers was discussed as part of the "(i) Disease setting and affected population" category). Strong competition among competitors reduces market attractiveness. Market attractiveness of drug R&D is often perceived as higher, based on larger organizations reaching economies-of-scale more easily. The opposite is true for small pharmaceutical organizations, that often perceive R&D as less attractive, based on difficulty to compete with larger competitors, and difficulty in reaching economies of scale.

(v) Profitability and market forces

Various aspects that improve the market attractiveness of the pharmaceutical R&D market can be categorized into one overarching category, namely profitability and a higher-than-average ROI. Aspects that contribute toward a potentially higher ROI in drug R&D are, first, the size and certainty of the market. The aforementioned include access to international markets improving the export potential, and market certainty provided through set agreements. Second, the ability of the pharmaceutical organization to influence drug prices, or uncapped drug price policies. Lastly, a stronger sales force of procurers and consumers (higher-income settings often have stronger sales force, as mentioned in the disease setting category). For smaller pharmaceutical organizations, high profits can be made, if the organizations are sold to larger pharmaceutical organizations.

In contrast, aspects that reduce the market attractiveness of pharmaceutical R&D include, first, a lack of financial and economic incentives if the expected ROI is poor. The aforementioned also links to the difficulty for smaller organizations to compete with larger organizations, resulting in reduced motivation to innovate. Second, fixed drug prices do not allow pharmaceutical

organizations to influence the prices of drugs sold, leading to uncertainty of expected return and causing reluctancy toward investing money and resources. Lastly, the patent-protected monopoly of pharmaceutical organizations makes it difficult for competitors to enter the market, though beneficial for IP holding organization. However, once the patents expire, the organization who held the IP rights, then needs to 'share' the market with manufacturers of generic versions. Significant controversy exists within the sphere of IP rights and market exclusivity, with patents stated to both improve and reduce market attractiveness of the pharmaceutical industry. For this research purposes, both the pros and cons of IP protection are regarded as important.

(vi) Governance and leadership

A strong political will of government and public entities aiming to both steer a country to achieve health equality, as well as advance a country's economic development, improves the attractiveness of the market. The aforementioned is based on expected market certainty as well as the public's responsibility to subsequently achieve the intended health and economic development goals. On the contrary, a lack of-, or very strict domestic policies, together with low political willingness reduce the incentive of organizations to invest resources into the market. In addition, when regulatory exclusivity provisions and no regulatory oversight is provided nationally, then market attractiveness decreases.

(vii) Sustainability

Due to the perspective on the need for a reduced carbon footprint in the contemporary political climate, the green R&D of pharmaceutical products is encouraged. From a profitability perspective, the activities involved in ensuring environmentally friendly R&D processes, increases the cost, and therefore reduces the attractiveness of, investing in the market. From a social impact perspective, the transformation of R&D processes into more environmentally sustainable practices, is positive, and improves the attractiveness.

(viii) Research and development process

As mentioned in Section 1.1, the R&D process is resource intensive and time consuming. Various characteristics of the R&D process reduce market attractiveness, including:

- Clinical trials are time consuming and costly;
- Processes that are required to comply with legal and ethical regulations are time consuming; and
- R&D costs cannot easily be recovered (especially by smaller organizations) if the R&D attempt was unsuccessful.

Consequently, the shorter the clinical trials and the smaller the barriers dictated by regulatory authorities to complete R&D (in terms of time required); the more attractive performing R&D for that market will be.

(ix) Manufacturing of drugs

Generic organizations can manufacture generic versions of the drugs, once patents expire. This reduces the time window for the innovating R&D organization to recoup all R&D costs, consequently reducing market attractiveness for completing R&D of drugs.

5.7. Requirement specifications

Table 5.13 provides an overview of the requirement specifications, identified in Chapter 5. These specifications will act, together with the other requirement specifications in Chapters 3, 4, 6 and 7, to form the foundation of the developed solution in Chapter 8.

Table 5.13: Requirement specifications, as derived from Chapter 5.

Reference		Requirement definition	Section
Functional requirements	F.4	The designed solution must incorporate characteristics to improve the market attractiveness of the desired scenario, as well as provide a means to bridge the characteristics that reduce market attractiveness in the pharmaceutical R&D industry.	5.3.3
	F.5	The designed solution must overcome disease-specific pharmaceutical drug R&D characteristics that lead to diseases becoming neglected.	5.4
	F.6	The designed solution must focus on improving the state of disease-specific characteristics, that enhance the attractiveness of the pharmaceutical drug R&D industry.	5.5.3
User requirements	U.4	The developed solution should address the customer requirements and unmet needs of the consumers of the developed drug.	5.3.1.1
Boundary conditions: Not applicable for this section.			
Design restrictions: Not applicable for this section.			
Attention points	A.2	The solution should take strategic uncertainties of the pharmaceutical drug R&D market into account, providing a means, within the boundaries of this research to address the strategic uncertainties applicable to this research.	5.3.1.4

As seen in Table 5.13, three functional requirements, one user requirement, and one attention point were derived from this chapter. No boundary conditions or design restrictions were identified in this chapter.

5.8. Conclusion: Market attractiveness

This chapter investigated the concept of market attractiveness of drug R&D for diseases. Where characteristics that both improve and reduce market attractiveness were discovered by performing a market analysis on the pharmaceutical R&D industry, as well as structured literature reviews on diseases that are neglected diseases and on those that are not. Characteristics that both enhance and reduce market attractiveness were derived.

CHAPTER 6

Existing incentive interventions

Significant effort and funding have been invested in mobilizing pharmaceutical organizations, private institutions and researchers to engage in the R&D for NDs (Dimitri, 2012). There is, however, still an urgent need for a new set of solutions to drive research towards NDs (Le, 2014). Academic institutions, pharmaceutical organizations, charities, and governments should, therefore, be catalysed to respond to the R&D need for NDs (Herrling, 2009). Incentive interventions is a method used to promote a desired activity, where most incentive interventions provide a means to maximize profit of research output, but other means might also serve as an incentive, such as optimizing productivity. In the pharmaceutical industry, an incentive solution is needed that offers fewer risks for the innovators and more results for the donors (Le, 2014). The solution needs to mitigate the challenges of the failed market and provide sustainable development in drug R&D for NDs.

According to Le (2014), a discrepancy exists within the current situation. The financial input in NDs is not displayed by the drug output for the diseases. One explanation includes that the funding allocated for NDs concentrates all its efforts on the innovation component of R&D, meaning the "R" and not enough financial resources is being allocated to the "D" in R&D, thus the development component.

The purpose of this chapter is to investigate existing incentive interventions. Firstly, background on incentive interventions are provided, with an investigation of the different entities that fund drug R&D. Second, context-non-specific criteria for incentive interventions are explored to indicate important aspects to ensure successful incentive interventions within the drug R&D sphere. Finally, the regulations involved in completing R&D of drugs are briefly described. A systematic literature review is conducted to identify different incentive types.

6.1. Pharmaceutical incentive intervention background

The following section provides insights into what pharmaceutical innovation incentives refer to, as well as the role that different stakeholders play in funding them. Reasoning behind the market failure of incentive schemes for motivating pharmaceutical R&D innovation in developing countries are explored. Finally, the capacity of drug R&D innovation in developing countries are investigated.

6.1.1. Defining the terminology used in this chapter

The terminology used in this chapter might be unclear if the meaning for this context is not clearly defined. Consequently, some of the terms which might be confused with one another are briefly defined in Table 6.1.

Table 6.1: Terminology defined for the use in this research.

Terminology	Definition of terminology used for this research purposes
Incentive	An intervention that motivates a certain action from someone.
Innovation	The process or action of innovating something novel.
Incentive strategy	Overarching approach of the incentives. Consists of a number of incentive types.
Incentive type	Incentive intervention instances categorized according to their functions.
Incentive intervention	An incentive instance proposed or implemented, grouped into an incentive type.
Agreement	An agreement is a mutual understanding, usually not enforced by law.
Formal agreement	An agreement that is enforced by law.
Legislation	A description of legal requirements enforced by national government.
Policy	Policy includes principles that are adopted by an organization. Does not overrule regulations.
Regulation	Detailed principles that supports the legislation, more dynamic than legislation.

6.1.2. Funders of drug R&D

The funders of drug R&D differs between diseases, as well as stages of drug R&D. The stakeholders involved in financing drug R&D include (Le, 2014): (i) public organizations, includes universities, public funded institutes as well as governments (focus on governments as public organizations in this research); (ii) private institutions, which typically constitutes out of pharmaceutical organizations and venture capitalists; and (iii) philanthropic organizations. Details regarding the funding of drug R&D by each of the three sectors, are described in the following section.

6.1.2.1. Government funding

The government of countries can play an enabling role in drug R&D by either funding it directly, or by implementing drug R&D policies, which must be adhered to by the government and private organisations (MSF, 2001). Given that government funding is a scarce resource in most countries, it is important that the funds that are available are used effectively to target the projects that has the potential to reduce the health burden in a country (Becker, 2015). The public policy should, therefore, guide government actions and decisions, including decisions on the funding for health care in a country.

Standard public policies to support government decision-making, with regard to health R&D financing, consist of three categories, namely (Becker, 2015):

(i) R&D tax credits and direct subsidies;
(ii) University research system support; and
(iii) Support of formal R&D cooperation's.

Based on the aforementioned three categories, it can be derived that the government incentivizes R&D by making it more attractive to perform R&D through funding interventions such as tax credits, direct subsidies, and direct funding support; or by implementing policies; as opposed to offering rewards for successful innovations. This supports the argument of the (IOM, 2009), stating that governments primarily fund basic discovery research which is the initial stages in drug R&D. Another argument on why the public sector mainly funds early stage drug R&D, is that it aims to increase the scientific knowledge behind neglected, and NTDs, rather than producing new chemical entities to treat them (Le, 2014).

6.1.2.2. Private funding

The private pharmaceutical industry is dominated by what is known as large pharmaceutical organizations. Given that these corporations are private institutions, they are primarily profit driven. Consequently, actions that increase profits take precedence over those that are primarily considered with satisfying global health needs (Chaudhuri, 2010).

The current incentive for private corporations to invest in the R&D of diseases, primarily rests on the patent system to offer market monopoly to the innovating organization. Trouiller et al. (2002) argue that this current system will not provide the means it should for NDs, given that the market prospects for these diseases, that primarily occur in developing countries, are absent.

Consistent with the above statements, it does not come by surprise that IOM (2009) found private pharmaceutical organizations to mostly allocate their funding and resources to late stage R&D (as opposed to government and philanthropic funding being more focused on early stage funding). Although more expensive (Section 4.1), late stage R&D has a higher probability of success, given the high attrition levels of projects in discovery, pre-clinical and phase 1 clinical trial phases (O'Keefe and Wintermantel, 2013).

6.1.2.3. Philanthropic funding

In 2001, MSF (2001) observed that the number of philanthropic organizations that fund and complete R&D for NTDs has increased. Since the financial crisis in 2008, however, there has been a decline in philanthropic funding for NDs (Le, 2014).

In response to the lacking market incentives for private organizations to invest in R&D for these diseases; philanthropic and public funds are required to stimulate and generate incentives to encourage interest. Berdud *et al.* (2016) found that this is true for philanthropic organisations, stating that over 90% of the funding for public-private partnerships (PPPs) is sourced from philanthropic and aid agencies.

6.1.3. Market failure

As mentioned in Section 6.1.2.2, private pharmaceutical organizations aim to maximize profits (Chaudhuri, 2010). Consequently, in the case of NDs, where the affected population does not offer a promising ROI, research agendas and priorities are instead focused on drug R&D that provides greater purchasing power (MSF, 2001). The aforementioned statement is known as the market failure; as it is the neglected disease market in itself that results in a shortage of investment.

Additionally, it should be taken into account that the purchasing power of the affected population is often weak, forcing private pharmaceutical organizations to provide drugs at cost price, leading to the risk that drug R&D expenses might not be covered (Webber and Kremer, 2001). It can, therefore, not be merely assumed that the private pharmaceutical industry doesn't have the public's interest at heart.

To counteract the market failure of NDs, researchers suggest that governments should take the necessary action to address the health needs of their countries (MSF, 2001). Governments have the ability, as mentioned in Section 6.1.2.1, to influence the drug R&D by either direct research funding and initiatives or by implementing policies for private organizations to adhere to (MSF, 2001).

The aforementioned raises questions, for example: how should instances where governments lack the capacity to influence research by providing finances be handled; or how should scenarios be handled where private organizations with appropriate capacity do not exist in a country and it is therefore not possible to generate R&D activity by means of public policy. The topic of capacity in developing countries is explored in the following section.

6.1.4. R&D capacity of developing countries

Diseases most common to LMICs, have the highest demand for treatments from people with minimal financial resources which, in theory, leads to severely limited profit potential (Le, 2014). Furthermore, LMICs are known for poor infrastructure and sanitation, lack of political commitment, bad health sector governance, lack of drug safety harmonization, and weak legal frameworks (Aerts *et al.*, 2017). The latter results in no certainty that developed products will reach the population in need, consequently discouraging investment in R&D (Aerts *et al.*, 2017).

According to Chaudhuri (2010), incentives such as product patents play an important role in incentivising innovation. However, in the case where the competencies necessary to enable innovation is absent, such incentive interventions do not encompass the capacity to create innovation. In cases such as this, infrastructure to perform R&D needs to be developed. The topic of IP and patent rights is discussed in more detail in Section 6.3.

It is, therefore, evident that for an incentive intervention to be successful in developing countries, contextual considerations, such as available infrastructure and government involvement, should also be addressed. Further research on vital requirements that incentive interventions should comply with, is discussed in the following section.

6.2. Context-non-specific criteria for incentive interventions

Incentives should create an attractive and supportive environment for investment in R&D for NDs (Renwick *et al.*, 2016). Furthermore, Granville and Trushin (2010) argue that the incentive interventions should take any possible conflicts of interest between sponsors, consumers, innovators and the quality of new vaccines into account. To this end, literature contains various suggestions of generalised criteria that incentive interventions should comply with. These criteria

are not context-specific, i.e. they are not subject to the specific circumstances in which the incentive will be applied.

Five publications were reviewed to derive a set of generalised criteria that incentive interventions should adhere to. The criteria identified by the respective sources are listed and categorized in Table 6.2. Three of the five studies investigated incentive interventions for antibiotics, whereas the studies by Granville and Trushin (2010) and Allarakhia and Ajuwon (2012), looked into ND incentive mechansims specifically. Nonetheless, all of the criteria identified in Table 6.2, are deemed to be applicable to the incentivisation of pharmaceutical R&D for NDs in general.

Table 6.2: Literature-based criteria that incentive interventions should adhere to.

	Renwick *et al.* (2016) [1]	Larsen (2016)	Chatham House (2015)	Allarakhia and Ajuwon (2012)	Granville and Trushin (2010)
Access					
Improve patient access*	x				
Not harm patient access		x			
Funding sustainability and timing					
Provide long term R&D financing*				x	x
Public subsidies for clinical trials*					x
Timed across drug lifecycle*			x		
Governance and leadership					
Equitable health-focused governance*				x	
Promote transparency and accountability for public funds*					x
Implementation feasibility and security					
Affordable to implement incentive*				x	
Minimizes barriers to implementation*	x				
Possess minimal disruptive effects*		x			
R&D project insurance*					x
Innovation process attributes					
Efficient innovation*				x	
Ensure conservation (minimal waste)*		x			
Participation and cooperation					
Allow for great competition among parallel experiments*					x
Enable participation of small-and medium organizations*	x				
Encourage large firm participation*	x				
Facilitate cooperation and synergy*	x				
Platform for coordinating innovators*					x
Profitability and market forces					
Delink sales revenue from sales volume*			x		
Improve NPV*	x	x			
Rewards focus					
Payoff based on drug cost effectiveness*					x
Reward innovation*		x			
Scenario specific					
Appropriate magnitude			x		
Appropriate intervention			x		

Notes

[1] The criterion: "promoting antibiotic stewardship", stated by Renwick *et al.* (2016), is excluded from the list as it is not applicable to incentive interventions applicable to NDs specifically.

* The context-non-specific criteria that are included in the CLIC (Refer to Section 8.4.1 and Section 8.4.2)

The incentive solution of this research needs to incorporate this set of criteria suggested in literature in order to ensure the feasibility, as well as the likelihood of success of the incentive intervention. This set of criteria should, consequently, be considered as an integral part of

providing an incentive solution. By incorporating these criteria, also seen as critical success factors, frequent failures of incentive interventions can be both forecasted, and avoided by taking precaution measures.

The public sector contributes to the R&D of medicines, but the private sector is needed, in most cases, to conduct final product development (MSF, 2001). In 2001, MSF also observed that all current government initiatives for the neglected disease R&D crisis, depend on market forces to a certain extent; and none of them comprise the ability to serve as an adequate strategy to effectively develop drugs for NDs (MSF, 2001).[12]

Some argue that the cost of R&D does not explain the market failure that is commonly attributed to NTDs. It is suggested by Webber and Kremer (2001), that pharmaceutical organizations are willing to make risky and expensive investments in products for which they believe a market exists. Consequently, the unviable market attractiveness of NTDs, regarding the cost and risk of R&D investment, is a more credible explanation for the market failure (Webber and Kremer, 2001).

6.3. Innovation patent laws, policy and regulations

It is well known that patents are currently the most widely used incentive for pharmaceutical innovation globally. This section explores the role of patents in incentivizing pharmaceutical innovation, and how the TRIPS agreement added to the global patent sphere. The role of public policy in drug regulation is also briefly investigated.

6.3.1. The role of intellectual property

Currently, the development of new drugs is incentivised through the patent system, where patents are a form of IP. Two types of IP exist: (i) industrial property (includes, for example, patents for inventions, trademarks, and industrial designs); and (ii) copyright (Hoen, 2016). IP law intends to protect the creators of intellectual goods or services, by granting time-limited rights to control the use of the intellectual goods (Hoen, 2016). Consequently, if a patent is granted to an innovator by a government, the innovator has the right to prevent others from using, importing or selling the invention for the given time period; which provides the innovator with a monopoly over the market. The patent system is intended to create a balance between incentivizing innovation, protecting innovators, and ensuring that the public benefits from the scientific advances (Hoen, 2016; Grabowski, DiMasi and Long, 2015).

According to Pugatch (2011) patents have played a visible role in incentivising investment in pharmaceutical R&D, and the authors estimate that between 60 - 65% of the innovations considered in the study would not have been developed, if it were not for the patent system. Conversely, Hoen (2009) and Aerts *et al.* (2017) suggest that the conventional patent system is not effective in impacting R&D for NDs, and needs to be altered. The ability of pharmaceutical innovators to obtain monopolistic power over a drug causes a lack of competition, leading to drug prices being set high above marginal costs, and resulting in high recoupment costs. The ability to

[12] This research did not uncover literature that indicates whether the aforementioned statement is still accurate at present.

recoup costs is one of the major drivers of the patent system, which in turn leads to a reluctance amongst pharmaceutical organizations to invest in R&D for diseases of LMICs (Mueller-Langer, 2013b), given that the consumers have a reduced ability-to-pay (Aerts *et al.*, 2017).

The high prices for innovated drugs are justified by the industry to compensate for the high cost of the R&D process. If it were not for patents, certain organizations would market the product without carrying any R&D costs. The aforementioned is also known as the 'free-rider' problem, which often refers to the actions of generic pharmaceutical organizations (Hoen, 2016).

6.3.2. TRIPS agreement

The TRIPS agreement, created in 1995, sets out global standards for the protection of IP (Hoen, 2016). The TRIPS agreement obliges member states to grant patents in all fields of technology for at least 20 years. Prior to TRIPS, generic companies in some LMICs could make relatively new products available at much lower prices than the innovating companies.

A medical breakthrough for HIV/AIDS medicine occurred in 1996, when HAART (a combination regimen of three classes of antiretrovirals) was discovered. Unfortunately, this treatment was only purchasable from original organizations, at significantly high prices, as a result of patent control (Hoen, 2016). Generic companies, mostly from India, started producing these medicines at lower prices, however, controversy grew as patents in certain countries restricted the procurement of the generic drugs (Hoen, 2016). Public health was in effect suffering as access to essential medicines was being restricted due to the strict patent regulations (Hoen, 2016).

In response to the TRIPS agreement that restricted public health improvement for the HIV/AIDS epidemic; the Doha Declaration on TRIPS public health was adopted (Hoen, 2016). The Doha declaration provided a means to overcome patent barriers that impeded access to medicines. The Doha declaration is seen as the root of numerous events launched to reformulate IP laws to ensure that society benefits, as opposed to only protecting limited commercial interest.

The TRIPS agreement has several flexibilities and policy options. One of the TRIPS flexibilities includes to extend the transition period in which least developed countries should become compliant with the TRIPS agreement. The extension enables least developed countries to confront health burdens in a more effective and affordable way, by making use of generic drug manufacturers (UNAIDS, 2013).

6.3.3. Drug regulation

Drug regulation, according to Levaggi *et al.* (2017), is an essential policy tool that has the potential to positively influence the amount of drug innovation in the future. The regulation of drug prices also has a great influence on incentivising drug innovation. According to Levaggi *et al.* (2017), two regulatory interventions exist, namely (i) cost-effectiveness thresholds; and (ii) risk-sharing agreements. The cost-effectiveness threshold usually involves price cuts when a certain expenditure is exceeded. On the contrary, performance-based agreements address the risk related to clinical outcomes. Levaggi *et al.* also argue that policy makers aim to accomplish the following list of objectives through both the regulatory interventions:

(i) Offering effective products to patients, in a timely manner;
(ii) Ensuring that the innovations that are adopted are good value for money;
(iii) Providing incentives to the industry to invest in R&D; and
(iv) Reducing the risk of new drug effectiveness falling below a threshold level, at the time of adoption.

In terms of price regulation, a trade-off between two factors is possible, namely: (i) static efficiency, i.e. making drugs accessible to individuals and population groups who need it; and (ii) dynamic efficiency, i.e. ensuring that the pharmaceutical organizations are making profits which are sufficiently robust to sustain R&D investments.

6.4. Incentive strategies

Incentives to encourage innovation in R&D can be categorized into two broad strategies, namely 'push' or 'pull' incentives (Webber and Kremer, 2001; Dimitri, 2012; Mueller-Langer, 2013a; Larsen, 2016). These strategy categories contain numerous interventions aiming to increase the interest of pharmaceutical organizations to invest in the R&D of diseases. In addition to the two broad incentive strategy categories, namely push and pull interventions, hybrid incentive interventions which employ a combination of the two strategies, also exist.

Consequently, in this research, the three aforementioned categories of incentive strategies are defined, as discussed in the remainder of this section. The pull strategies used in this research are based on Renwick *et al.* (2016), leading to the following incentive strategies: (i) Push strategies; (ii) Pull strategies (sub-categories of outcome-based, and lego-regulatory-based pull strategies); and (iii) Hybrid strategies.

6.4.1. Push strategies

Push interventions have a direct impact on R&D expenditure, aim to support drug discovery and often offer upfront research grants and subsidies to pharmaceutical organizations, which is financed by public institutions or charities (Dimitri, 2012; Aerts *et al.*, 2017). These incentives reduce the entry barriers, especially for small- and medium[13] pharmaceutical organizations, lacking the necessary capital to translate research into clinical development (Munos, 2009). Consequently, push interventions seek to make drug R&D more attractive by lowering the cost for R&D (Munos, 2009).

6.4.2. Pull strategies

Pull interventions aim to indirectly stimulate research efforts, by improving the potential ROI and/or by lowering drug delivery costs (Dimitri, 2012). Pull interventions thus offer a variety of rewards that are contingent on successful product discoveries (Aerts *et al.*, 2017). One of the fundamental advantages of pull interventions, is that they ensure a demand for the final product, consequently implying a positive ROI on R&D (Aerts *et al.*, 2017).

[13] Munos (2009) does not define the size of small- and medium pharmaceutical organizations. In line with the threshold employed in Section 4.1.2.3, for the purpose of this research, small- and medium organizations are defined as having a revenue of less than $1 billion per annum.

As mentioned, pull interventions can be categorized into two sub-categories, namely (Renwick *et al.*, 2016): (i) outcome-based strategies; and (ii) lego-regulatory pull strategies. Both outcome- and lego-regulatory-based pull strategies aim to encourage research output.

6.4.2.1. Outcome-based pull strategies

Outcome-based interventions increase the expected project revenue through offering monetary rewards (Renwick *et al.*, 2016). Outcome-based pull incentives only compensate successful development. In outcome-based pull incentives, all R&D risk lies with the developer, and not with the donor. The aforementioned leads to the pharmaceutical organizations, maximizing efficiency and striving to adhere to all efficacy requirements set by the funder (Renwick *et al.*, 2016).

6.4.2.2. Lego-regulatory based pull strategies

Lego-regulatory-based pull incentives, on the contrary, are government policies that facilitate higher market returns for research output (Renwick *et al.*, 2016). Lego-regulatory incentives are based on market factors such as price and market exclusivity, thus eliminating the difficulty of determining the size of the incentive. Lego-regulatory interventions might also include the extension of market exclusivity, thus possibly reducing competition and innovation. The extension of market exclusivity, consequently, prevents generic manufacturers from entering the market at an earlier stage. Similar to outcome-based pull incentives, most of the risk in lego-regulatory strategies are borne by the developer (Renwick *et al.*, 2016).

6.4.3. Hybrid strategies

According to Renwick *et al.* (2016) all push and pull strategies have distinct advantages, but none provide a comprehensive solution to adequately address the problems experienced as result of the market failure. A number of literature sources support the proposition that a single incentive solution is not adequate, arguing that a hybrid between push and pull interventions is necessary to adequately address market failure in R&D (Mossialos *et al.*, 2010; Dimitri, 2012; Jaczynska *et al.*, 2015).

6.5. Types of incentive interventions

Thus far in the chapter, background on various concepts that are relevant to the topic of incentivising pharmaceutical R&D has been presented. The previous section considered three broad strategies for incentivising pharmaceutical R&D. The focus now turns to identifying specific incentive interventions that have been applied to pharmaceutical R&D for NDs.

The section starts with a systematic literature review through which 96 instances of incentive interventions that have been applied to NDs are identified. Next, these instances are categorised into 26 types of incentive interventions for NDs. The advantages and disadvantages of each of the 26 incentive types are considered. Finally, the funding of different incentive strategies is considered at a high level.

6.5.1. Systematic literature review: Incentive interventions

The systematic literature review ensures that all incentive types that exist to incentivize investment in R&D of drugs for NDs are investigated. The method used, as well as inclusion and exclusion criteria are discussed in the following section.

6.5.1.1. Systematic literature review method: Incentive interventions

The literature search was completed in Scopus database, similar to the literature review completed in Section 4.1, 5.4 and 5.5. The objective of this review was to identify all incentive strategies implemented or proposed to encourage the R&D of drugs for NDs (with specific reference to NTDs). To this end, the following research question was formulated:

RQ: What incentives, policies, interventions or strategies exist to enable and encourage R&D or innovation for neglected, specifically NTD, diseases.

Keywords were derived from the research question, leading to the formulation of the following search function: ((neglected OR "neglected tropical" OR NTD) W/5 (disease*) AND (research OR development OR R&D OR innovation) AND (incentive* OR policy* OR intervention* OR "business model*" OR strategy*)).

6.5.1.2. Systematic literature review results: Incentive interventions

1338 documents were uncovered using the search function. The document set was further refined to include only articles published in English from 2009 to 2019. This reduced the number of documents to 1146. The following three keywords were subsequently excluded from the search: (i) animal; (ii) animals; and (iii) nonhuman. This resulted in 547 relevant documents. The 547 document titles were then examined to establish whether they were relevant to the RQ, as defined in the previous section. Of the 547 documents, 178 were relevant to the RQ.

To further refine the document set, inclusion and exclusion criteria, listed in Table 5.3, were defined. The abstracts of the 178 documents were subsequently scanned and evaluated based on both the RQ and the inclusion-exclusion criteria. This resulted in 89 relevant documents.

The full text of 87 of the 89 relevant documents could be obtained[14]. The set of 87 documents were then read to identify any incentive mentioned, that adheres to the RQ stated and to the criteria listed in Table 6.3. *ATLAS.ti* was used to assist in evaluating the literature. From the 87 documents, 96 distinct instances of incentive interventions that have been proposed and/or implemented were identified.

Table 6.3: Inclusion and exclusion criteria for systematic literature review.

	Criteria considered	Motivation
Include	Infectious diseases of the developing world	When incentive stated to incentivize not ND's but infectious diseases of developing world.
	Orphan diseases	Included when neglected diseases are also referred to in the article
Exclude	Control programs	Excluded when only focused on control, and not R&D
	Diagnostic implementation and control	Excluded when no reference to R&D
	Target repurposing procedures	Not incentive intervention, rather method of R&D
	Drug repositioning	Excluded when no reference to R&D
	Intervention programs	Excluded when incentives only focus on improving access to medicine/distribution of existing drugs
	Scientific and experimental designs of R&D	The design of clinical trials, are viewed as out of scope
	Drug donation programs	Drug donation links to providing adequate access to drugs, and not necessarily to improving the R&D pipeline
	The sustainable development goals, also the millennium development goals	Although the sustainable development goals encourage R&D for NDs, it is not seen as an incentive strategy or instance, as its focus is not solely on NDs but global interventions for sustainability
	HIV/AIDS incentives	A significant number of incentive intervention instances focus exclusively on HIV/AIDS, rather than on NDs in general
	Vaccine R&D	The R&D of vaccines is vastly different than the R&D of drugs, consequently leading to the exclusion of vaccine R&D in this literature review.

6.5.2. Categorization of existing incentive interventions

The set of 96 incentive interventions were grouped according to the three incentive strategy categories described in Section 6.4. Furthermore, a set of 24 incentive types were also defined[15], these types are defined in Table 6.4. In addition to the 24 incentive types, 2 incentive types (marked with an * in Table 6.4), that has not been used to incentivize drug R&D, but rather used to incentivize vaccine R&D of neglected diseases, are included in the list of incentive types to consider in this research study. The reason for including these incentives is to provide a more holistic list of incentives, and that even though it has not been used for neglected drug R&D incentives, it is deemed feasible interventions to consider. Thus, this study considers 26 incentive types as feasible incentive intervention solutions. Most of the hybrid interventions are operationalized through PPPs, but are viewed as hybrid incentive interventions, given the nature of the incentive approaches employed.

[14] Efforts to obtain access to this document through the Stellenbosch University library's interlibrary loans network, were also unsuccessful.
[15] The set of 24 incentive types, were not obtained from a literature source, but were deduced inductively, based on the findings of the structured literature review.

Table 6.4: The 26 incentive type definitions.

Incentive intervention strategies and types	Sources
Push strategies	
Grant Funds, usually non-repayable, distributed to entities. Grant funds are often provided by the government, or non-profit organizations (Cambridge University Press, 2020) to enhance R&D (Renwick *et al.*, 2016).	(Mackey and Liang, 2012; Sachs-Barrable *et al.*, 2014; Berdud *et al.*, 2016; Fitchetta *et al.*, 2016; Starr *et al.*, 2016; Hotez, 2017)
Open-source initiative Open source refers to a collaborative initiative where parts of a project are made available and known publicly, or a specific group of selected stakeholders. The information can be accessed and/or sometimes modified by the public or the stakeholders involved (Berdud *et al.*, 2016). The open source initiatives serve as a platform, where access to these data sets could benefit all participants (Munos, 2006).	(Allarakhia and Ajuwon, 2012)
Patent pool Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties (Weilbaecher, 2009). Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners (Weilbaecher, 2009).	(Weilbaecher, 2009; Pugatch, 2011; So and Ruiz-Esparza, 2012; Johnson and Kar, 2014)
PPP (Include product-development and public-private-academic partnerships) Public-private partnerships is any arrangement between one or more public and private entities (Hussaarts *et al.*, 2017). PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.	(Geraghty, 2009; Witty, 2011; Ioset and Chang, 2011; Pugatch, 2011; So and Ruiz-Esparza, 2012; Towse *et al.*, 2012; Moon *et al.*, 2012; Mueller-Langer, 2013b; Li and Garnsey, 2014; Berdud *et al.*, 2016; Starr *et al.*, 2016; Hotez, 2017; Pierce *et al.*, 2017; Ferpozzi, 2018; Weng *et al.*, 2018)
Tax credits* Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities (Koh Jun, 2012).	(Koh Jun, 2012; Mueller-Langer, 2013b)
Pull strategies	
Outcome-based pull strategies	
Advanced market commitments (AMC)* Advanced market commitments are legally binding pre-order contracts that are made between funders, and pharmaceutical developers (Hoffman *et al.*, 2014). The sponsors of advanced market commitments thus guarantee future purchase of drugs that are currently in the development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors (Hoffman *et al.*, 2014).	(Koh Jun, 2012; Mueller-Langer, 2013b; Berdud *et al.*, 2016)
Differential pricing Differential pricing is when people with different socio-economic status or that are from different regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental, or economic indicators (Berdud *et al.*, 2016).	(Towse *et al.*, 2012)
Patent buyouts IP rights can be purchased by donors. Thus, the patent holding organization is financially compensated in exchange for the IP rights of the R&D of the drug or vaccine (Koh Jun, 2012).	(Røttingen *et al.*, 2013)
Pooled fund A coordinating body, where multiple donors contribute to one fund and then utilizes the funding to support a single or multiple projects (Moran, 2014).	(Weilbaecher, 2009; Pugatch, 2011; So and Ruiz-Esparza, 2012; Johnson and Kar, 2014)
Prize fund Prizes are large monetary rewards, provided mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded for milestones met by the pharmaceutical organizations (Mueller-Langer, 2013a).	(Weilbaecher, 2009; Mueller-Langer, 2013b; Kameda, 2014)
Rating system Pharmaceutical organizations are rated according to a certain set of criteria; some of which can relate to the resourcing of R&D for NDs (Hassoun, 2012). The organizations are either rated on a scale, or in comparison to one another and their ability to meet the specified criteria set.	(Hassoun, 2012)

Table 6.4 continue on next page

Table 6.4 continued from previous page

Lego-regulatory pull strategies	
Intellectual property and market exclusivity Intellectual property refers to the right that the innovator receives, when an innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation; the exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.	(Koh Jun, 2012; Frank Mueller-Langer, 2013; Hoffman *et al.*, 2014; 't Hoen, 2016)
Policy instrument Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy.	(Manu, 2014)
Priority review voucher Law under which organizations that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher (Koh Jun, 2012). This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice(Sanchez, 2014).	(Ridley and Sánchez, 2010; Dimitri, 2012; Mueller-Langer, 2013b; Sachs-Barrable *et al.*, 2014; Berdud *et al.*, 2016; Starr *et al.*, 2016)
Trade, tariff adjustments Adjustments are made to trading or taxes and related costs associated with trading of manufactured drugs to the advantage of organization performing R&D.	(Mackey and Liang, 2012)
Hybrid strategies	
Collaboration network and consortiums A collaboration network refers to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are similar with two or more entities coming together, to complete a common activity towards achieving a common goal.	(Wilson, 2013; Keating, 2014; Squire, 2015; Starr *et al.*, 2016; Molyneux, 2017)
Colloquium and symposium An academic conference or seminar held, focussing on a specific topic, in this case NDs, R&D in the field, operational research and access.	(Kameda, 2014; Pierce *et al.*, 2017)
Policy and legislation Legislation includes laws constructed by governments; whereas policies must adhere to the law and comprises practical objectives and principles to guide decisions and actions within the pharmaceutical industry. Includes incentives such as drug acts to promote research in domestic markets.	(Mackey and Liang, 2012)
Drug status designation Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical organizations.	(Sachs-Barrable *et al.*, 2014)
Joint venture Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures are associated with a specified end-date.	(Towse *et al.*, 2012)
Independent organization Independent organizations do not require the approval of a government agency for decision-making and/or financial planning. Include for example advocating certain R&D priorities or providing evidence for informed decision-making.	(Manu, 2014)
Hybrid PPP This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive type included in this list of incentive types.	(Weilbaecher, 2009; Hunter, 2011; Allarakhia and Ajuwon, 2012; Mueller-Langer, 2013b; Hussaarts *et al.*, 2017)
Research laboratories Research laboratories are scientifically orientated facilities equipped with the necessary equipment to complete the necessary experimental studies aimed at R&D of drugs.	(Towse *et al.*, 2012)
Treaty Formal agreement between two or more states, subject to international law. A treaty can for example, enforce the coherence, fairness, and efficiency of the R&D system.	(Moon *et al.*, 2012; Hoffman *et al.*, 2014)
Working Group Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings. Therefore, a group of individuals or entities can complete R&D collectively.	(Hoffman *et al.*, 2014; Manu, 2014)
Coordination mechanism and platform Initiatives launched to coordinate R&D investments and activities. Operate to clarify investment priorities, increase transparency and diversify stakeholders to better align to R&D needs and investments.	(Beyeler *et al.*, 2019)

The distribution of the incentive instances, by strategy category (as opposed to type), is summarized in Figure 6.1. With reference to Figure 6.1, it is noticeable that 47% of the incentive interventions make use of a push strategy. Hybrid strategy interventions occur second most frequently, with 34% of the incentives falling in this category.

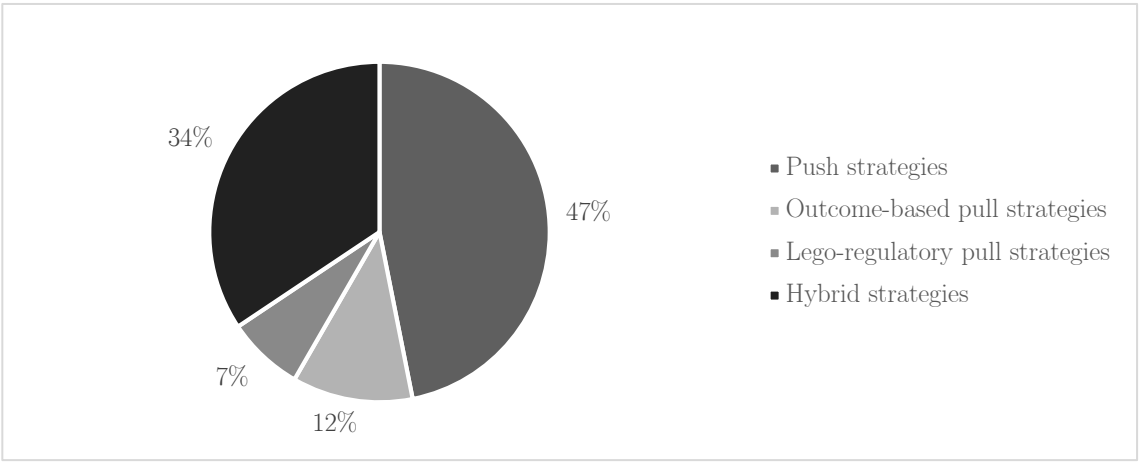


Figure 6.1: Distribution of incentive strategies.

Table 6.5 contains a summary of the number of distinct incentive interventions that were classified into each incentive type. (Refer to Appendix E for the complete categorised list of 96 incentive intervention instances observed in the literature set). As indicated in Table 6.5, PPPs is by far the most frequently proposed/implemented incentive sub-category for incentivising R&D for NDs (29 of the 96 incentive intervention instances observed in the literature set fall in this category). Open-source initiatives, together with collaboration networks, are the second and third most widely observed interventions, represented by 10 and 9 examples from the literature set respectively.

Table 6.5: Incentive type and strategy occurrence.

Incentive strategy and types	#	Incentive strategy and function	#
Push strategies		**Hybrid strategies**	
Grant	3	Collaboration network	9
Open-source initiative	10	Colloquium and symposium	2
Patent pool	3	Coordination mechanism	2
PPP (include PDPs)	29	Policy and legislation	2
Tax credits	0	Drug status designation	1
Outcome-based pull strategies		Joint venture	2
Advanced market commitment	0	Independent organization	2
Differential pricing	1	Hybrid PPP	7
Patent buyouts	1	Research laboratories	1
Pooled fund	1	Treaty	1
Prize fund	6	Working group	4
Rating system	2		
Lego-regulatory pull strategies			
IP and market exclusivity	2		
Policy instrument	2		
Priority review voucher	2		
Trade and tariff adjustments	1		

6.5.3. Advantages and disadvantages of incentive interventions

As stated in Section 6.4, each incentive strategy holds certain attributes, either giving the intervention a competitive advantage over the other strategies or making it less desirable. In the following section, each incentive intervention is briefly investigated in terms of advantages or disadvantages identified in the systematic literature review. The interventions are discussed in the incentive strategy categories.

It should be noted that, because the incentive interventions are grouped together in sub-categories according to their functions; details regarding specific incentives might get lost. It is however, accepted in this research that the value of the details that might get lost under categorization is not greater than the benefit of categorizing the incentives into 26 types.

An important consideration to note is that each incentive intervention's success is dependent on the environment in which it operates. With the advantages and disadvantages being, to a certain extent, context- and environment-specific.

6.5.3.1. Push strategy interventions

Push interventions subsidize research input, and not research output, which might finance unsuccessful R&D activities (Renwick *et al.*, 2016). Moral hazard as well as adverse selection problems are common to arise in push interventions (Aerts *et al.*, 2017). This is due to the fact that there might be asymmetric information between the donors and the recipients (Renwick *et al.*, 2016). The donors might not have all the information about the success probability, cost and evolution of a project, as it is difficult to monitor for all except the grant recipients. Consequently, the donors struggle to select the right grant recipients. Push interventions are advocated to decrease the cost of R&D; however, some argue that the cost of R&D does not explain the market failure that is commonly attributed to NTDs. Table 5.6 provides a summary of the advantages and disadvantages of push interventions used for NTDs.

As seen from Table 6.6, 6 types of push strategies are used to incentivize innovation for ND and NTDs. Of the push strategies, PPPs are the most commonly occurring. Push incentives are advantageous, as they allow innovators to obtain the capital means to reach more advanced R&D stages, which increases the possibility of developing a product that successfully reaches the market (Renwick *et al.*, 2016).

Table 6.6: Push interventions advantages and disadvantages.

Incentive types	Advantages	Disadvantages
Grant	Specifically focused on small- and medium-sized enterprises by providing funding support, academic collaboration, and strategic partnerships for early-stage research (Mackey and Liang, 2012).	Primary employment must be with small business (Mackey and Liang, 2012). Large-scale resource investments are required to stimulate the transition of preclinical research findings into translational technologies with a lasting impact on global health (Hotez, 2017).
Open-source initiative	An efficient and cost-effective manner for LMICs to access data (Allarakhia and Ajuwon, 2012). Reduces the R&D costs (Maurer *et al.*, 2004). Feasible targets can be identified early (Munos, 2006). Collaboration is facilitated among entities (Munos, 2006). Research duplications are minimized (Mossialos *et al.*, 2010).	Relies on the voluntary work of researchers, industry and academic institutions (Mossialos *et al.*, 2010). Online tools do not always go beyond data repositories (Allarakhia and Ajuwon, 2012).
Patent pool	Allows patent owners to access multiple antigens, which reduces transaction costs (Weilbaecher, 2009). Allows patent owners to identify compounds and set licensing terms, as well as collaborate on R&D (So and Ruiz-Esparza, 2012).	Difficult to encourage current patent holders to contribute to the patent pool, given that most ND antigen patents are primarily licensed to private organizations (Weilbaecher, 2009).
PPP	A long-term focus allows a comprehensive R&D portfolio to be established (Burrows *et al.*, 2014). Synergizes priorities of multiple sectors (Starr *et al.*, 2016). ROI on projects is potentially greater than for exclusively public or private initiatives (Jakobsen *et al.*, 2011). Financial cost and risk of drug development are shared among partners (Burrows *et al.*, 2014; Starr *et al.*, 2016).	Project profits may vary based on perceived risk, and project complexity (Jakobsen *et al.*, 2011). PPP limits competitiveness that is required for cost-effective partnering (Jakobsen *et al.*, 2011).
Targeted tax credits	Organizations are entitled to pay less taxes, thus organizations are encouraged to pursue R&D in specific areas (Koh Jun, 2012).	Only organizations with large tax liabilities benefit from these incentives (Koh Jun, 2012).

6.5.3.2. Outcome-based pull strategy interventions

Pull intervention donors might have difficulty in setting an appropriate monetary value, as too low prizes might discourage organizations, and too high prizes might lead to market inefficiency (Webber and Kremer, 2001). Furthermore, pull interventions often assume that pharmaceutical organizations always have enough upfront funding for R&D, which is not necessarily the case (Aerts *et al.*, 2017). Granville and Trushin (2010), also state that pull interventions might encourage me-too drugs, by encouraging R&D of close substitutes, which inadvertently distorts incentives for R&D in novel drugs. Table 6.7 depict advantages and disadvantages of outcome-based pull interventions.

Outcome-based pull strategies are used more frequently than lego-regulatory strategies but are not used as widely used as either push or hybrid strategies. This type of incentive is ideal for the funder, as the risk is mostly borne by the developer. Small and medium pharmaceutical organizations might struggle to benefit from these incentives, as they may lack the capital to advance their product through the clinical trial stages, without a capital input from donors.

Milestone-related prizes could, however, assist smaller organizations to encourage innovation for different stages of the R&D process.

Table 6.7: Outcome-based pull interventions advantages and disadvantages.

Incentive types	Advantages	Disadvantages
Advanced market commitments	Used to stimulate drug R&D at all stages of development (Hoffman *et al.*, 2014). Commitment to sell at a marginal cost (Berdud *et al.*, 2016). Reduces market uncertainty (Mueller-Langer, 2013b).	Due to long R&D process, it might be difficult to pre-determine a suitable "fixed" price (Koh Jun, 2012).
Differential pricing	The ability of LMICs to afford drugs might be enhanced (Berdud *et al.*, 2016). Improved access to essential medicines (Towse *et al.*, 2012).	ROI for innovator organizations may decrease as a result of a low selling price (Towse *et al.*, 2012).
Patent buyouts	Improvements to the drug or vaccine can be made if the patent becomes available (Koh Jun, 2012). Public funds are not spent, unless the product is developed (Røttingen *et al.*, 2013).	The developers are not responsible for the product uptake, but are compensated for R&D completed (Røttingen *et al.*, 2013). May not be politically feasible to pay large amounts to purchase patents upfront (Koh Jun, 2012).
Pooled fund	Could disperse funding to not one single entity (Viergever, 2013). Mi that only promising projects are funded, and that resources are not wasted (Hassoun, 2012).	Organizations might not have adequate funding to finance early-stage clinical trials (Hassoun, 2012).
Prize fund	Reward only given when innovation made a significant health impact (Mueller-Langer, 2013a). Decoupling of incentives for innovation from the price of final products for consumer (Mueller-Langer, 2013a).	Potential problem if the product developer wants to patent a product (Weilbaecher, 2009). Might lead to duplicated R&D efforts and investments (Mueller-Langer, 2013a). Only one winner. Does not require open licensing of registered drugs (Mueller-Langer, 2013b).
Rating system	Should encourage organizations to make sustainable changes to their policies for long term results (Hassoun, 2012).	The ratings are primarily subjective and do not only consider outputs (Hassoun, 2012). Highly rated organizations might try to distract the public from their generally poor behaviour in other arenas (Hassoun, 2012).

6.5.3.3. Lego-regulatory pull strategy interventions

Since lego-regulatory incentives constitute policy changes, it can be assumed that these incentives differ significantly, based on the country in which they are applied. Table 6.8 captures the advantages and disadvantages of the various sub-categories of lego-regulatory pull incentives, identified to encourage R&D for NDs.

Priority review vouchers are one of the only incentives that are exclusively developed for NDs. Initially priority review vouchers were only implemented in the USA, but more recently these have been considered and implemented by other countries and in other regions, including in the European Union. As per outcome-based pull incentives, it is difficult to determine the proper reward size for pull strategy interventions.

Table 6.8: Lego-regulatory pull interventions advantages and disadvantages.

Incentive types	Advantages	Disadvantages
Intellectual property	Associated with an increase in early-stage science on both neglected and non-neglected diseases (Mueller-Langer, 2013b). Excludes competitors for the limited time of a patent (Grabowski *et al.*, 2015).	Little evidence that this extension to standard patents increases the number of drugs generated for NDs (Mueller-Langer, 2013b).
Policy instrument	These are dependent on the specific policy instrument (Martin, 2016).	Difficulty integrating new policy with existing policies (Martin, 2016).
Priority review vouchers	Entitles the holder a faster priority review process of the FDA (or other administration bodies) than for other drugs under development (Ridley and Sánchez, 2010).	The granting of a PRV does not assure drug delivery and uptake (Koh Jun, 2012). Drug safety can be questioned under accelerated procedures (Ridley and Sánchez, 2010).
Trade and tariff adjustments	Lowers trade-related costs and/or reduces trade barriers (Mackey and Liang, 2012).	Time consuming and requires significant effort to negotiate/set up agreements suitable for both parties (Mackey and Liang, 2012).

6.5.3.4. Hybrid strategy interventions

Hybrid strategies provide a comprehensive solution that makes the most of both push and pull approaches. As mentioned previously, most of the hybrid interventions are operationalized through PPPs, but are viewed as hybrid incentive interventions, given the nature of the incentive approaches employed. The advantages and disadvantages of the hybrid incentive interventions are summarised in Table 6.9.

Table 6.9: Hybrid interventions advantages and disadvantages.

Incentive types	Advantages	Disadvantages
Collaboration network and consortiums	Defined milestones can be reached for different diseases in specified countries (Starr *et al.*, 2016; Molyneux, 2017). Duplications of R&D efforts are avoided (Souder and Nassar, 1990).	The loss of proprietary opportunities (Souder and Nassar, 1990).
Colloquium and symposium	Uses interdisciplinary approach to optimize new drugs to specific diseases (Pierce *et al.*, 2017).	Might be time-consuming.
Policy and legislation	The acquired right can be sold to another company (Villa *et al.*, 2009). Having a patent extended could appeal to organizations with highly successful products but would result in a delay in the introduction of generic forms of the drug (Villa *et al.*, 2009).	The review of other drugs could be held up (Villa *et al.*, 2009).
Drug status designation	Comprehensive solution which joins push and pull interventions, to initiate innovation (Sachs-Barrable *et al.*, 2014).	Preclinical research is rarely funded as part of this method (Sachs-Barrable *et al.*, 2014).
Joint venture	Share costs and risks with other parties (Hoffman *et al.*, 2014).	Requires strong coordination (Hoffman *et al.*, 2014).
Independent organization	Creates widespread awareness of the gap in funding allocated to diseases occurring primarily in LMICs (including ND) (Manu, 2014).	None articulated in data set.
Research laboratories	Provides a facility for independent researchers, or researchers without the needed technology, to perform R&D.	None articulated in data set.

Table 6.9 continue on next page

Table 6.9 continued from previous page

Incentive types	Advantages	Disadvantages
Treaty	Could complement existing incentives by addressing affordability, sustainable financing, efficiency and equitable governance (Moon *et al.*, 2012).	National government involvement is key for the success of the incentive (Moon *et al.*, 2012; Hoffman *et al.*, 2014).
Working group	A large number of countries can be involved, which might improve access to resources (Manu, 2014).	Some countries might rely on the contributions of other countries, without any concerns for adding to the advancement of R&D for essential medicines (Manu, 2014).

6.5.4. Funding involved for incentive interventions

Detailed information on the financing of the 96 incentive intervention instances observed in the data set were not reported in the majority of cases. Consequently, it is not feasible to present a detailed discussion of the typical amount of financing linked to each of the 26 incentive types. Instead, a brief discussion of the financing of each of the three incentive strategies is presented here. As a general remark, it is important to consider that, even if detailed financing information were published, the funding allocated to each incentive intervention instance is difficult to compare. This is due to the diverse ways in which funding is applied in the various incentive strategies.

The funding discussed in this section focuses on the financing of the R&D process. The finances required to fund the drugs itself for distribution purposes are not discussed; as it forms part of the intervention and control programs, which fall outside the scope of this study.

6.5.4.1. Push strategy interventions

The fundamental intention of push strategies is to provide a means for organizations to reduce the barriers to entry. This push strategies involve providing R&D organizations the required capital to use for translating preclinical research into clinical development (Renwick *et al.*, 2016). The strategies, therefore, all provide some funding means to enable the R&D process for the translational or discovery stages of drug R&D. Consequently, SMEs are likely to benefit from push strategies, as they may lack the capital to translate their basic research into the more costly clinical-trial phases of drug R&D (Aerts *et al.*, 2017).

Grants are one of the push incentives that provide a lump sum of money, or incremental lump sums, to innovators. According to data found in the systematic literature review, the grants for neglected and NTDs range from \$150 k to \$10 mil per project (provided by the Small Business Innovation Research Program (Mackey and Liang, 2012) and Global Health Investment Fund respectively (Fitchetta *et al.*, 2016; Starr *et al.*, 2016; Hotez, 2017).

The amounts of funding involved in establishing and financing PPPs is substantially higher than for grants, with one PPP project requiring up to \$2.8 - \$3.7 billion to develop one vaccine, namely the CEPI PPP project targeting 11 diseases most prevalent in LMICs (Hotez, 2017). The primary sources of PPP funding are large pharmaceutical organizations, governments, and philanthropic organizations. The capital invested in PPPs also covers the cost of failures and the cost of capital (Moran, 2005). Furthermore, many PPPs also include the cost of delivering and improving access to the drugs developed through these initiatives (Aerts *et al.*, 2017). It can consequently be derived, that when an entity considers initiating a push incentive for encouraging the R&D of

drugs, it should be taken into account that the immediate availability of capital is essential for these interventions to be launched.

6.5.4.2. Pull strategy interventions

The outcome-based pull, and lego-regulatory pull incentive strategy interventions are described in the following section.

Outcome-based pull strategy interventions

According to Renwick *et al.* (2016) outcome-based pull strategies differ from push incentives primarily based on the argument that all the R&D risk is borne by the developer and not carried by the funder. The essence of this incentive is for the funder to encourage R&D by offering a monetary award for successful development.

Prizes are one of the most frequently occurring outcome-based incentive strategies, where 6 of the 14 instances of outcome-based pull interventions identified in the systematic literature review were prize funds. Prize funds offer a lump sum of capital to drug developers, big enough for developers to be willing to take the risks involved with developing a drug and bearing all the costs associated with the drug R&D process.

Advanced market commitments offer a viable market once a drug or vaccine is fully developed. The rationale behind advanced market commitments is to match the revenues that organizations can expect for developing a new product for profitable markets, which provides incentives to develop products for neglected markets (Light, 2009). An example includes an advanced market commitments for pneumococcal vaccines exists, which entails six donors, entered in grant agreements, to make annual payments totalling to $1.5 billion (Vaccine Alliance, 2017).

Lego-regulatory pull strategy interventions

The amount of funding allocated to any of the instances of lego-regulatory pull strategy interventions observed in the data set could not be derived from this set of literature. The only lego-regulatory pull strategy with a known amount coupled to it; was a priority review voucher which was sold for $68 million in 2014 and was valued at $350 million in 2015 (Mueller-Langer, 2013b).

6.5.4.3. Hybrid strategy interventions

The monetary value associated with hybrid strategies differ significantly for each intervention. 10 of the 32 hybrid incentive instances observed in the data set have stated monetary values, however the function of the funding differs.

The funding allocated to instances of hybrid incentive interventions observed in the data set uncovered through the systematic literature review, ranges from $3 million for a PPP between Cambia (a global social enterprise) and the Queensland University of Technology (Johnson and Kar, 2014), to over $60 million for UNITAID's medicine patent pool (also a PPP) (Koh Jun, 2012). The Wellcome trust joint venture stated that it has made up to £11 billion worth of disbursements between 1936 and 2015 (Burci and Gostin, 2017), which equals to $14.3 billion (conversion rate of 1:1,3 pound to US dollar), or over $180 million per year for 79 years (Burci and Gostin, 2017), dedicated to vaccines for diseases that occur primarily in LMICs.

It was observed that some of the incentive instances had various sources of funding. With more than one donor or stakeholder involved in providing funding for one incentive intervention instance.

6.6. Requirement specifications

Table 6.10 provides an overview of the requirement specifications, identified in this chapter. Together with the other requirement specifications identified in Chapters 3, 4, 5 and 7, these specifications will form the foundation of the developed solution in Chapter 8.

Table 6.10: Requirement specifications identified in Chapter 6.

Reference		Requirement definition	Section
Functional requirements	F.7	Provide a formal platform as a means where different incentive programs, for encouraging R&D investments, can be compared.	6.1
	F.8	The suggested incentive intervention should comply with context-non-specific criteria, identified in literature, as this is essential for ensuring that the incentive intervention is feasible.	6.2
	F.9	The designed solution must show to what extent each incentive strategy complies with the criteria that the incentive strategy must adhere to.	6.4
	F.10	The framework must include all feasible incentive interventions, this includes: (i) push; (ii) both outcome-based and lego-regulatory pull; and (iii) hybrid strategies and types.	6.4, 6.5
	F.11	The designed solution must not only include incentive interventions, but also incorporate non-incentive-based interventions.	6.2, 6.3
User requirements: Not applicable for this section			
Boundary conditions: Not applicable for this section			
Design restrictions	D.1	The designed framework should be applicable to be used either for governmental, philanthropic and private organizations.	6.1.2
	D.2	The framework should not only provide one solution for the problem. In view of the multi-objective nature of the problem many feasible solutions exist that will provide different benefits for the respective stakeholders. Consequently, a set of feasible solutions, with different advantages and disadvantages, should be suggested instead of one 'optimal' solution.	6.5
Attention points	A.3	The proposed incentive interventions should contribute towards creating an attractive and supportive environment for investment in R&D for NDs.	5.2

In this chapter, five functional requirements, two design restrictions and one attention point were identified.

6.7. Conclusion: Existing incentive interventions

In this chapter various methods were identified with the potential to promote financial and resource input into the development of drugs for diseases. It was identified that the government, academic, private and philanthropic organisations collectively play a role in funding drug R&D. As discussed, however, the involvement of each of these stakeholders depends on various aspects such as: the lack of purchasing power of patients; the economic status of the country; as well as the IP rights associated with successfully completing the development of a drug. The influence of drug regulations and patents on the development of drugs was briefly investigated. A concise overview of the TRIPS agreement reported on flexibilities applicable to least developed countries.

This chapter also established that three major incentive strategies exist, where each strategy aims to urge involvement of pharmaceutical organizations with different approaches. By means of a systematic literature review, 96 incentive intervention instances often used in the pharmaceutical industry context were identified and categorized into 26 incentive types, which in turn can be categorized into one of the three incentive strategies. It was found that PPPs is the most commonly occurring incentive intervention. Each of the incentive interventions is appropriate for certain circumstances, while holding more value for certain instances and disadvantages for others. Hence, the advantages and disadvantages of each of the 26 incentive types were investigated.

CHAPTER 7

Stakeholder profiles

The process of selecting an incentive intervention, and the operationalization of an incentive intervention instance, both require the active involvement and engagement of different entities. For the purpose of this research, these entities are referred to as stakeholders.

This chapter explores the stakeholders involved in incentive interventions in the pharmaceutical system. Each of these stakeholders have different objectives for initiating an incentive intervention and/or different needs that the incentive intervention needs to deliver. An incentive intervention could also be initiated collaboratively by more than one stakeholder or could be designed for the purpose of encouraging collaboration between stakeholders during the R&D process. Therefore, both the roles of each of the stakeholders and potential collaboration instances between the stakeholders, are identified and investigated.

7.1. Stakeholder analysis and mapping

As illustrated in Section 3.1.1, the levels-of-care, defined by Rardin (2007), is used as a reference to investigate stakeholders that form part of the pharmaceutical drug R&D process. In this chapter, the stakeholders involved in specifically incentive interventions in the pharmaceutical system are explored, with Section 7.1.3 indicating the correlation between the two sets of stakeholders identified.

7.1.1. Stakeholder analysis

The definition of the term 'stakeholder' that is adopted in this research, is based on McGrath and Whitty's (2017) interpretation, being "an entity *with a stake (interest) in the subject activity*", with 'activity' referring to *"a task, project, programme, an undertaking of a corporation or government entity or even a particular instance of a person's behaviour"* (McGrath and Whitty, 2017, p. 727, 731).

Aside from identifying the primary stakeholders involved in selecting an incentive intervention, there is also the need to specify the level of involvement and influence, the interest, and the capabilities of the respective stakeholders. The latter is achieved by performing a stakeholder analysis.

A stakeholder analysis, which includes defining, analysing, and mapping the stakeholders, is a widely applied approach to establish and document the dynamics of stakeholders involved in the specific case or activity. Various techniques exist to evaluate the stakeholders involved, for

example (Benn *et al.*, 2016): (i) a stakeholder plot /matrix where stakeholders are mapped based on two key attributes, such as importance and influence, or impact and priority; (ii) a participation planning matrix, where project activities are mapped against different approaches for the engagement, with particular stakeholders included and excluded; and (iii) a three-dimensional power/legitimacy/urgency diagram, which gives an indication of the positioning of each stakeholder in terms of these three variables.

For the purpose of this research, McGrath and Whitty's (2017) 'stakeholder locus of interest map' is used as a stakeholder analysis technique, in an attempt to identify and categorize the stakeholders involved in the selection of an appropriate incentive intervention for encouraging R&D for neglected diseases. McGrath and Whitty's (2017) stakeholder locus of interest map provides a representation of the involved stakeholders, based on their involvement with each activity, as depicted in Figure 7.1. In the case of this research, the activity is the selection of an appropriate incentive intervention.

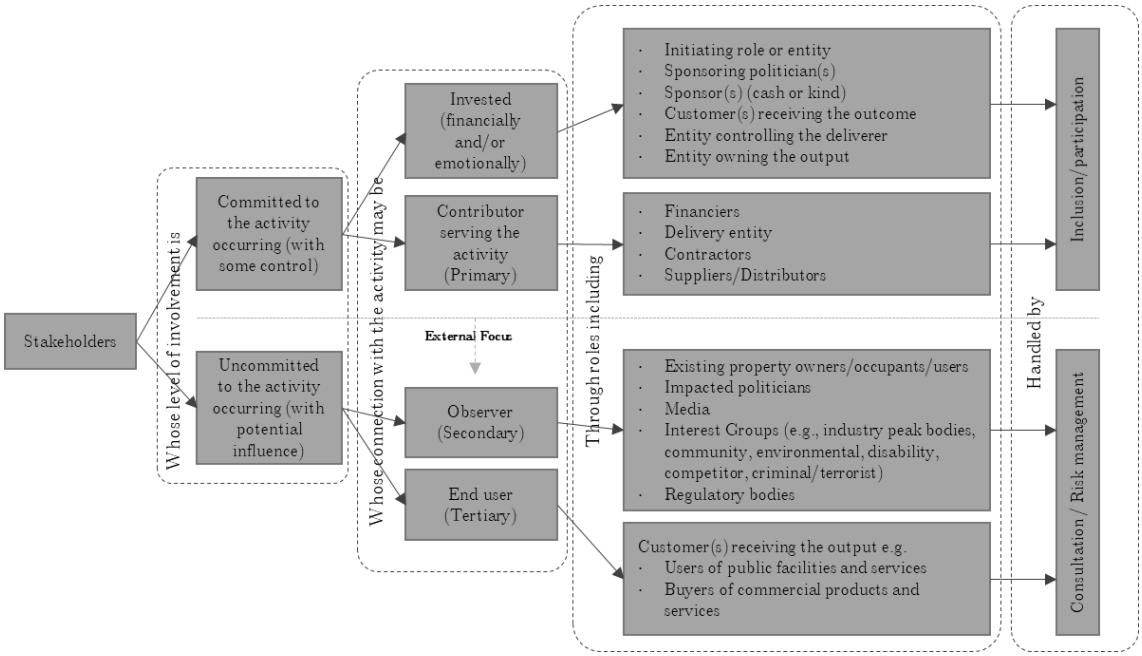


Figure 7.1: Stakeholder locus of interest map (reproduced from McGrath and Whitty (2017)).

As shown in Figure 7.1, when drawing up a stakeholder locus of interest map, stakeholders are firstly divided based on the level of stakeholder involvement, with the stakeholders classified as either 'committed to the activity', or 'uncommitted to the activity'. When the concept is applied to this research, this translates to classifying stakeholders as either: (i) playing a role in the decision-making process and being affected by the choice of incentive intervention to encourage R&D for the ND(s), i.e. being 'committed to the activity'; or (ii) not taking part in the decision-making process, but potentially having an influence on the decision being made, i.e. being 'uncommitted to the activity occurring'.

Secondly, stakeholders are categorized according to their level of 'connection' to the activity. In the context of this research, the concept is applied as follows. The stakeholders identified as 'committed' to the selection of an appropriate incentive intervention, are categorized as being: (i.1) "invested either financially or emotionally", meaning the stakeholder will financially contribute to the incentive intervention being selected, or is a key entity who wants to encourage R&D for neglected diseases and wants to actively play a role the mitigation thereof; or a (i.2) "contributor, that is serving the activity", meaning the stakeholder will be directly impacted by the incentive that is selected, and will take part in performing R&D for the neglected disease. The stakeholders identified as 'uncommitted' are categorized as being an: (ii.1) 'observer', in the process of selecting an incentive intervention, such as, for example, an entity that oversees local or global R&D; or an (ii.2) 'end-user', meaning the consumer of the product that will be developed as a result of the incentive being selected. As shown in Figure 7.1, categories i.1 and i.2 are defined as primary roles, category ii.1 is defined as a secondary role, and category ii.2 is defined as a tertiary role.

Thirdly, a more complete description of each of the four categories of stakeholders defined in the previous paragraph is generated by compiling a list of example 'roles' for each stakeholder. Lastly, the stakeholder locus of interest diagram indicates that the 'committed' and 'uncommitted' stakeholders are either 'included and/or participates', or 'consulted and/or part of risk management', respectively.

McGrath and Whitty (2017) highlight that a particular entity might represent more than one role, and that some entities might transition between roles over time. It is therefore suggested that the diagram should be interpreted to depict roles instead of specific entities. Another aspect mentioned by McGrath and Whitty (2017), is that the timescale is different for each level of connection. Meaning the contributors or primary roles might be affected immediately, secondary roles potentially immediately or once the activity is completed, and tertiary roles might only be impacted by the completed activity (McGrath and Whitty, 2017).

The stakeholders involved in- and impacted by the selection of an incentive intervention to encourage R&D for neglected diseases can, according to the stakeholder locus of interest technique, consequently, be divided into four main stakeholder groups, namely the: (i.1) investors (referred to as the 'enablers' in this research); (i.2) contributors (referred to as the 'innovators' in this research); (ii.1) observers; and the (ii.2) end-users. The properties of each of these stakeholders are further analysed in Sections 7.2 - 7.4 by means of the stakeholder locus of interest mapping technique.

7.1.2. Stakeholder characteristics

As seen throughout Chapters 3 to 6, the pharmaceutical R&D process and health care system is a complex system with various aspects requiring consideration in order to overcome frequently experienced problems and obstacles. The selection of a suitable incentive intervention among the 26 alternatives identified in Chapter 6, does not only depend on the pharmaceutical R&D system, but also depends on the stakeholders that are involved, their motivation for participating in selecting an incentive intervention, their resources, abilities and boundaries.

Decision-making requires the input of the participating and affected stakeholders in order to accomplish the desired outcome. The aforementioned is only possible when the specific characteristics of every stakeholder is considered and incorporated in the final decision-making strategy. This research, consequently, investigates the different components per stakeholder that should be considered to holistically review the 26 incentive interventions and their strengths and weaknesses to ultimately identify a feasible solution/set of solutions.

For the purpose of this research, the stakeholders' motive for taking part in the decision of selecting an incentive intervention, or for performing R&D for developing a treatment for NDs, will be considered. The requirements of the stakeholders that are initiating the incentive intervention or whom the incentive seeks to incentivize, also play a role in determining the appropriate incentive for the given scenario. In this case, the motive for the stakeholders to participate and the outcomes that stakeholders hope to achieve from the process, are collectively referred to as the objectives of the respective stakeholders.

In addition to the objectives of the participating stakeholders, the boundaries, and/or limitations that each stakeholder has should also be taken into account when selecting a specific incentive intervention. Taking stakeholder limitations into account will prevent the selection of an incentive, where one or more of the stakeholders involved are expected to provide resources or perform actions that are not feasible for the stakeholder. Consequently, suggesting an infeasible incentive for the stakeholders to pursue.

Therefore, the stakeholders' 'objectives' and 'internal capabilities' should be considered as part of the decision criteria in the selection of an appropriate incentive intervention. Sections 7.2 - 7.4 further elaborate on the objectives and internal capabilities per stakeholder. It should be noted that even though some characteristics were only identified during the verification and validation phases of this research, the final version of the stakeholder objectives and internal capabilities are presented in this chapter. The initial lists of objectives and internal capabilities of the stakeholders are depicted in the pre-read document in Appendix I.

7.1.3. Stakeholder correlation

The correlation between the stakeholders identified to be involved in incentive interventions in the pharmaceutical system and the stakeholders identified to form part of the levels of care defined by Rardin (2007), as depicted in Section 3.1.1, Figure 3.1, is depicted in Table 7.1. Visible from Table 7.1, is that each of the stakeholders identified in the stakeholder locus of interest map links with a one or more levels of care in the healthcare system, as identified in Section 3.1.1. With the environment level of care being categorized as both an investor and observer stakeholder.

Table 7.1: Stakeholder correlation.

Stakeholder locus of interest map, McGrath and Whitty (2017)	Levels of care, Rardin (2007)
Investors (enablers)	Network, environment
Contributors (innovators)	Organization
Observers	Environment
End-users (end-consumers)	Patients, population

7.2. Enabler stakeholder

As mentioned previously, the investor stakeholder, as defined in Section 7.1.1, is referred to in this research as the enabler stakeholder. The enabler stakeholder is the entity/organization whose aim is to incentivize R&D for a specific ND.

7.2.1. Enabler stakeholder analysis

According to the definition of McGrath and Whitty (2017), the enabler stakeholder is responsible for-, has some control over-, and is committed to the activity, namely the process of selecting an incentive intervention. Accommodating the aforementioned, an interpretation of Clarkson's (1994) definition of the enabler includes that the enabler would provide some form of investment into the incentive intervention (the activity), which might include a capital, human, or financial investment. This results in the enabler stakeholder bearing some form of risk as a result of their investment.

The enabler stakeholder can therefore be defined as the: (i) enabling entity, aiming to incentivize R&D for a specific disease (thus initiating the incentive); with (ii) primary control over the decision (this might be distributed among all stakeholders depending on the specific context); providing (iii) some form of investment for the incentive to be executed (encouragement or benefit for the innovator to participate); and as a consequence (iv) bearing some form of risk.

The entities and organizations that can represent the enabling stakeholder/s include governments, private for-profit organizations, academic, as well as philanthropic organizations. As stated previously, the third phase of defining each category of stakeholders, according to the stakeholder locus of interest map, is to provide a more complete description by compiling a list of example 'roles' for each stakeholder. The enabler stakeholder can fulfil some or all of the following roles: the (i) initiating role or entity (initiate or enable the incentive intervention); (ii) sponsoring politician(s) (a government or public institution funding the incentive); (iii) sponsor(s) (the monetary sponsor of the incentive); (iv) customer(s) receiving the outcome (this can include a scenario where a government enables the incentive with the intent of receiving the products that are developed); (v) entity controlling the deliverer (the innovator performing R&D might be informed by the enabler on the specifications of R&D specific to the incentive intervention; and (vi) the entity owning the output (with the output being e.g. IP, drugs or market exclusivity) . It should also be noted that the enabling stakeholders that are involved in incentivizing the R&D can be one, or more than one organization. Therefore, the stakeholder profile is not limited to one entity only.

7.2.2. Objectives and internal capabilities of the enabler stakeholder

The set of 26 incentive types uncovered during the structured literature review are analyzed to inductively derive a set of characteristics that holistically describe the objective(s) that an enabler may be pursuing through an incentive. Based on an analysis of the 26 incentive types, 5 distinct characteristics that collectively describe the enabler's objective(s) are derived, these are summarized in Table 7.2.

Table 7.2: Characteristics of the enabler's objective.

Objectives of the enabler profile				
Goal of incentive strategy	**Which innovators are targeted**	**Intention for patients**	**Desired relationship with innovator**	**Role and responsibility willing to play**
What should the incentive strategy deliver or aims that it should accomplish?	Does the enabler want to target all innovating organizations, or only some?	What is the desired output from the target innovators, for the consumers?	The nature of the relationship that the enabler is willing to have with the innovator.	What fundamental functions does the enabler want to provide?

The five characteristics of the enabler's objective(s) are further elaborated to provide various options that the enabler may be wishing to pursue. These options, that are not necessarily mutually exclusive, were inductively deduced from the set of 26 incentive types and are depicted in Table 7.3.

Table 7.3: Enabler objective(s) properties.

Enabler objectives of enabler profile	
1. Goal of the incentive strategy?	**3.** (continued) **Intention for the consumers?**
Improve the state of the R&D pipeline	Multi-purpose drug/vaccine
Reduce the burden of disease in an area	Play a role in improved access
Enable pharma to innovate more easily	Implement mass drug administrations
Gain market exclusivity over an innovation	Deliver regime treatment
Advance the R&D field	Improve body of knowledge
Deliver affordable and accessible treatment	**4. Desired relationship with innovators?**
Convey an important message	Once-off occasion
Fulfil corporate social responsibility	Limited to a number of years
Increase bandwidth and network	Milestone-related
De-risk R&D process	Engage at given time instances
Political obligations	Collaborate and build a partnership
2. Which innovators are targeted?	Alter or change regulation/policy
Large pharmaceutical organizations (private)	**5. Role and responsibility willing to play?**
SMEs (private)	Fund R&D
Governmental institutions	Partially fund R&D
Independent scientists	Facilitate collaboration between innovators
Academic institutions	Collaborate with innovator
NGO organizations	Facilitate regulatory process
All of the above	Provide market exclusivity
3. Intention for the consumers?	Adjust policies and regulations
Provide drug	Provide market certainty

The internal capabilities of the enabling stakeholder refer to the capacity of the enabler to play a role in incentivizing the innovator. Although the incentive interventions are not all based on funding the innovator, a significant number of incentives do entail providing financing to the innovator. Consequently, the internal capabilities primarily investigate the enabler's ability to provide funding and the timing thereof. It is known that policies and regulations play a significant role in drug R&D. Various policies and regulatory structures exist, and the ability of the enabling body to influence this, is a good indication of the incentive interventions that are a feasible option to consider. Table 7.4 portrays the four internal capability categories that the enabler profile

entails, these were also inductively derived from the set of 26 incentive types uncovered via the structured literature review.

Table 7.4: Internal capability categories of the enabler profile.

Internal capabilities of the enabler profile			
Funding available	**Timing of the funding**	**Ability to influence policy**	**Access and expertise**
If the enabler seeks to provide funding, how much funding is provided, or on what is the amount dependent?	If the enabler aims to provide funding, what will be the estimated timing of pay-outs?	The ability of the enabler to influence certain policies may affect the incentive intervention that is ideal for the circumstance.	The access to important resources and expertise that the enabler possesses and could therefore potentially share with innovators.

Furthermore, the internal capabilities of the enabler profile can be expanded to define various options for each of the four characteristics that are not necessarily mutually exclusive. These were inductively derived from the set of 26 incentive types and are depicted in Table 7.5.

Table 7.5: Internal capability properties of the enabler profile.

Internal capabilities of enabler profile	
1. Available funding?	**3.** (continued) **Ability to influence policy?**
Limited to an amount	Pricing policies
Full capacity	Tax credit policies
No capacity	National policies and legislations
2. Payoff to innovators?	National intellectual property policies
Beginning, once-off	International intellectual property policies
End, once-off	International trade law
Incrementally, based on output	**4. Access and expertise?**
Incrementally, based on timing	Access to key data
Incrementally, as innovator requires	Access to compounds
3. Ability to influence policy?	Access to intellectual property
Clinical trial regulation policies	Technology expertise and access
Market authorization policy	R&D expertise
Market exclusivity policies	

The objectives and internal capabilities of the enabler stakeholder are further discussed in Section 7.4.5.

7.3. Innovator stakeholder

As mentioned previously, the contributor stakeholder, as defined in Section 7.1.1, is referred to in this research as the innovator. The innovator stakeholder represents the organization or entity that needs to be incentivized to perform R&D for the desired ND.

7.3.1. Innovator stakeholder analysis

Based on the definition of McGrath and Whitty (2017), the innovator stakeholders are committed to the incentive, and their participation is essential in ensuring that the activity, being the

selection of the incentive intervention, is sustained. Meaning, that if the innovator stakeholder/s are not being incentivized to perform R&D, the selection of an appropriate incentive intervention is insignificant. The innovator stakeholder, like the enabler, can be described by means of Clarkson's (1994) definition, being that without the innovator's continuous participation, the incentive cannot 'survive' (meaning that it does not serve a purpose).

The innovator stakeholder can therefore be defined as the: (i) primary contributor in the R&D spurred by the selected incentive intervention (encouragement or benefit provided by the enabler); who (ii) sustains the decision being made, by performing R&D; and (iii) participates continuously until a drug is successfully developed (or otherwise specified by the incentive intervention).

Similar to the enabler, the innovator organization can be: (i) a public R&D organization; (ii) a private (for-profit)-; (iii) private (not-for-profit) organization; or a (iv) academic institution. With reference to the stakeholder locus of interest map, roles that the innovator stakeholder can fulfil include: the (i) delivery entity (delivering the R&D needed); (ii) contractors (performing the R&D); or the (iii) suppliers (of the research output or product). Lastly, the innovator stakeholder can be a single organization, or more than one organization who is targeted and intended to be incentivized by the selected incentive intervention.

7.3.2. Objectives and internal capabilities of the innovator stakeholder

Based on the analysis of the 26 incentive types, four distinct characteristics that describe the innovator's objective(s) for developing drugs are derived, these are summarized in Table 7.6.

Table 7.6: Characteristics of the innovator's objective.

Objectives of the innovator profile			
Reason for performing R&D for diseases	**Focus area of R&D and intention for consumers**	**Required from the enabler**	**Preferred or required funding timing**
The just for the organization to perform R&D for the disease.	The R&D focus area might vary based on what the intention of the R&D is for the consumer.	The innovator requirements from the innovator should be clear from the beginning.	In the case when the innovator requires funding, establish the ideal timing.

The innovator profile objectives are further elaborated, to include a list of options for each of the four objective characteristics, that are not necessarily mutually exclusive. These options, which were inductively derived from the set of 26 incentive types, are depicted in Table 7.7.

Table 7.7: Innovator objective(s) properties.

Objective characteristics of innovator profile	
1. Reason for performing R&D for the disease?	**3.** (continued) **Required from the enabler?**
Profit maximization	Facilitate regulatory process
Profit improvement	Provide market exclusivity
Corporate social responsibility	Provide market certainty
Not for profit	Provide a collaboration platform
Political obligations	Provide risk insurance or security
2. Focus area of R&D and intention for patients?	Improve export potential
R&D of drug/novel drug	**4. Preferred or required funding timing?**
R&D of multi-purpose drug	Beginning, once-off
Play a role in improved access	End, once-off
Drug repurposing	Incrementally, based on output
Deliver regime treatment	Incrementally, based on timing
3. Required from the enabler or incentive?	Incrementally, as required
Fund all R&D costs	Once output provided
Partially fund R&D	No preference
Collaboration with enabler	Do not require any funding
Adjust policies and regulations	

The internal capabilities of the innovator stakeholder refer to the capacity and limitations associated with the innovator performing R&D targeted at NDs. The internal capabilities highlight potential needs that the innovator might have, and which either the incentive intervention or the enabler should therefore seek to fulfill. If the applicable internal capabilities of the innovator stakeholder are taken into consideration during the selection of a suitable incentive intervention, the intervention is more likely to be successful. Table 7.8 portrays the internal capability categories of the innovator profile. The set of internal capabilities, similar to those of the enabler profile, are inductively derived from the set of 26 incentive types uncovered via the structured literature review.

Table 7.8: Characteristics of the innovator's internal capability.

Internal capabilities of the innovator			
Nature of organization	**Capacity to provide own funding**	**R&D limitations**	**Authorization standards adhered to**
The nature of the innovator organization affects the appropriateness of an incentive intervention.	The ability of the innovator to provide their own means of funding for drug R&D for the ND.	Any limitation inhibiting innovators from optimally delivering on drug R&D for the ND.	The authorization standard that the innovator organization is able to adhere to.

The internal capabilities of the innovator stakeholder can, similar to the enabler profile, be expanded into options for each of the four characteristics. The aforementioned options, that are not necessarily mutually exclusive, are inductively deduced from the 26 incentive types and are depicted in Table 7.9.

Table 7.9: Internal capability properties of the innovator profile.

Internal capabilities of innovator stakeholder	
1. Nature of innovator stakeholder?	**3. R&D limitations?**
Small to medium organization (includes start-up)	Don't have research laboratory
Large pharmaceutical organization	Don't have adequate equipment
Not-for-profit organization	Lack of information (knowledge) on disease
Governmental institution	Cumbersome nature of clinical trials
Academic institution	Shortage of finances
Independent scientist (no organizational link)	Policies or regulatory limitations
2. Capacity to provide own funding?	No market certainty
No capacity	**4. Authorization standards adhered to?**
Limited to an amount	None
Full capacity	Accredited authorization organization

7.4. Observer stakeholder

The observer stakeholder in this research refers to the stakeholders that are not directly involved in the selection of the incentive intervention, or the R&D of drugs for neglected diseases. The approval of this stakeholder is, however, necessary for the incentive to be selected and R&D to occur. Due to the limited nature of this stakeholder's involvement, the objectives and roles of the observer stakeholder are not analysed in similar detail to the analysis performed for the enable, innovator, and end-consumer stakeholders.

7.4.1. Observer stakeholder analysis

The observer stakeholders' compliance and acceptance are required for the incentive to realize, and for drug R&D to be achieved, though they are not 'committed' to the activity being completed. Another attribute of the observer stakeholder, considering the definition of McGrath and Whitty (2017), is that they might influence or be affected by the incentive intervention being selected, though they are not engaged in the operationalization of the incentive and the development of drugs.

The observer stakeholder can be defined as the: (i) entities or bodies that needs to authorize the compliance of the incentive intervention; and (ii) entities that are potentially affected by the selected incentive intervention. With reference to the stakeholder locus of interest map, the observer stakeholder can fulfil some or all of the following roles: (i) impacted politicians (being public sector governors that need to oversee the roll-out or actualization of the incentive); (ii) media (reporting on the incentive intervention, or playing a part in incentive marketing); (iii) interest groups (including the community, competitors, and industry peak bodies); and (iv) regulatory authorities (responsible for ensuring the quality and efficacy of the drugs developed as a result of the incentive intervention selected).

Given the broad and externally focused nature of the observer stakeholder, it is important to relate it to the larger environment in which the incentive intervention will operate, and the drug R&D will occur. As mentioned in Chapter 6.5.3 the environment in which incentive interventions operate differ greatly depending on the context. For the incentive to operate, the following aspects

of the external environment must be considered: (i) country-specific regulations and policies; (ii) regulatory authorities that have jurisdiction; (iii) community acceptance; (iv) competition; as well as (v) media. These aspects form part of the incentive operating environment.

The observer stakeholder can therefore be classified as forming part of the operating environment in which the incentive will operate once implemented. This stakeholder also contributes to the considerations for the incentive to realize. Though the incentive should comply to the demands of the operating environment, the selection of an incentive does not depend on it. The observer stakeholder is not explicitly included in the framework that is developed in this research; however, relevant aspects of the operating environment are included through alternative mechanisms.

7.5. End-consumer stakeholder

The end user stakeholder, referred to as the end-consumer in this research, includes the tertiary entities, thus the consumers receiving or buying the developed drugs that results from the selected incentive intervention.

7.5.1. End-consumer stakeholder analysis

Based on the definition of McGrath and Whitty (2017), the end-consumer stakeholders are the stakeholders who uses the output of the activity, thus the drug that is developed as a result of the incentive that is selected. Stated differently, the consumer stakeholder is the entity that has the need for the developed product in the first place, thus they are the individuals that for whom the drug is developed.

The end-consumer profile, for the purpose of this study, is divided into two primary groups, namely: the consumers, i.e., the patients; and the procurers of drugs, that serve as a consumer of drugs on a national and/or regional level. The process of drug procurement differs between health system. Drugs can thus be procured by a variety of stakeholders, ranging from public- to private organizations, or a combination of the two. The procurer group, consequently, further consist of: (i) public procurers (governments and/or central medical stores); (ii) private for-profit procurers (insurers and local wholesalers); and (iii) private not-for-profit organizations (donors and NGOs agencies). Although the requirements of the different consumers are likely to be similar, there is still a need to depict the different types of consumers, for the purpose of thoroughness.

With reference to the stakeholder locus of interest map, roles that the end-consumer stakeholder can fulfil: the (i) users of the drug developed (being the population suffering from the neglected disease); and the (ii) buyers of the product (being the procurers of the drug).

The WHO Health Systems Framework defines four outcomes that any health system should reach. These four outcomes link directly to the expectations of the end-consumer stakeholders. The four outcomes are drug: (i) access; (ii) coverage; (iii) quality; and (iv) safety. It is evident from literature that drug access is one of the most important requirements of consumers (Stevens, 2004; Holt *et al.*, 2012; Luchetti, 2014; Bors *et al.*, 2015). With the five dimensions of access to drugs, as described in Section 3.4.1, being (Jackson, 2018): (i) availability, (ii) accessibility; (iii) affordability; (iv) appropriateness; and (v) acceptability. In Section 3.4.1, these dimensions of

access are described based on how they relate to the overall health care system. Here, each of the five dimensions of access are described in terms of how they relate to drugs specifically. The purpose in doing so is to explore the requirements of the consumer as a stakeholder in the drug R&D process that should be taken into consideration when developing a framework.

(i) Availability: Availability refers to whether drugs are readily available to the consumer. This depends on a variety of factors, including: the supply chains for medicine in countries; the licensing of the drug for specific therapeutic use in a country; whether the drug is included on a country's essential medicines list, etc. Given that certain incentive interventions (e.g. drug status designation) do play a role in an increased availability of medicines, the availability of drugs should be taken into consideration when selecting an appropriate incentive intervention.

(ii) Accessibility: Consumers should be able to acquire drugs that are made available for consumption. Accessibility to drugs depend on the ability of consumers to physically get to a point of care providing the drugs. The act of delivering drugs into the hands of the consumers, is not included as part of the scope of this project, as the focus area of the incentive interventions are to promote R&D and not to ensure end-to-end access to the developed drugs. Accessibility of drugs are, however, a potential point of elaboration in future work that builds on the framework.

(iii) Affordability: Having the ability to afford the drug, without excessive OOP is essential for patients. The principle of not incurring excessive OOPs when accessing essential healthcare is a cornerstone of the UN's Sustainable Development Goal 3, which describes the ambition to achieve universal health coverage. Affordability is also an important consideration from the perspective of the procurement consumers, and this can be affected by the incentive intervention that is chosen. Differential pricing is also an aspect of affordability, as it allows different stakeholders to afford the same drug, even if payment capacities differ.

(iv) Appropriateness: The incentive intervention should incentivize the development of drugs that are appropriate for the target population. For example, if the target population inhabits a sparsely populated remote area in an LMIC, the health systems that serve the population may be inadequate and drugs that are developed for the ND would therefore need to be easy to administer (e.g. to have a short treatment duration, be dosed orally, and ideally once per day) to be considered appropriate (Burrows et al., 2014). The appropriateness of drugs can also link to the quality standards adhered to by the developed drugs. Although drug quality and quality assurance are a priority of all the consumer stakeholders, these are viewed as firstly being the priority of the procurers, whereas drug quality is assumed by the end-consumers to be acceptable. Drug quality is further discussed under the quality outcome of the WHO Health Systems Framework and is therefore not considered as part of the access component of the consumer profile.

(v) Acceptability: The drug must be accepted by the consumers as a feasible solution for the disease at hand. Acceptability refers to the drugs being designed to achieve the

optimal outcome for the target population, consequently taking the culture and social needs of the target community into account when deciding on a type of drug.

The coverage outcome of the WHO Health Systems Framework relates to the proportion of the population that benefit from the incentive intervention. From the perspective of the consumer stakeholder, coverage can be incorporated by taking the socio-economic status inequalities into account therefore considering the option of differential pricing as an incentive intervention. Another aspect of coverage that is not considered in this study relates to the distribution- and supply chain channels that exist to ensure full coverage of drugs for a target population.

The third outcome of the WHO Health Systems Framework, quality, was discussed as part of the appropriateness dimension of access. It is of high importance for both the patient and procurement consumers. The drug quality outcome is incorporated as a consideration for the procurement consumers, but not for the patient consumer as it is expected that patient consumers assume that the drugs that are provided to them by procurers are of acceptable quality. The final outcome of the WHO Health Systems Framework is ensuring the safety of drugs. Drug safety closely relates to the quality of drugs and is incorporated into the consumer profile together with drug quality. The stakeholder requirements for the combined end-consumer are populated and depicted in Table 7.10.

Table 7.10: End-consumer requirement characteristics.

CONSUMER REQUIREMENTS	
END CONSUMER (patient)	
1.	**Socio-economic inequalities**
	Require differential pricing
	Must eliminate all financial risk
2.	**Contextual treatment criteria**[16]
	Accommodates contextual criteria
PROCUREMENT: PUBLIC/PRIVATE (FOR-/NOT FOR PROFIT)	
3.	**Affordability**
	Require differential pricing
4.	**End-price profit margins**
	Any profit margins allowed
	Restricted profit margins
	No profit
5.	**Availability**
	IP regulation allows procurement of drugs to target area
	Existing drugs not allowed in target area
	Drug status designation required

7.6. Exploring the collaboration between stakeholders

As established in Sections 7.1 - 7.5, the roles of the stakeholders can be summarized as depicted in Table 7.11. These roles represent the responsibilities of the stakeholders in the context of

[16] Contextual treatment criteria of the consumer stakeholder include various aspects that the developed treatment needs to adhere to. This includes ethical considerations, clinical trial diversity requirements, type of consumer considered, drug safety, side-effects, useability, administration, advocacy, stigma consideration as well as WASH and sanitation initiatives.

neglected disease, the selection of an incentive, as well as the environment in which the incentive will occur.

Table 7.11: Stakeholder roles.

Enabler	Innovator	Observer	End-consumer
Mastermind behind implementing an incentive	Incentivized to perform R&D	Observe the incentive intervention	Suffer from neglected disease (require drug)
Observe all decision criteria	Perform drug R&D	Observe drug R&D	Procure drugs for neglected disease
Select an incentive			

Collaboration instances, where the stakeholders need to engage with one another in order to make decisions or share information, can be derived from the roles of the stakeholders. Where collaboration between one or more entities refers to the process where the entities are working together to achieve or produce something (Oxford University Press, 2019). Within the context of this research, collaboration occurs between the defined stakeholders, and include all forms of communication, engagement, or the making of agreements. Figure 7.2 illustrates the points of collaboration between the stakeholders.

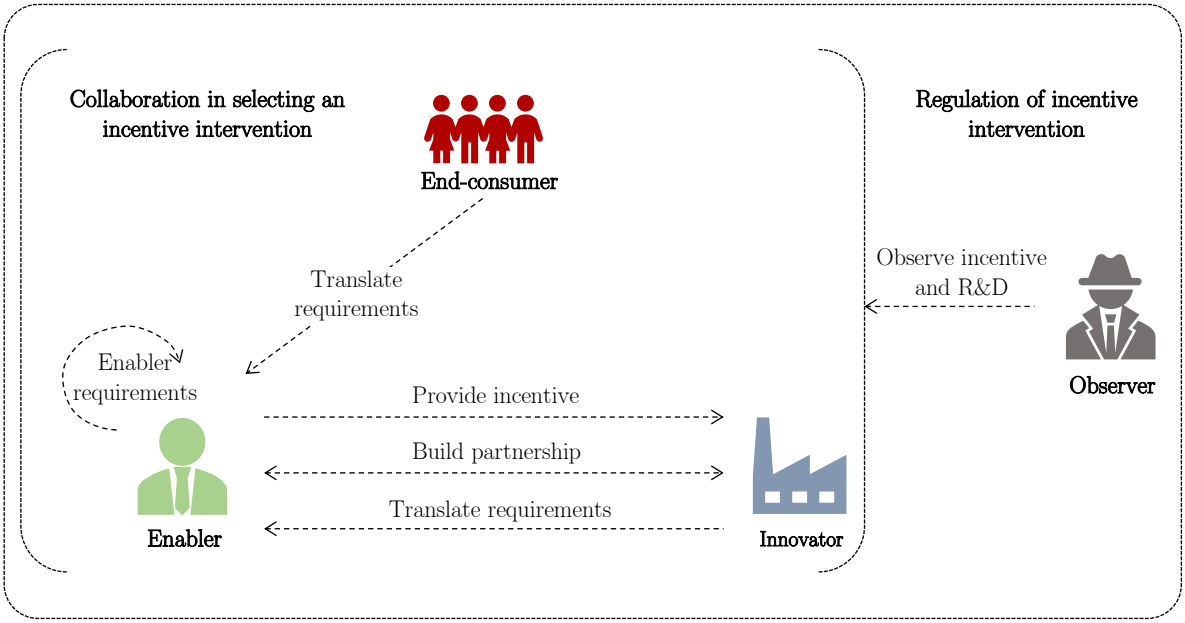


Figure 7.2: Stakeholder collaboration instances.

As seen in Figure 7.2, the collaboration between the stakeholders is divided into the two environments in which collaboration will take place. Firstly, the collaboration between the enabler, innovator, and end-consumer stakeholders that results from the selection of an incentive intervention. Secondly, the regulation of the incentive intervention by the observer stakeholder will occur which is, as mentioned in Section 7.4, outside of the scope of this research. In summary, Figure 7.2 depicts that: (i) the end-consumers, innovators and other enablers (if present), will translate their requirements in terms of objectives and internal capabilities to the enabler

stakeholder; (ii) the enabler will provide some form of incentive to the innovator; and (iii) the enabler and innovator stakeholders will build a partnership.

An important aspect of collaboration that should also be considered is how the interactions between the stakeholders will be facilitated. Because the role of the enabler stakeholder includes being the instigator of the selection of an incentive, most of the facilitation should also be done by them. In the case where more than one enabler stakeholder is present, different options of facilitation exist, such as establishing of a committee, or voting for a facilitating entity.

7.7. Requirement specifications

Table 7.12 provides an overview of the requirement specifications, identified in this chapter. Together with the other requirement specifications identified in Chapters 3, 4, 5 and 6, these specifications will form the foundation of the developed solution, presented in Chapter 8.

Table 7.12: Requirement specifications identified in Chapter 7.

Reference		Requirement definition	Section
Functional requirements	F.12	The suggested solution should allow for more than one stakeholder of a type to be incorporated.	7.2.1
User requirements	U.5	The suggested solution should incorporate the objectives and internal capabilities of the enabler and innovator, as well as the requirements of the consumer stakeholders.	7.2, 7.3 and 7.4
	U.6	The suggested solution should accommodate stakeholder collaborations.	7.6
	U.7	Conflicting interests of the different stakeholders, and the suggested solutions, should be taken into account and considered within the boundaries of this research. This will also bring about the necessary trade-offs to be made by the various stakeholders.	7.6
Boundary conditions: Not applicable for this section			
Design restrictions: Not applicable for this section			
Attention points: Not applicable for this section			

One functional requirement specification, and three user requirement specifications were identified in this chapter.

7.8. Conclusion: Stakeholder profiles

The stakeholder locus of interest technique was applied to identify the involved stakeholders for this problem setting. The stakeholders involved in the selection of an incentive intervention for encouraging R&D for neglected diseases include the enabler, innovator and the consumer stakeholders. A fourth stakeholder, namely the observer stakeholder is also acknowledged, but does not operate within the decision-making sphere of selecting an incentive, but rather plays a regulatory and observing role, once the incentive is implemented. This chapter elaborated on the objectives and internal capabilities of the involved stakeholders, and further highlights the stakeholder requirements that should be considered in the selection of a feasible incentive intervention.

CHAPTER 8

Decision-support framework design and development

Based on the literature reviews, as well as the market attractiveness analysis presented in the preceding chapters, it is evident that various factors have an impact on the efficiency and effectiveness of the R&D process, the state of the R&D pipeline, as well as the market attractiveness as it relates to diseases and/or drugs in the pharmaceutical sphere.

This chapter portrays the design and development of the decision-support framework. The aim of the framework is outlined with the objective outcomes highlighted. Furthermore, the development process followed in the operationalization of each framework component is described. The final decision-support framework is presented at the end of this chapter.

8.1. Aim of the decision-support framework

The decision-support framework is intended to assist governmental, private or public entities, aiming to encourage investment in R&D of drugs for a disease that is currently experiencing neglect, with the selection of an appropriate incentive intervention. The objective of the framework is to provide a shortlisted set of recommended solutions (incentivising interventions) based on the: (i) current pharmaceutical R&D system being addressed; (ii) needs, abilities, and limitations of the enabling organization or body; (iii) requirements and limitations of the innovator stakeholder; (iv) considerations regarding the end-consumer; and (v) abilities of the incentivizing interventions to address the priority improvement areas of the scenario under investigation. Thus, the framework does not select an incentive intervention on behalf of the decision-maker; instead, it guides the involved stakeholders to provide inputs on a number of factors that are relevant to the selection of an appropriate incentive intervention, and consequently provides a shortlist of incentive interventions that are likely to be appropriate to a specific scenario under consideration. Furthermore, a key notion that underpins the development of the framework, is that incentive interventions, in isolation, are most likely not sufficient to address the challenges that exist in a specific setting. Consequently, a set of non-incentive-based interventions that are likely to hold value in a given scenario are also recommended as part of the framework outputs.

Although the framework verification and refinements are only presented in Chapter 9, the final version of the framework, that incorporates all the adaptions, refinements, and changes as a result of the verification and validation processes, are presented in this chapter. The preliminary framework is depicted in the validation pre-read document in Appendix I. This approach is followed to allow for brevity, to avoid the duplication of the framework in the main document,

and to not interrupt the flow of the narrative of the dissertation with a detailed discussion of the verification and validation feedback, before the framework itself is presented.

8.2. Scope of the decision-support framework

The scope of the decision-support framework is specified as defined in this section. Given that the decision-support framework aims to find appropriate incentives to encourage R&D for diseases that do not have adequate drugs available; it is firstly important that the current environment where innovation is desired, is conceptualized. However, the status-quo in the pharmaceutical environment is not the only determinant that affects what is required from an incentive intervention to be effective in encouraging R&D. To encourage pharmaceutical organizations to invest resources into the R&D for diseases, the stakeholders that are involved should also be considered, namely: (i) the enabler, whom will act as the initiator of the incentive intervention; (ii) the innovator, defined as the pharmaceutical organization that performs R&D for delivering drugs to the market; and (iii) the user, referring to the end-user patients and/or procurers who will be using and/or procuring the drugs developed by the innovator organization. The observer stakeholder is not included in the decision-support framework, as their role is not to assist in 'selecting' an incentive intervention, but rather to 'approve' an incentive, once selected.

In the conceptualization of the decision-support framework, it is therefore acknowledged that the capabilities, objectives and needs of all three these stakeholders are important to provide a solution that will comply to what is needed and expected.

The pharmaceutical R&D *system*, considered in the decision-support framework, is defined as including: characteristics of the setting where the disease is prevalent as well as the affected population, and the health care system; characteristics of the pharmaceutical R&D environment; and sustainability considerations. Lastly, the framework encompasses various elements with several variables that emerge and flow through the framework. A summary of the terminology that is used in the framework description is provided in Table 8.1.

Table 8.1: Elements of the decision-support framework.

Variable	Definition
Background logic (BL)	The BL processes are hardcoded and run in the background of the domains, with the aim of analyzing and interpreting the data used in the domains.
Cluster-score	The ability of each incentive interventions to address each of the 12 criteria clusters.
Context-specific criteria	System elements that should be addressed by incentive-based interventions.
Context-non-specific criteria	Criteria, based on literature, that incentive-based interventions should adhere to.
Combined list of intervention criteria (CLIC)	Criteria that the incentive-based intervention should adhere to. This set of criteria includes context-specific as well as context-non-specific criteria.
Consumer criteria	Characteristics relevant to the specified consumers.
Decision criteria	Includes all the CLIC, enabler-, innovator-, and consumer criteria.
Domain	The framework comprises five domains. Each domain requires input data from the stakeholders and delivers output that is used in background logic functions to inform the final solution.
Enabler criteria	The characteristics relevant to the specific enabler.
Innovator criteria	Characteristics relevant to the specified innovators.
System elements	The system demarcation comprises of 67 system elements.
Priority rating	Evaluation of a decision criterion importance, allocated by either a stakeholder, or hardcoded if a context-non-specific criterion.

8.3. Decision-support framework overview

The decision-support framework consists of five main process steps, referred to as domains, and six background processes, referred to as background logic' (BL). 'The first four domains involve the collection of scenario-specific information and are completed by the framework users. The BL functions are not to be completed by the user of the decision-support framework but are hardcoded and intended to run in the background, using, amongst other inputs, the inputs provided by the user, and is conducted without the knowledge of the user. Figure 8.1 depicts the overarching view with the logical flow of domains and BL functions. The output of each domain is evaluated in the BL functions, and serves as input for the Solution set in Domain 5.

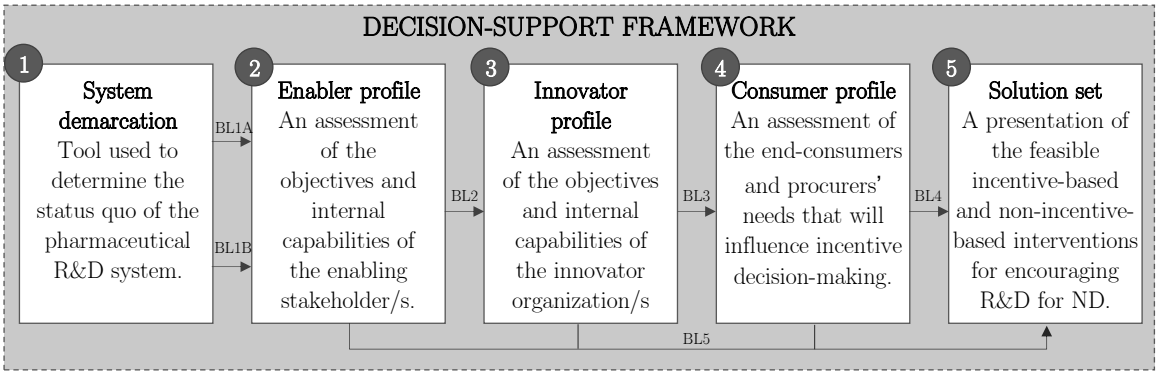


Figure 8.1 Decision-support framework overview.

The decision-support framework follows a typical input-process-output layout, highlighted in Figure 8.2. Figure 8.2 also provides detailed insights into the flow of input (needed from the stakeholders), the operation of the input data in the BL functions and the output of the framework. Figure 8.3 guides the reader through the logical flow of the decision-support framework.

Two fundamental perspectives were adopted in the development and in the operationalization of the decision-support framework. First, the selection of an appropriate incentive intervention for encouraging R&D of a neglected disease is a multi-objective decision. This resulted in two development fundamentals, namely: (i) an overall feasibility score per incentive is not calculated, rather the ability of the incentive to address the different criteria clusters (i.e. defined focus areas of any incentive intervention that are inductively derived as part of the framework development, refer to Section 8.4.10.1 for more detail) is indicated; and (ii) the framework, though calculating a numeric score per incentive intervention per criteria cluster, does not present this quantitative score to the user. The motivation for not calculating an overall feasibility score per incentive, is that it is considered fundamentally flawed to base a decision with multiple objectives on a single, aggregate score. The motivation for not presenting the quantitative score per incentive per criteria cluster, is that such a score can easily be misinterpreted and create a misconception of the incentive's abilities. Instead, the outcomes of the framework are presented using alternative means such as heatmaps and spider diagrams (that are drawn up based on the quantitative scores that are calculated in the background) to present the relative performance of the incentives, in relation to one another.

The second fundamental perspective adopted in the development of the decision-support framework is that, although the objectives and capabilities of the enabler, innovator and consumer stakeholders are taken into account as decision criteria for the selection of an appropriate incentive intervention, only the enabler's internal capabilities are used as exclusion criteria and viewed as a restraint for feasibility. The enabler internal capabilities used as exclusion criteria include the: (i) intention of the incentive for the consumers; (ii) role and responsibility that the enabler is willing- or has the ability to play; and (iii) the available funding of the enabler stakeholder.

The reason for the aforementioned, is that when the incentive does not align with the capabilities of the enabler (the primary decision-maker in selecting an incentive intervention), then the incentive is not a feasible option for the enabler to consider. In contrast, though misalignment with a potential innovator's internal abilities, for example, may negatively impact the effectiveness of the incentive intervention, it does not make the operationalization of the incentive fundamentally infeasible. Misalignment with innovator's abilities is therefore handled similarly to (mis)alignment with objectives and requirements of all other stakeholders, in that it is communicated as part of the results of the framework (i.e. this impacts the quantitative score of the incentive intervention for the specific criteria cluster, which is reported to the user in a number of ways).

The first step in the framework is concerned with documenting a holistic overview of the pharmaceutical R&D environment for the scenario being investigated (Domain 1). This is achieved through a set of questions that are intended to guide the user to systematically consider all relevant contextual factors. The system demarcation questions are categorized into ten pharmaceutical R&D environment categories (sourced from literature; refer to column one in Domain 1, Appendix G for the detailed list of system criteria).

Secondly, by evaluating the state of the pharmaceutical R&D system the priority improvement areas of the current landscape can be identified, and thirdly, classified as being suited to be addressed by either an incentive-based intervention or a non-incentive-based intervention (Domain 1). Though proposing, non-incentive-based interventions are not intended as one of the primary aims of the decision-support framework, it is recognised that not all of the challenges that exist with regard to a lack of investment in R&D can be appropriately addressed through incentive interventions alone. Therefore, the framework includes 43 non-incentive-based interventions that have been identified from literature. The non-incentive-based interventions are briefly described, and the priority rating provided as indicated in Domain 1 per intervention, the priority rating can be used as a priority benchmark per intervention (Section 8.4.12).

Based on the classification of the priority areas, a set of context-specific criteria are derived from Domain 1 (BL 1A). The context-specific criteria serve as one of the three bases on which the shortlisted set of incentive interventions that are recommended by the framework is selected. The second base for selecting the shortlisted set of interventions is grounded in literature (context-non-specific criteria). More specifically, a set of criteria that are proposed to be essential for any incentivizing intervention to be successful, regardless of the context in which the incentive intervention is applied, is derived from literature (BL 1A).

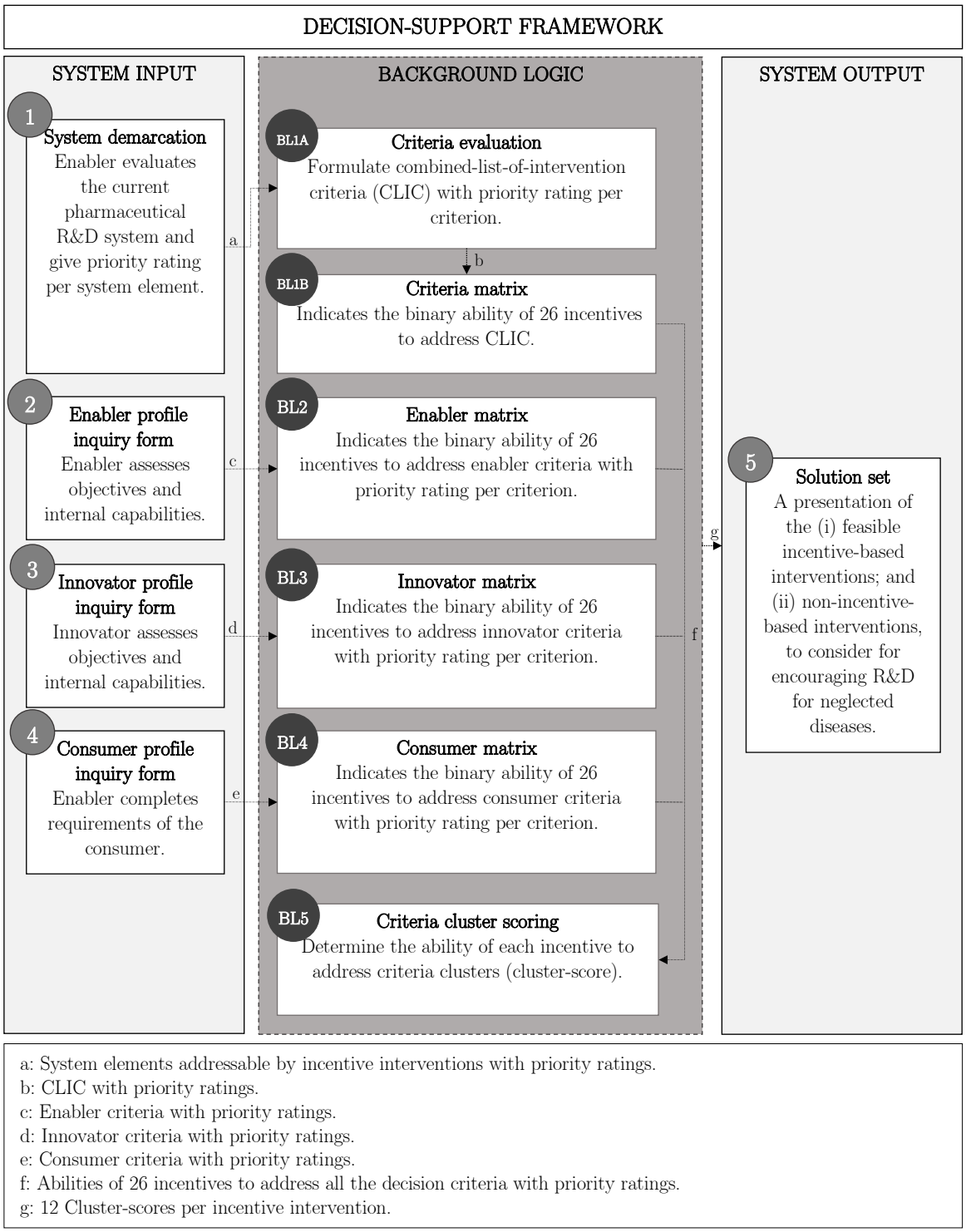


Figure 8.2: Input-process-output layout of decision-support framework.

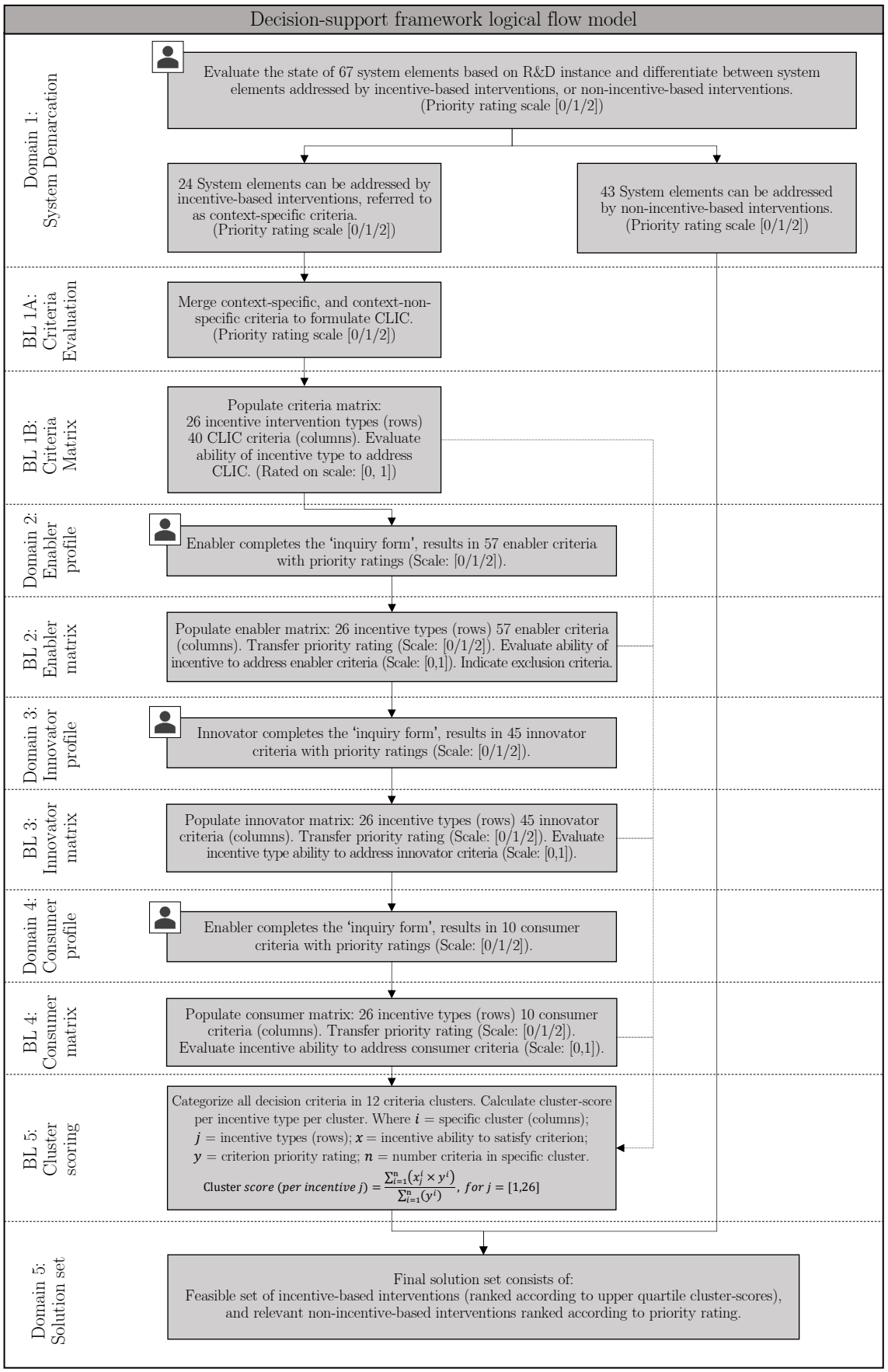


Figure 8.3: Logical flow model of the decision-support framework.

Consequently, a set of decision criteria is constructed which consists of context-specific (based on the system demarcation, Domain 1), as well as context-non-specific (based on literature) criteria; this list is called the *combined list of intervention criteria* (CLIC). This CLIC list summarizes the critical decision criteria that the incentive intervention solution must satisfy.

A set of incentive interventions is established by performing a structured literature review. A set of 96 incentive intervention instances, grouped into 26 incentive intervention types were identified, and categorized as either: (i) push incentives; (ii) lego-regulatory pull; (iii) outcome-based pull; or (iv) hybrid; incentive strategies. Refer to Appendix E for the complete list of 96 incentive instances, with definitions of each. The CLIC is subsequently evaluated (in the background (see BL 1B)) against the abilities of the 26 incentive interventions to determine the extent to which each incentive intervention can address the CLIC. The ability of each incentive intervention to satisfy the CLIC, will further be referred to in BL 5, where each incentive intervention's ability to address all the decision criteria is investigated.

Next, the third and final base influencing the selection of the solution set, namely the objectives, the capabilities, and limitations of the stakeholders (Domains 2 - 4), is considered. The stakeholders involved include the enabler (the entity that provides the funds or incentive), the innovator (the entity that is being incentivised to perform R&D work) as well as the end-consumer profile (the intended consumers and procurers of the drug). The objectives and capabilities of the enabler and innovator profiles are obtained by providing the enabler and innovator with inquiry forms (Domains 2 and 3) to complete, thereby establishing what decision criteria each of the stakeholders prioritize. The requirements of the consumers are also determined by an inquiry form (Domain 4) which is intended to be completed by the enabler stakeholder and not by the consumers. Specifically, the *limitations* (internal capabilities) of the enabler have a significant influence on the feasibility of a given incentive type, as described in Section 7.2. In the case where more than one stakeholder of a type is present, a domain (inquiry form) will be completed for each, with feasible solutions calculated for the stakeholders combined. A combined solution set where a weighting (other than equal) should be defined by the users of the framework, falls outside of the scope of this research inquiry.

The information gathered from the respective stakeholders by means of the enabler-, innovator-, and consumer inquiry forms (Domains 2 - 4), is subsequently translated into the enabler-, innovator-, and consumer matrices (BL 2 - 4), which is hardcoded, similar to BL 1B, indicating the binary ability of each of the 26 incentive interventions to address the corresponding stakeholders' criteria. The output of BL 1B, BL2, BL3 and BL4 is interpreted in BL 5. BL 5 involves the final evaluation of the incentive interventions by means of two fundamental functions. Firstly, all the decision criteria from BL 1B, BL2, BL3, and BL4 are combined and categorized into 12 criteria clusters (depicted in Figure 8.4, the development of the clusters is discussed in Section 8.4.10.1 and, a detailed overview of the clusters is provided in Appendix H). Secondly, a score per criteria cluster is calculated indicating the extent to which each of the incentive interventions satisfies all the criteria in the cluster, this is referred to as the *cluster-scores* per incentive per criteria cluster.

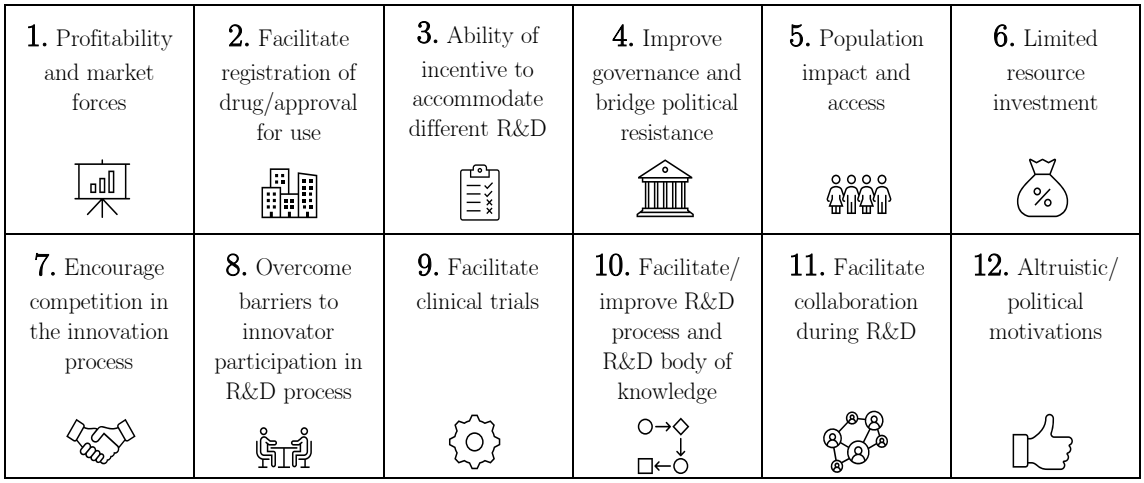


Figure 8.4: 12 Criteria clusters.

Finally, the output of the framework is a shortlisted set of incentive-based and non-incentive-based interventions (Domain 5), that are recommended as feasible options for a specific scenario. The feasible incentive interventions (excluding incentives deemed infeasible, due to not satisfying the exclusion criteria of the enabler stakeholder), are (as an output from Domain 5) depicted in a heatmap format (see Figure 8.19), demonstrating the ability of each incentive to address each of the 12 criteria clusters. The incentives are then ranked from the incentive with the highest to lowest number of criteria-score values that were in the upper quartile of all the feasible solutions. The presentation of the final results, as mentioned earlier, is grounded on multi-criteria decision-making (discussed in Section 8.4.11), therefore not aiming to provide a single feasibility score for the incentives, but rather to provide a concise and objective overview of the feasible incentives' strengths and weaknesses regarding the multiple-decision criteria clusters. The presentation of the results is intended to allow the decision-maker to make an informed decision regarding the selection of an appropriate incentive intervention.

Note that the developed framework does not provide one solution for the scenario under consideration. Rather, it offers a multi-criteria, subjective overview of the relative performance of various potential feasible solutions to the problem.

A final remark regarding the decision-support framework is that, although there are many BL functions and hardcoded information that may seem to add a level of complexity for users, the decision-makers and stakeholders involved/using the framework are only confronted with the five domains, i.e. the inquiry forms and then presented with the results. Therefore, the perceived complexity, from the perspective of the users, is significantly simplified. This approach is deemed preferable as it allows for a significant amount of relevant information to be taken into consideration when proposing and evaluating feasible solutions, without rendering the framework unnecessarily cumbersome and complex. Furthermore, this approach is deemed valid, given the rigorous approach that was followed in the framework development, refinement, verification, and validation.

8.4. Decision-support framework development and operationalization

This section includes a breakdown of the process followed to develop each domain and BL process. The framework components are discussed sequentially, thus the BL functions are discussed amid the domains to enable the reader to follow the flow of information and logic in the framework. The content of this section describes the process followed to design the decision-support framework, followed by a description of the operationalization of each of the domains and BL functions.

As mentioned previously, in order to facilitate ease of implementation, the framework is operationalized in the form of an MS Excel workbook. The BL is coded in MS Excel, and macros[17] are employed to enable users to execute activities such as refreshing results (e.g. after changes are made to inquiry forms). The transfer media is further described in Section 8.5.

8.4.1. Domain 1: System demarcation

The system demarcation is the first domain of the decision-support framework that the user needs to complete[18]. The following sections describe the development and operationalization of Domain 1.

8.4.1.1. Development of the system demarcation

The system demarcation domain is developed to develop an holistic understanding of the pharmaceutical R&D system based on the specific scenario being investigated. Consequently, the scope of the domain is extensive in nature. Figure 8.5 depicts the development process of the system demarcation.

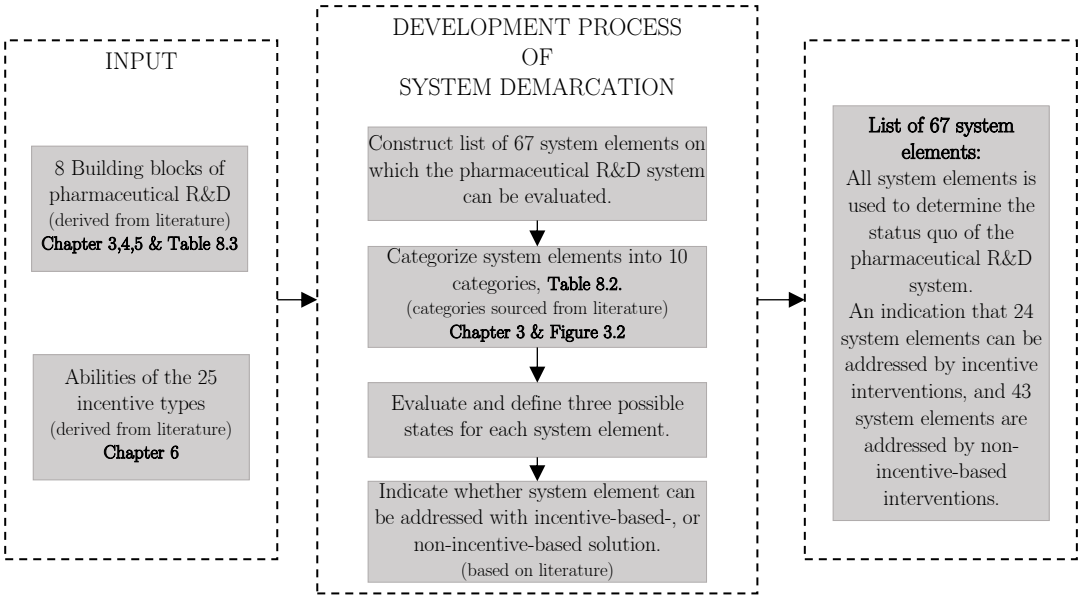


Figure 8.5: Development of the system demarcation.

[17] A macro is an action or set of actions to perform an intended task or sequence of tasks

[18] As discussed in Section 8.2, the pharmaceutical R&D *system*, considered in the decision-support framework, is defined as including: characteristics of the setting where the disease occurs as well as the affected population and the health care system; characteristics of the pharmaceutical R&D environment; and sustainability considerations.

The system demarcation domain is developed by using two sets of inputs, namely: (i) the eight building blocks of pharmaceutical R&D (further explained in Section 8.4.1.2), and (ii) the abilities of the incentive intervention types (discussed in Section 6.5). Both sets of input have been derived from literature. As shown in the central column in Figure 8.5, the 'eight building blocks of pharmaceutical R&D' input is used to construct a list of 67 system elements, categorized into ten categories (the ten categories are listed in Table 8.3). For each of the 67 system elements, three possible states, are defined as described in more detail in the remainder of this section.

8.4.1.2. System demarcation categories and properties

The 67 system elements that constitute the system demarcation domain, are grounded in the literature analysis conducted in Chapters 3, 4 and 5. Table 8.2 summarizes the eight sets of factors, attributes and properties used to construct the system demarcation elements list. These eight sets of factors are viewed as the building blocks according to which a system can be evaluated to determine its status quo. Table 8.2 includes a description of the applicability of each set of elements, as well as the section in the dissertation where the elements were sourced from.

Table 8.2: The 8 building blocks of the system demarcation system elements and its applicability.

	System demarcation elements	Description of element applicability	Section
1.	Factors that influence the R&D pipeline	These factors indicate where a lack of efficiency in the current drug pipeline and R&D process occurs. Therefore, identifying which of these factors are applicable to the instance on hand, aids in the ability to address them.	Section 4.1.2 (Table 4.1)
2.	Building blocks of the WHO health systems framework	The WHO health systems framework provides a holistic overview of the components that a health system consists of. This allows for the consideration of all aspects of the health care system, thus not excluding essential elements.	Section 3.1.2 (Figure 3.2)
3.	Common trends of the R&D drug pipeline	Identifying trends in terms of the general advancement of drugs through the pipeline.	Section 4.1.3 (Table 4.2)
4.	Properties of an attractive market	The extent to which properties identified to resemble an attractive market, apply to the instance being investigated, aids in identifying improvements that can increase attractiveness of the instance.	Section 5.1.2
5.	Factors that improve pharmaceutical market attractiveness	Both the internal and external pharmaceutical R&D market elements are analysed. This provides a holistic view of all the market forces that improve the market attractiveness.	Section 5.3.3 (Table 5.9)
6.	Factors that reduce pharmaceutical R&D market attractiveness	Similar to factors improving market attractiveness. This provides a holistic view of all the market forces that inhibit market attractiveness. By addressing these factors, market attractiveness can potentially be improved.	Section 5.3.3 (Table 5.10)
7.	Factors leading to diseases becoming more attractive	By establishing these factors, improvements can be made to current R&D environments.	Section 5.5.3 (Table 5.12)
8.	Factors leading to diseases becoming more neglected	These factors aid in establishing what factors should be addressed in order to prevent neglected status, or to improve the neglect of the disease.	Section 5.4.1.2 (Table 5.11)

As shown in Figure 8.5, the 67 system elements are categorised into ten categories. Each of these categories are described in Table 8.2. These ten categories all emerged from the 8 building blocks listed in Table 8.3.

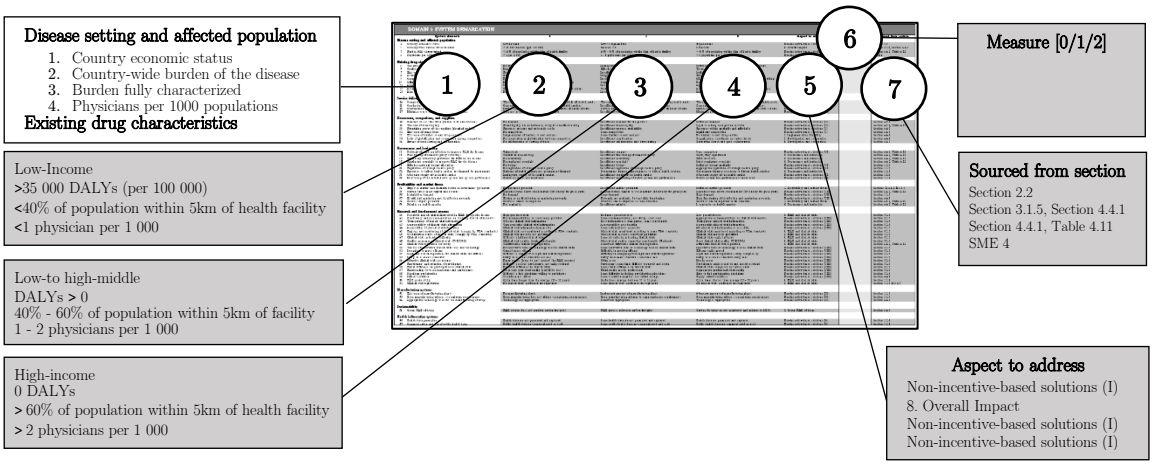
Table 8.3: Domain 1, system element categories.

	System element categories	Category description
1.	Disease setting and affected population	The characteristics of the population group affected by the disease, as well as the economic status of the country.
2.	Existing drug characteristics	The availability and characteristics of-, and the health value added by, existing drugs intended to treat the disease.
3.	Service delivery	The characteristics of both health and drug delivery systems.
4.	Consumers, competitors, and suppliers	The effect of- and roles that different stakeholders play within the pharmaceutical R&D system.
5.	Governance and leadership	The political will of government, and the adequacy of public health services.
6.	Profitability and market forces	Relates to expected/potential ROI.
7.	Research and development process	The regulations involved, including information on the nature of clinical trials.
8.	Manufacturing systems	Existing plants, appropriateness of technology, and the regulatory requirements for drug manufacturing.
9.	Sustainability	Characteristics of environmentally friendly drug R&D.
10.	Health information systems	The generation and communication of health data.

8.4.1.3. View of the system demarcation landscape

Figure 8.6 depicts the seven components of the system demarcation domain. A version of this table in which all of the detail is legible is included in Appendix G. The example highlighted in the figure relates to three system elements that fall in the 'disease setting and affected population' category. Component 2, 3, and 4 in Figure 8.6 give an example of three possible states that are defined for each system element and that are used to evaluate the status quo of the system for which a shortlisted set of incentive- and non-incentive-based interventions are to be proposed.

For example, for the 'burden fully characterized' system element (Component 1 in Figure 8.6), the 'non-ideal' state is defined as less than 40% of the population living within 5 km of a health care facility (Component 2 in Figure 8.6), while the 'ideal' state is defined as more than 60% of the population living within 5 km of a health facility (Component 4 in Figure 8.6). This system element is best addressed by a non-incentive-based mechanism (Component 5 in Figure 8.6). Information on this system element (burden fully characterized) has been sourced from Sections 5.2 and 4.2.1 (Component 7 in Figure 8.6).



Domain components	
1. System elements (67 elements)	5. Aspect to address (incentive/non-incentive)
2. 'Non-ideal' state of system elements	6. System evaluation (operationalization)
3. 'Average' or 'neutral' state of system elements	7. Section (of this dissertation) where information is sourced from
4. 'Ideal' state of system elements	

Figure 8.6: Domain 1 system demarcation layout and sub-components.

8.4.1.4. Operationalization of the system demarcation

To revise, the intention of the system demarcation is to analyze the R&D system for which an incentive intervention must be selected. The system demarcation domain encompasses 10 dimensions (derived from literature as described in Section 8.4.1.2). The dimensions sketch the status quo of the system and were identified by listing and then categorizing all the system elements (building blocks).

(i) Input of system demarcation domain

The enabler of the incentive intervention will complete the system demarcation, thereby giving a description of the status quo of the system. Each of the system elements will be ranked by the user, based on selecting the most accurate state description. Each state description is linked to a score of 0, 1 or 2 – this is hard-coded (see Section 8.5.2).

(ii) Functioning of the system demarcation domain

As mentioned, the system demarcation is carried out by the enabler stakeholder through the evaluation of the current system and rating the pharmaceutical R&D system for each of the 67 system elements on a three-tiered scale.

Reverse scoring was used to measure the level to which the investigated pharmaceutical R&D system meets the 67 system elements (2 indicates the most 'undesired state', and 0 the 'ideal typical state').

Other than in the remainder of the decision-support framework, a reverse scoring approach is used, thus an ideal state is scored 0, while a non-ideal state is scored 2. The reasoning is because, in addition to measuring the extent to which the current environment satisfies the system

elements, the score is also used as a measurement of the 'gap' between the current pharmaceutical state and the ideal typical state. Therefore, a score of 0 indicates that a negligible (or no) gap exists between the current and ideal typical state of the system element, meaning that the specific system element does not need to be addressed by a potential intervention solution, and vice versa. This measure is subsequently carried over as input for BL 1A & 1B of the decision-support framework.

Evident in the system demarcation domain, is the differentiation made between system elements that may be addressed by either incentive-based interventions or non-incentive-based interventions. The two sets of system elements are treated differently in the framework (refer to Figure 8.3 for a logical flow model of the decision-support framework variables). The system elements that may be addressed by non-incentive based interventions are provided in a list format, with a concise list of non-incentive based interventions for every system element, which is provided as part of the solution set (Domain 5). The non-incentive based interventions are ranked according to the priority assigned to the corrospending system element in Domain 1, therefore 2 (highest), 1 or 0 (lowest). No further discussions or evaluations of these system elements and interventions are included in the decision-support framework. In contrast, the system elements that may be addressed by incentive interventions are discussed in detail in subsequent sections that outline the decision-support framework domains. Refer to Section 8.5.1 for the detailed system demarcation view.

Note that although the 'aspect to address' column indicates that an incentive intervention is sufficient to address the criteria, it is not assumed that incentive interventions are the only interventions with the ability to address the specific system element.

(iii) Output of the system demarcation domain

The output of the system demarcation domain is as follows: (i) 43 system elements, that articulate the status quo of the current pharmaceutical R&D system that are addressable by non-incentive-based interventions; and determine the set of non-incentive-based interventions that are presented in Domain 5; (ii) 24 context-specific criteria (based on the 24 system elements that can be appropriately addressed by incentive interventions), that articulate the status quo of the current pharmaceutical R&D system and are used as input for BL 1A; and (iii) a measurement of the 'gap' between the instance evaluated, and the 'ideal typical' environment for both the set of 43 system elements, and the set of 24 context-specific criteria. This is also referred to as the priority rating per system element.

8.4.2. Background Logic 1A: Criteria evaluation

The BL components of the decision-support framework refer to processes that are completed based on hard-coded logic, that the user of the framework is not involved in, but as the name suggests, runs in the 'background'. Each BL component performs different functions, essential for the decision-support framework to operate.

BL 1A and 1B occur between Domains 1 and 2. The purpose of the BL 1A function is to merge the output of the system demarcation (Domain 1, this is also referred to as context-specific

criteria), as well as criteria that is suggested as being critical for the success of an incentive intervention in literature (this is also referred to as context-non-specific criteria).

The primary function that occurs in BL1A, is the scoring of the context-specific criteria (from Domain 1), and context-non-specific criteria (identified in Section 6.2), for the criteria matrix (Domain 2). The scoring method used for this framework is guided by the principles that underpin the analytic hierarchy process technique, a mathematical method used to derive ratio scales from paired comparisons.

The process for synthesizing the context-specific-, and context-non-specific-criteria into a combined list of criteria for the criteria matrix, is as follow:

(i) The evaluation in Domain 1, rates the environment under investigation as follows: the 'non-ideal' state is rated 2; the 'neutral' or 'average' state is rated 1; and the 'ideal' state is rated 0 (refer to Section 8.4.1.4 for more details on the scale used in Domain 1).

(ii) The sub-set of system elements that are addressable by incentive-based-interventions (24 of the 67 elements) is termed the *context-specific* criteria.

(iii) In addition to the 24 context-specific criteria, 22 criteria that have been identified in literature as essential to the success of any incentive intervention, regardless of context, and that can be addressed by an incentive-based intervention, are also included. This set of *context-non-specific criteria* is based on literature presented in Section 6.2. and is summarized in Table 6.2. All context-non-specific criteria are given a rating of 2. This is done to accentuate the importance of adhering to the critical success factors, as suggested by literature. Therefore, the context-non-specific criteria are viewed as critical aspects that should be addressed by the intervention solution.

Note that the criteria in Table 6.2, that is not addressable by an incentive intervention, is not included in the context-non-specific criteria list.

(iv) The context-specific, and context-non-specific criteria are subsequently combined (i.e. 40 criteria) and called the *combined list of intervention criteria* (CLIC) and is categorized into 8 categories (see Table 8.4). The categories are primarily based on the WHO Health Systems Framework shown in Figure 3.2.

The similarities between the analytic hierarchy process method, and the scoring method used for this research include: (i) both methods entail the construction of a list of criteria that needs to be fulfilled by the solution that is being investigated; (ii) both the methods make provision for sub-criteria; (iii) both methods make use of ratios to determine the ability of the solution investigated to fulfill the criteria and sub-criteria. A fundamental difference is that the scoring method used in the framework rates the criteria on the basis of the system status quo, rather than weighing the criteria against one another.

The output of BL 1A is a list of 40 criteria (i.e. CLIC) divided into 8 categories, depicted in Table 8.4, that serves as the refined input to BL 1B. Each criterion has a priority rating of 0 (lowest), 1 or 2 (highest), indicating the importance of addressing the criteria. The CLIC (i.e. BL 1A and B), together with the enabler-, innovator- and consumer- criteria (i.e. BL 2, 3, and 4) are referred to as the *decision criteria of* this framework.

Table 8.4: Combined list of intervention criteria and categories.

No	CLIC categories and criteria	No	CLIC categories and criteria
	1. Profitability and market forces		**6. Governance and leadership**
1.	Improve NPV	20.	Promote equitable health-focused governance
2.	Delink revenue from sales volume	21.	Promote transparency and accountability
3.	Improve product export potential	22.	Advances the priority of disease on health agenda
	2. Implementation feasibility and security	23.	Advance functioning of domestic policy structures
4.	Minimizes barriers to implementation	24.	Regulatory oversight to promote R&D for the disease
5.	Minimize disruptive effects to population	25.	Regulatory exclusivity provisions for R&D of disease
6.	Affordable to implement the incentive	26.	Resources to deliver health is government financed
7.	Provide R&D project insurance		**7. Rewards focus**
	3. Green and sustainability	27.	Payoff to innovators based on drug cost-effectiveness
8.	Ensure conservation of resources in R&D	28.	Reward innovation
9.	Encourage efficient innovation	29.	Financing timed across drug lifecycle
10.	Green R&D of drugs	30.	Provide long term R&D financing
	4. Population impact and Access	31.	Provide sustainable financing
11.	Potential to reduce burden of disease	32.	Provide public subsidies for clinical trials
12.	Encourage R&D of a drug/intervention		**8. Impact on R&D process and clinical trials**
13.	Improve consumer access	33.	Reduce clinical trial risk involved
14.	Enable mass drug administration	34.	Assist in registration and monitor of trials
	5. Participation and cooperation	35.	Globalize clinical trial methods
15.	Enable participation of small/medium organizations	36.	Reduce clinical trials activation difficulty
16.	Encourage large firm participation	37.	Enhance or prompt the quality of clinical trials
17.	Facilitates cooperation and synergy	38.	Assist in expensive clinical trial regulation
18.	Platform for coordinating innovators	39.	Improves R&D productivity
19.	Allow for great competition among parallel experiments	40.	Enlarge number of clinical trials registered

8.4.3. Background Logic 1B: Criteria matrix

The criteria matrix provides the user with the ability to obtain a holistic overview of a comprehensive set of available incentive interventions. The criteria matrix also provides an indication of the extent to which each incentive intervention can address the CLIC list constructed in BL 1A.

8.4.3.1. Development of the criteria matrix

Figure 8.7 depicts the development process of this BL function. As shown in the figure, three sets of input information were taken into account during the development of the criteria matrix.

Figure 8.8 depicts a breakdown of the criteria matrix components. The structure of the criteria matrix, is as follows: each row represents one of the 26 incentive types (Component 1 in Figure 8.8 and each column represents one of the 40 criteria from the CLIC list (Component 2 in Figure 8.8), sourced from the BL 1A process. The 26 incentive intervention types were identified in the structured literature review, presented in the previous chapter, which aimed to identify all the existing types of incentive to encourage R&D in NDs. As discussed previously, these 26 incentive intervention types can be divided into three primary incentive strategies, namely: (i) push; (ii) pull (including outcome-based pull and lego-regulatory pull); and (iii) hybrid.

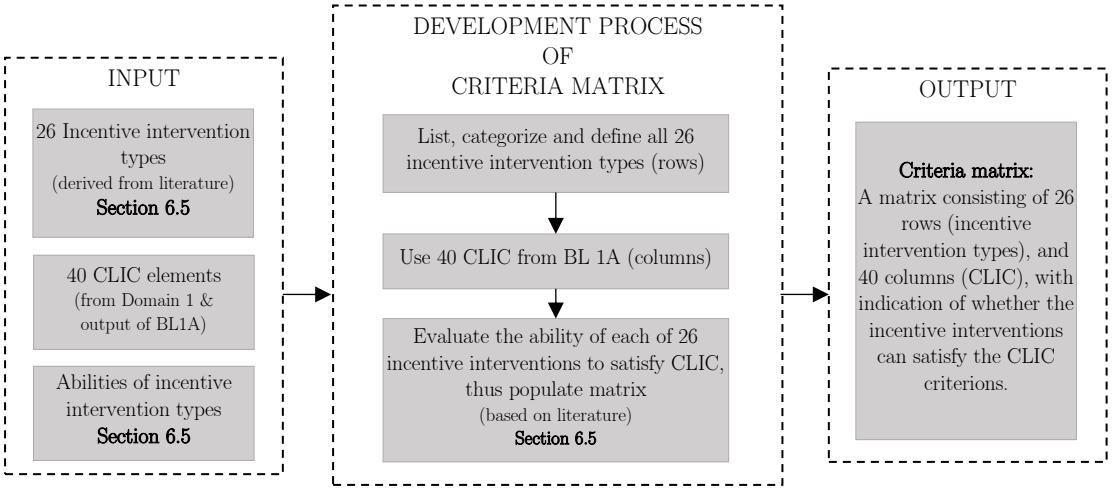
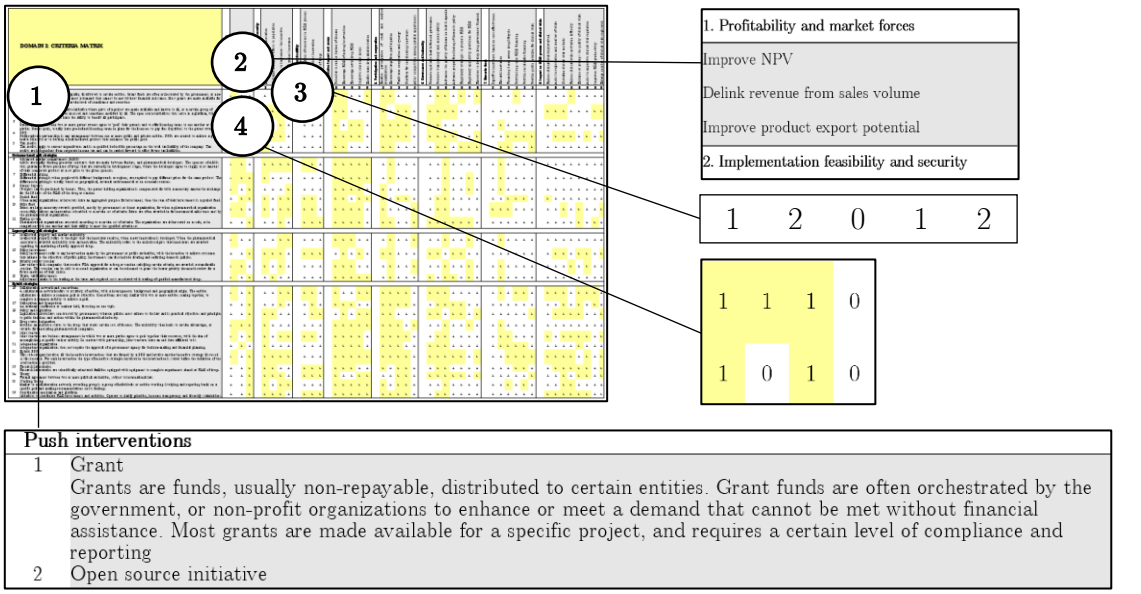


Figure 8.7: Development process of criteria matrix.

The priority rating of each criteria (Component 3 in Figure 8.8), an outcome of BL1A, is indicated. Finally, the indication of the extent to which each incentive intervention type can address the CLIC (Component 4 in Figure 8.8) is hardcoded and has been derived based on information on the various incentive interventions that is provided in literature. Two values are used to indicate whether an incentive intervention is able to address a criterion, namely: 0, when the incentive intervention cannot address the criterion, and 1 when the criterion can be addressed by the incentive intervention.



Domain components	
1. 26 Incentive intervention types	3. Rating for each CLIC
2. CLIC list (40, divided into 8 categories)	4. Incentive ability to address CLIC

Figure 8.8: Criteria matrix domain components.

8.4.3.2. Operationalization of the criteria matrix

In summary, the criteria matrix provides an overview of the incentive interventions and CLIC that each intervention fulfills.

(i) Input of the criteria matrix

No stakeholder input is required for the criteria matrix domain. As mentioned in Section 8.4.3.1, the input used for the criteria matrix consists of the 26 incentive intervention types (sourced from Section 6.5), as well as the 40 CLIC (derived from Domain 1 and further interpreted in BL 1A).

(ii) Functioning of the criteria matrix

The criteria matrix does not have to be completed by the enabler but is rather a tool used to evaluate the incentive types based on their ability to satisfy the CLIC. The CLIC are categorized into eight categories, covering the most salient areas that incentive interventions can positively impact in the pharmaceutical R&D system (Table 8.4). These eight categories are referred to as focus areas and depend on the combination of CLIC criteria satisfied. These focus areas also articulate the primary intent that the solution set of the decision-support framework will advise.

(iii) Output of the criteria matrix

The criteria matrix output is a binary indication of the ability of incentives to satisfy the CLIC. This serves as input to BL 5, which will be used to calculate the cluster-scores per incentive intervention type. This, in turn, serves as input for the final solution set.

8.4.4. Domain 2: Enabler profile

The stakeholder profiles, as previously mentioned, consists of 3 stakeholders, the enabler (Domain 2), innovator (Domain 3) and consumer (Domain 4). Each of the stakeholder profiles consists of an inquiry form, with the corresponding stakeholder matrix depicted by the BL functions. The development of the enabler inquiry form is described in this section.

8.4.4.1. Development of the enabler inquiry form

The enabler stakeholder refers to the organization or entity aiming to incentivize a pharmaceutical innovator to devote resources to R&D in a desired field. The enabler has the ability to either (i) empower the innovator to innovate, by providing some or other resource; or to (ii) encourage the innovator to innovate by offering some kind of (potential) benefit. What is important to consider in the profile of the enabling body, is the ability or desire that the entity has to either empower or encourage R&D. Furthermore, it is important to ascertain what the enabling body hopes to achieve through the incentive mechanism. In this research, the aforementioned is achieved by investigating both the objectives and the internal capabilities that the enabling body might have.

As discussed in Section 7.2, characteristic that describe the objective(s) that an enabler may be pursuing as well as relevant aspects of enabler's internal capabilities were inductively derived from the structured literature review that identified incentive interventions for drug R&D. Five characteristics that describe the objective, and four internal capabilities (summarized in Tables 7.1 and 7.3), were identified. The objectives and internal capabilities, as listed in the enabler

inquiry form, are referred to as the *enabler criteria*. The development of the enabler inquiry form is depicted in Figure 8.9.

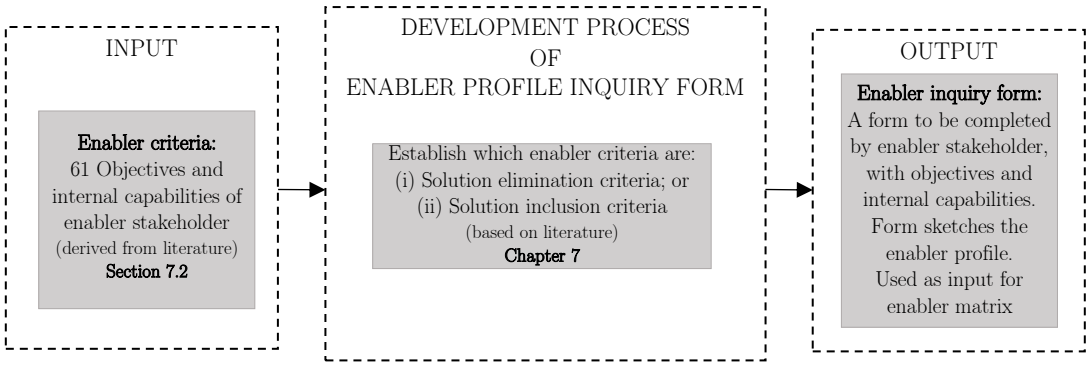


Figure 8.9: Development of enabler inquiry form.

8.4.4.2. Operationalization of the enabler inquiry form

In summary, the enabler profile is used to develop an understanding of the enabler stakeholder's objective in initiating an incentive intervention, as well as their internal abilities in terms of supporting such an incentive intervention.

(i) Input of the enabler profile

The input required for the enabler profile is the feedback from the enabler stakeholder, in terms of their internal capabilities, needs and objectives. The stakeholder is required to complete the inquiry form, that is predefined with a short list of objectives and internal capabilities. The stakeholder should select all the criteria applicable to them in the inquiry form rather than selecting only one criterion per category.

(ii) Functioning of the enabler profile

Each enabler criterion is rated by the enabler stakeholder according to its priority (on a scale from 0 (unimportant) to 2 (high priority). More than one criterion can be selected as high priority per criteria category.

It is foreseen that in some scenarios, more than one enabler stakeholder might be present (e.g. two private pharmaceutical companies aim to initiate an incentive intervention). In such cases, each enabler is required to complete a separate enabler profile. In the aforementioned case, the feasible set of incentive interventions suggested as the solution set, will either be: (i) calculated by using a weighted average per enabler of the decision-criteria completed, with the weights per enabler stakeholder defined by the primary enabler stakeholder/ stakeholders involved; or (ii) in the case where weights cannot be assigned to the respective enabler stakeholders, a single solution set will be determined, assigning the highest priority rating (rated by any of the enabler stakeholders) to the specific enabler criterion. This second option ensures that, in cases where an enabler weighting cannot be provided, all enabler criteria that are prioritized by any of the enabler stakeholders are included. The incorporation of the multiple enabler stakeholder profiles is further discussed in BL 5 and Domain 5.

(iii) Output of the enabler profile

The output of the enabler profile is the completed inquiry form of internal capabilities and objectives which serve as input for the enabler criteria matrix.

8.4.5. Background Logic 2: Enabler matrix

The enabler matrix does not have to be completed by the enabler but is rather a hardcoded tool used to evaluate the incentive types based on their ability to satisfy the enabler criteria. The development process of the enabler matrix is depicted in Figure 8.10.

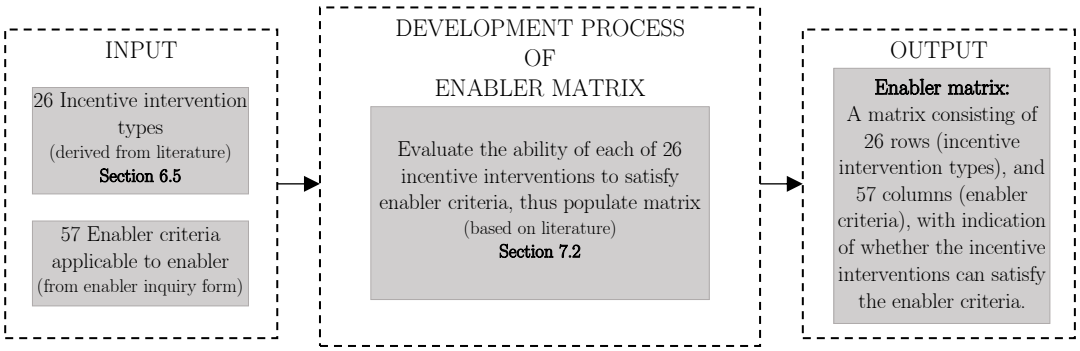
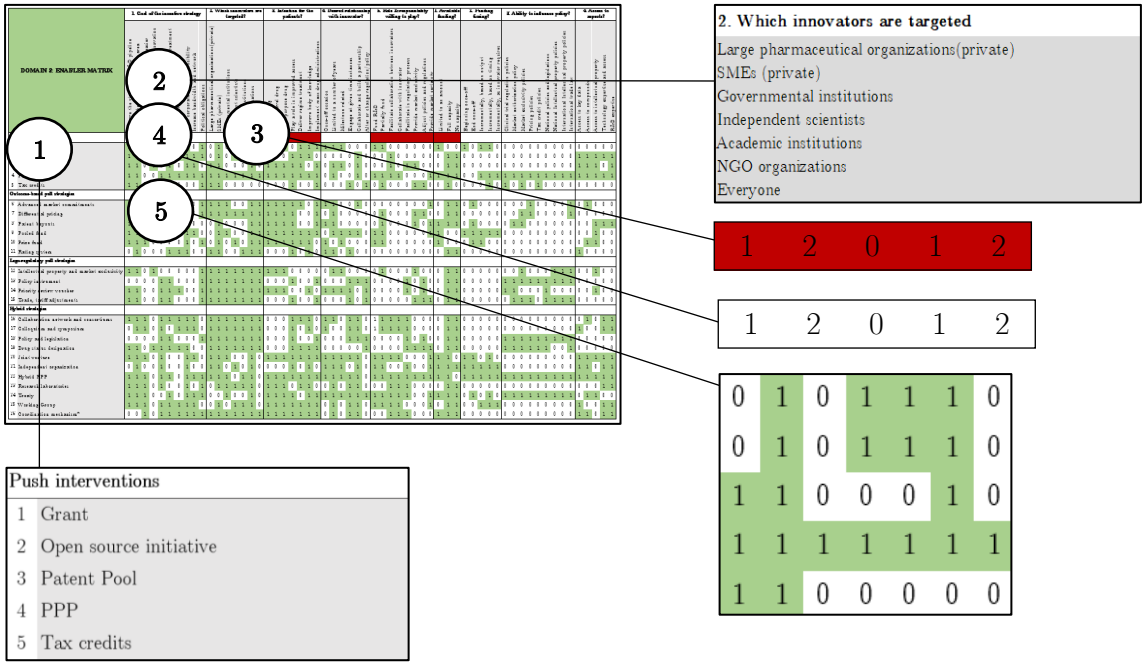


Figure 8.10: Development of enabler matrix.

As shown in Figure 8.10, two sets of input information were used for the development of the enabler matrix. Figure 8.11 depicts a breakdown of the enabler matrix components. The structure of the matrix is as follows: each row represents one of the 26 incentive types (Component 1 in Figure 8.11); and each column represents one of the enabler objectives, or internal capabilities (Component 2 in Figure 8.11, 57 enabler criteria). The priority rating assigned to each criterion by the enabler stakeholder(s) is depicted (Components 3 and 4 in Figure 8.11). To provide an additional visual aid, the exclusion criteria is shaded in dark red in the matrix (while the inclusion criteria is white). Similar to the criteria matrix in Domain 2, this matrix contains hard-coded information indicating the ability of each incentive intervention type to satisfy each enabler criteria rated on a binary scale, represented with either a 0 or a 1 (Component 5 in Figure 8.11).

It should be noted that incentives not satisfying any of the exclusion criteria in one criteria category, are categorized as infeasible, whereas, if inclusion criteria are not met, the incentive intervention is not deemed an infeasible incentive (but it will receive a lower score in the final framework output, based on the enabler profile preferences).



Domain components	
1. Incentive interventions	4. Inclusion criteria priority from enabler inquiry form
2. Enabler criteria	5. Incentive's ability to address enabler criteria
3. Exclusion criteria priority from enable inquiry form	

Figure 8.11: Enabler matrix and component breakdown.

Note that the exclusion and inclusion criteria rating (#3 and #4 in Figure 8.11) is not the same as the binary ability of the incentive to satisfy the enabler criteria (#5 in Figure 8.11), this might be easily confused to have the same meaning.

The output of BL2 is the enabler matrix indicating the ability of the 26 incentives to satisfy the enabler criteria. This serves as input, together with other decision-criteria, to determine the cluster-score per incentive intervention (BL 5), which is further used to determine the final incentive-based solution set (Domain 5).

8.4.6. Domain 3: Innovator profile

The innovator stakeholder refers to the organization or entity to be incentivized to perform R&D in a desired field. The innovator stakeholder will be either empowered or encouraged to perform R&D by being provided with or offered some kind of benefit.

8.4.6.1. Development of the innovator inquiry form

The requirements and organizational capabilities of the innovator stakeholder(s) must be properly investigated to ensure that the incentive intervention aligns not only with the goals and objectives

of the enabler, but is also successful in satisfying the objectives and limitations of the innovator, to ultimately be successful in incentivizing ND drug R&D.

Similar to the objectives and internal capabilities of the enabler profile, the characteristics of the innovator profile were derived from the structured literature review conducted to identify the existing incentive interventions to encourage drug R&D for NDs. The objectives and internal capabilities of the innovator profile are summarized in Tables 7.6 and 7.8. These innovator characteristics should be considered when a suitable incentive intervention is selected, as the incentive intervention will only be successful if it satisfies the identified needs of the innovator stakeholder(s) that needs to perform R&D for the desired disease. The objectives and requirements of the innovator stakeholder are referred to as the *innovator criteria*.

The development of the innovator inquiry form is depicted in Figure 8.12.

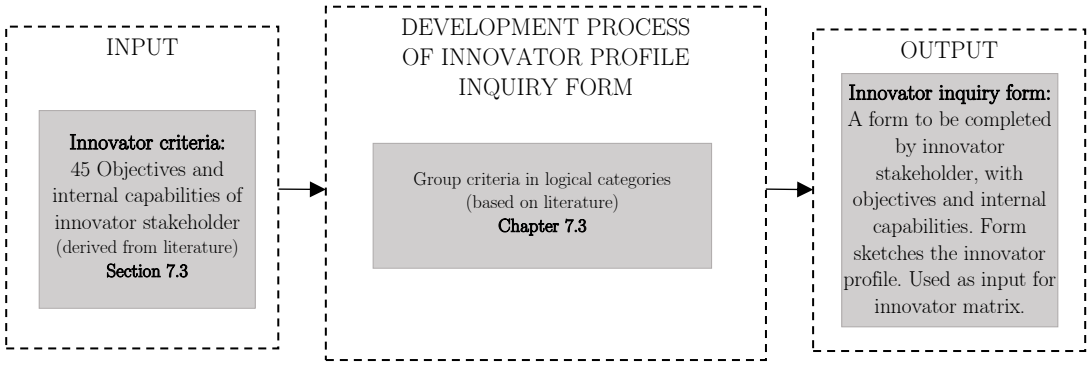


Figure 8.12: Development of innovator inquiry form.

The innovator inquiry form, in contrast to the enabler inquiry form, does not have exclusion and inclusion criteria. The logic that underpins this is discussed in Sections 8.3 and Section 8.4.4.

8.4.6.2. Operationalization of the innovator inquiry form

In summary, the innovator inquiry form is used to gather information on the objectives and internal capabilities of innovator(s) that the enabler(s) seeks to target with the incentive intervention.

(i) Input of the innovator profile

The innovator profile uses the input from the innovator stakeholder(s), provided via the 'innovator inquiry form', to obtain information on the objectives and capabilities of the innovator stakeholder(s). Similar to the 'enabler inquiry form', all the applicable criteria should be selected, rather than only one criterion per category.

(iv) Functioning of the innovator profile

The innovator inquiry form must be completed by the innovator stakeholder. Completion of the form comprises assigning a priority rating of either 2 (high priority, i.e. important), 1 (relevant), or 0 (not relevant/applicable) to each of the innovator criteria.

Again, similar to the enabler inquiry forms in Domain 2, an innovator inquiry form should be completed by every innovator stakeholder involved in the specific R&D scenario. A single solution set will be constructed by assigning the highest priority rating per innovator criteria (assigned by any of the innovators involved). The case of multiple innovator profiles will be further discussed in BL 5 and Domain 5.

(v) Output of the innovator profile

The output of the innovator profile is the completed inquiry form of innovator criteria which serves as input for the innovator matrix.

8.4.7. Background Logic 3: Innovator matrix

The innovator matrix is a hardcoded tool, indicating each incentive intervention's ability to satisfy the innovator criteria. The development process of the innovator matrix is depicted in Figure 8.13.

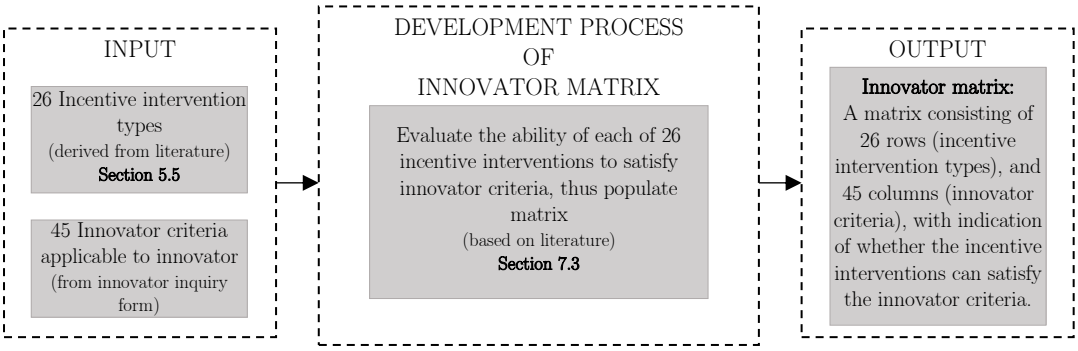
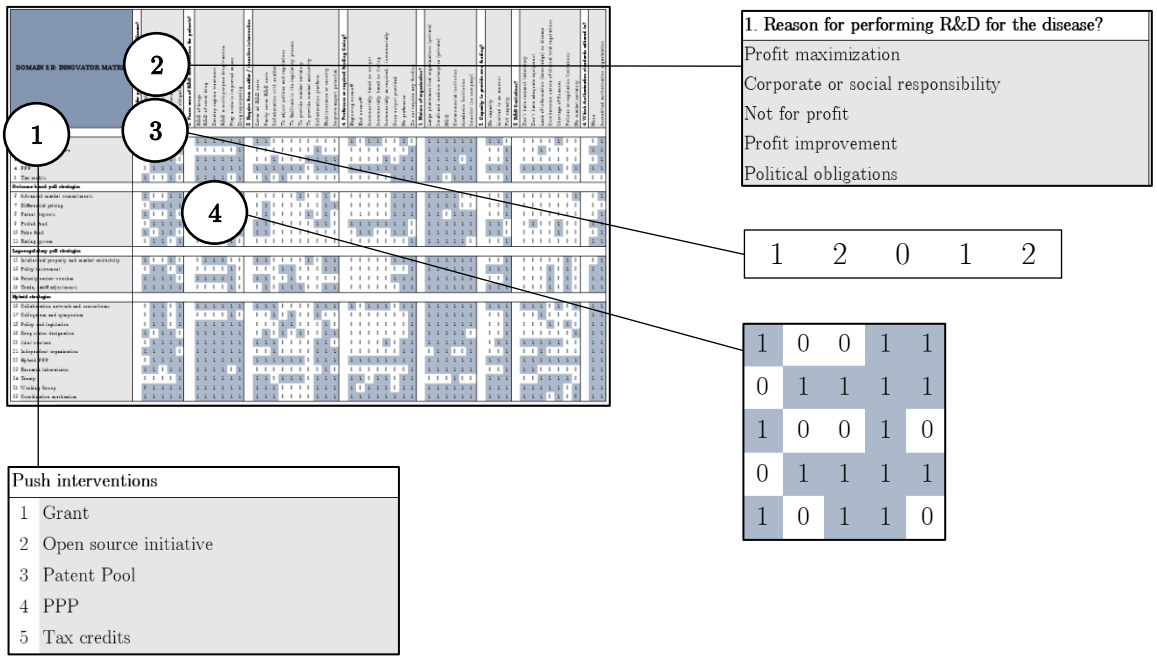


Figure 8.13: Development of innovator matrix.

Similar to the enabler matrix, two sets of input information were used for the development of the innovator matrix. Figure 8.14 depicts a breakdown of the innovator matrix components; this structure is similar to that of the enabler matrix which was previously described. The structure of the matrix is as follows: each row represents one of the 26 incentive types (Component 1 in Figure 8.14; this is the same set of rows as the ones in the criteria and enabler matrices); and each column represents one of the innovator objectives, or capabilities (Component 2 in Figure 8.14; 45 innovator criteria, sourced from the innovator inquiry form). The priority rating of each criteria is indicated (Component 3 in Figure 8.14). Finally, this matrix again contains hard-coded information indicating the ability of each incentive intervention type to satisfy each innovator criteria, rated on a binary scale, represented with either a 0 or a 1 (Component 4 in Figure 8.14).



Domain components	
1. Incentive intervention types	3. Criteria's priority from innovator inquiry form
2. Innovator criteria	4. Incentive's ability to address innovator criteria

Figure 8.14: Innovator matrix and component breakdown.

8.4.8. Domain 4: Consumer profile

The consumer profile refers to the intended end-user or the procurer of the drug. As described in Section 7.5, for the purpose of this study the end-consumers are divided into two groups, namely patients and procurers. The patients being the end-consumers of the drugs, and the procurers consisting of three sub-divisions namely (i) public procurers (governments and/or central medical stores); (ii) private for-profit procurers (insurers and local wholesalers); and (iii) private not-for-profit organizations (donors and all NGO agencies).

8.4.8.1. Development of the consumer inquiry form

The consumer profile consists of the requirements and needs of the consumer that are deemed to play a role in determining the feasibility / appropriateness of an incentive intervention for drug R&D. Similar to the approach followed for the other two stakeholder profiles, an inquiry form is utilized to gather information which is then converted into the consumer criteria matrix by BL.

A set of characteristics that describe the relevant requirements of the consumer, were derived from the structured literature review that identified incentive interventions for ND drug R&D (Section 6.5.5), as well as from the contextualization of health care systems in Section 3.4. The relevant set of characteristics are listed in Table 7.5. Two primary differences between the consumer stakeholder and the other two stakeholder profiles are that firstly, it is expected that the consumer will not complete the inquiry form but rather that the enabler stakeholder will complete the inquiry form on behalf of the consumer. Secondly, the consumer profile consists not

only of one entity but can consist of two primary consumers, namely the patients and/or drug procurers.

The set of characteristics that describe the relevant consumer requirements, listed in the 'consumer inquiry form', are referred to as *consumer criteria*. The development of the consumer inquiry form followed a similar process to that of the enabler- and innovator inquiry forms and is depicted in Figure 8.15.

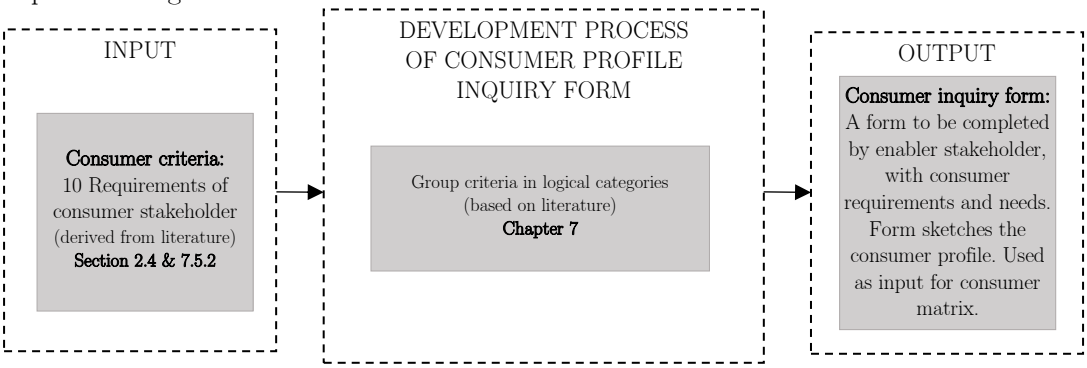


Figure 8.15: Development process of the consumer inquiry form.

8.4.8.2. Operationalization of the consumer profile

As mentioned, the consumer profile, in contrast with the innovator and the enabler profiles, does not use the input from the consumer profile directly. Instead, the enabler stakeholder completes this profile, based on research and possible engagements with the consumers and/or procurers of the drugs. Similar to both the enabler- and innovator inquiry forms, completion of the inquiry forms involves providing a priority rating for each of the pre-defined consumer criteria, with the prioritization being on a scale from 2 (high priority, i.e. important), 1 (relevant), or 0 (not relevant/applicable).

(i) Functioning of the consumer profile

The consumer profile, other than the enabler and innovator profiles, consist of more than one end-consumer with the profile incorporating both patients and procurers. Consequently, the profile allows for the requirements of more than one consumer to be incorporated into the decision-support framework. It is therefore not needed for more than one consumer profile to be completed, except for the case where more than one consumer stakeholder of one type is present, subsequently two or more consumer profiles can be completed. The multiple consumer profiles will be incorporated into the framework by assigning the highest priority rating (given by any of the consumer respondents) per consumer criterion, resulting in a single priority rating per consumer criterion.

(ii) Output of the consumer profile

The output of the consumer profile is the completed consumer inquiry form of consumer criteria that serves as input for the consumer matrix. The consumer matrix indicates the ability of the incentive types to satisfy the consumer criteria (similar to the enabler and innovator stakeholder matrices).

8.4.9. Background Logic 4: Consumer matrix

The consumer matrix is, again, a hardcoded tool with consumer criteria and the incentive intervention types as input, showing the incentive intervention's ability to satisfy the consumer criteria. The development process of the consumer matrix is depicted in Figure 8.16.

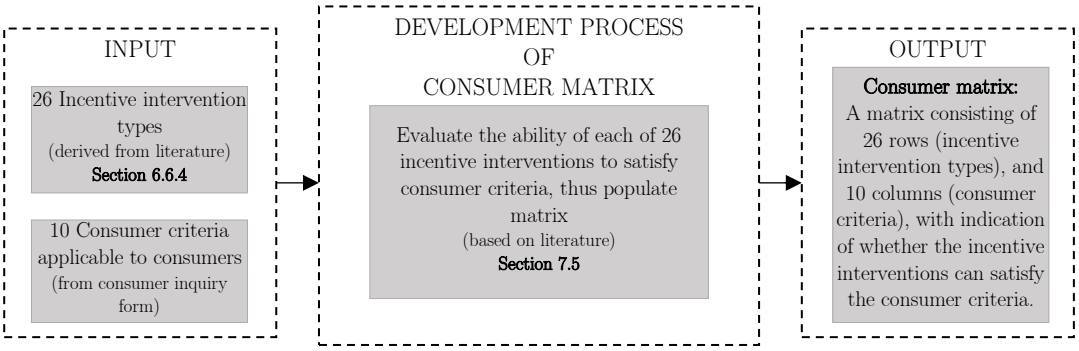
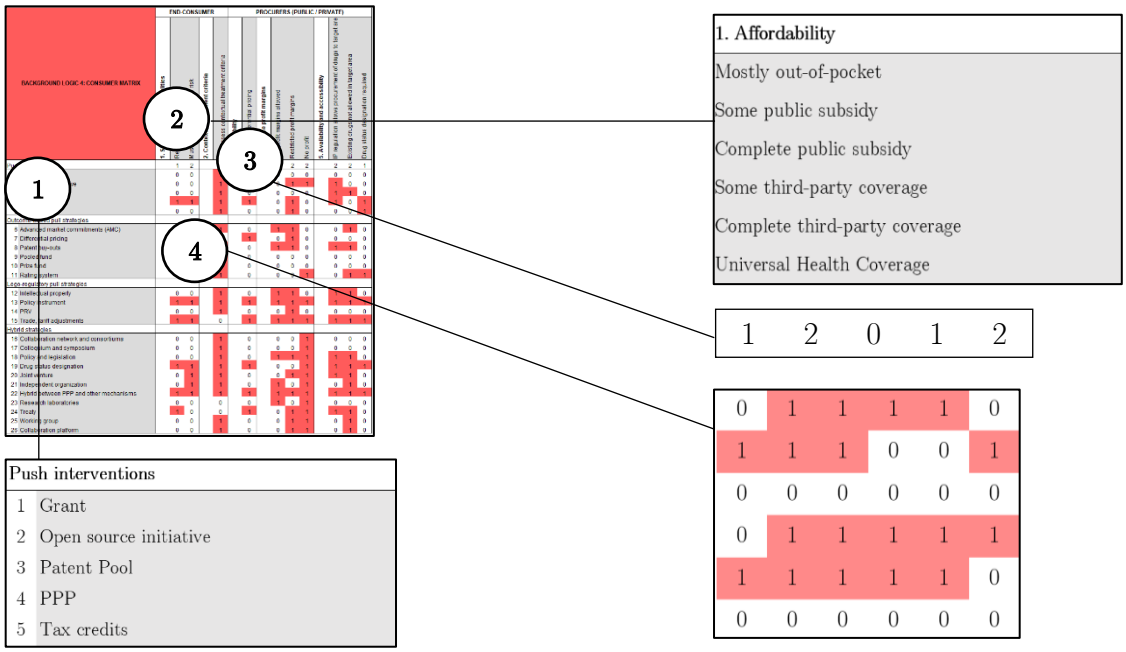


Figure 8.16: Development of consumer matrix.

Figure 8.17 depicts a breakdown of the consumer matrix components. The matrix has a similar structure to the enabler- and innovator matrices, with 26 rows (incentive types, Component 1 in Figure 8.17), and 10 columns (consumer criteria sourced from the consumer inquiry form Component 2 in Figure 8.17). The priority rating of each criteria is indicated (Component 3 in Figure 8.17).



Domain components	
1. Incentive intervention types	3. Consumer criteria relevant from inquiry form
2. Consumer criteria	4. Incentive ability to address consumer criteria

Figure 8.17: Consumer matrix breakdown and components.

The consumer matrix also contains hard-coded information indicating the ability of each incentive intervention type to satisfy each consumer criteria (rated on a binary scale, represented with either a 0 or a 1).

8.4.10. Background Logic 5: Cluster scoring

BL 5 performs the categorization and evaluation of the incentive interventions to address all the decision criteria. As discussed in the introductory sections of this chapter, the final results of the framework are presented on the basis of the performance of the various incentive mechanisms in terms of 12 criteria clusters. The development of the criteria clusters is described, followed by a description of the cluster scoring.

8.4.10.1. Criteria cluster development and descriptions

As summarized in Table 8.5, the framework utilizes a large amount of decision criteria (input variables), namely a rating on a scale of 0 - 2 for each of the following: the 67 system elements of Domain 1; 57 enabler criteria from Domain 2; 45 innovator criteria from Domain 3; and 10 consumer criteria from Domain 4. Several of these criteria address the same theme, for example the enabler criteria "provide market exclusivity to innovator stakeholder" and the innovator criteria "require market exclusivity from enabler stakeholder", both address the question of overcoming profitability and market force barriers. In order to reduce the complexity of the output of the framework, the large number of input variables are therefore organized into criteria clusters, and a score per criteria cluster, rather than for each individual variable is reported.

Table 8.5: Complete set of decision criteria (i.e. input variables).

	Decision criteria set	Description of decision criteria set	Reference
1.	The CLIC (combined list of intervention criteria and categories)	The combined list of context-specific and non-specific criteria from Domain 1, the system demarcation	Table 8.4
2.	Enabler criteria	The requirements and internal capabilities of the enabler stakeholder / stakeholders from Domain 2, the enabler inquiry form	Tables 7.2, 7.3 7.4 and 7.5.
3.	Innovator criteria	The requirements and internal capabilities of the innovator stakeholder/ stakeholders from Domain 3, the innovator inquiry form	Tables 7.6, 7.7, 7.8 and 7.9
4.	Consumer criteria	The requirements of the consumer stakeholders from Domain 4, the consumer inquiry form	Table 7.10

The set of criteria clusters are derived by evaluating all the decision criteria incorporated in the decision-support framework, and subsequently categorizing the decision criteria according to its function and definition. Thus, the 12 criteria clusters, described in Table 8.6, are inductively derived from the four sets of decision criteria listed in Table 8.5.

Table 8.6: Description of the 12 criteria clusters.

	Criteria cluster	Description of criteria cluster
1.	Profitability and market forces	The ability of the incentive to overcome profitability and market force barriers, and to provide a means to the innovator stakeholders to achieve a profit in the performed R&D.
2.	Facilitate registration of drug/approval for use	The ability of the incentive intervention to provide innovators with some means to assist in the approval or registration of the developed intervention.
3.	Ability of the incentive to accommodate different R&D initiatives	The incentive intervention allows and assists innovators to perform various R&D interventions, not placing confinements on certain innovations and types of R&D.
4.	Improved governance	Describes the ability of the incentive interventions to promote and advance transparency, accountability and equity in R&D, and ensuring that the policies that are in place are enforced.
5.	Population impact and access	The incentive has the ability to allow the end-consumer or population to have improved access to the developed innovations, therefore having a high impact on the end-consumer instead of merely the body of NTD knowledge.
6.	Enabler resource investment	The ability of the enabler stakeholder to provide various types and quantities of resources for the R&D that will be performed by the innovator stakeholders.
7.	Encourage competition in the innovation process	The incentive's ability to incorporate various types of innovator stakeholders, and to encourage R&D through some form of competition or rivalry.
8.	Overcome barriers to innovator participation in R&D process	The ability of the incentive interventions to facilitate innovator stakeholders to participate and contribute in the R&D of interventions against NTD's.
9.	Facilitate clinical trials	The ability of the incentive interventions to reduce the difficulty and risk involved in clinical trials and enhance the innovators ability to succeed in the taxing clinical trials.
10.	Facilitate/ improve R&D-process and body of knowledge	The incentive intervention focuses on improving the body of knowledge and process, instead of focusing on the delivery of a physical intervention.
11.	Facilitate collaboration during R&D	The incentive promotes the collaboration and engagement of more than one stakeholder to perform or enable R&D for NTD's.
12.	Altruistic /political motivations	The ability of the incentive intervention to accommodate altruistic motivations that the stakeholders participating in the R&D might have.

8.4.10.2. Operationalization of BL 5

The aim of the BL 5 function is firstly to categorize all the decision criteria from BL 1B, 2, 3 and 4 into clusters that represent all the subject areas considered in the framework that influence the selection of an appropriate incentive intervention. The criteria clusters contain sub-clusters of criteria which are grouped together based on similarity, and therefore act as one criterion with a maximum priority-rating of 2, with the priority allocated to the sub-cluster being the highest priority rating of a criteria in that specific sub-cluster (the 12 criteria clusters are summarised in Table 8.6, a list detailing all of the sub-clusters and individual criteria, is included in Appendix H).

Secondly, BL5 combines the binary-rated abilities of the incentives to address all the decision-criteria and the priority ratings per decision criteria (from BL 1B, 2, 3 and 4) into a score that measures the extent to which each incentive type satisfies each of the 12 criteria clusters. This

score is referred to as the *cluster-scores*. As highlighted in Sections 8.1 and 8.2, the framework output includes an indication of the degree to which each incentive intervention addresses the criteria clusters (multiple-criteria decision) but it does not include an overall feasibility score for each incentive, due to the risk of misinterpretation. The output enables the decision-maker to evaluate the different incentives' relative strengths and weaknesses in terms of the different criteria clusters. Refer to Appendix G for an overview of BL 5.

The 12 cluster-scores per incentive intervention are calculated by taking the sum product of the incentive's ability to address all the decision criteria in that cluster (binary ability rating hard-coded in the matrices produced by BL 1B, 2, 3 and 4), and the decision criteria priority rating (0, 1 or 2, as provided by the relevant stakeholders in Domains 1 to 4 and summarised in the matrices produced by BL 1B, 2, 3 and 4), and dividing this number by the sum of the priority rating per criteria cluster, for every incentive (j). The cluster-score for each incentive intervention per cluster is calculated as depicted in Equation 1:

$$Cluster\ score\ (per\ incentive\ j) = \frac{\sum_{i=1}^{n}(x_j^i * y^i)}{\sum_{i=1}^{n} y^i}, for\ j = [1,26] \quad (1)$$

Where i refers to the criteria in the cluster (columns of matrices produced by BL 1B, 2, 3 and 4), and j refers to the 26 incentive intervention types (rows of the matrices produced by BL 1B, 2, 3 and 4); x refers to the rating of the incentive intervention's ability to satisfy the criterion (hard-coded content in the matrices produced by BL 1B, 2, 3 and 4); y refers to the priority rating of the criterion (column sub-headings in the matrices produced by BL 1B, 2, 3 and 4); and n refers to the number of criteria in the respective criteria cluster.

The priority rating of the decision criteria is sourced from the respective BL functions. In the case where more than one enabler, innovator or consumer stakeholder is present, the highest priority rating (i.e. 2) assigned by any of the stakeholders for the specific criterion will be assigned. Unless, in the case of multiple enabler stakeholders, where the additional option to apply a weighting to the enablers' objectives and capabilities exists.

The output of BL 5 is firstly, the list of 26 incentive intervention types with a cluster-score for each of the 12 criteria clusters, indicating the extent to which each incentive satisfies each criteria cluster. A ranking logic determines the order in which incentives are listed in the output generated by the framework. This ranking is based on the overall relative performance of the incentives, per criteria cluster. More specifically: For each criteria cluster, the incentives that fall in the top quartile in that cluster (based on the cluster-score achieved by each incentive) are awarded a count of 1. For each incentive, these counts are subsequently summed across the 12 criteria clusters, and the incentives are ranked according to these total counts. Thus, the highest ranked incentive will be the one that most frequently achieved a cluster-score that fell in the top-quartile.

The aforementioned approach is preferred to simply using the sum of the criteria-cluster scores for each incentive as the basis for ranking a number of reasons, set out here. A general perspective that is employed in this research, is the importance of a holistic approach. In line with such a

holistic perspective, the ranking approach that is employed gives precedence to incentive interventions that perform relatively strongly in terms of a larger number of different criteria clusters, rather than to incentive interventions that may perform particularly strongly in only a small number of criteria clusters while performing poorly in the remaining majority of criteria clusters. Throughout the framework, qualitative information is translated to quantitative information in order to facilitate a process of synthesizing a significant amount of information into outcomes that can effectively support decision-making. An aggregated, quantitative, representation of a large amount of qualitative information is, necessarily, crude at least to some extent.

Furthermore, the score for each criteria cluster is normalized to facilitate the construction of heatmaps and spider diagrams, this normalization further contributes to somewhat crude quantitative results. Given that these scores are somewhat crude, it is preferable not to base the ranking of incentives on the sum of the criteria-cluster scores in cases where there may be a relatively small difference in this sum between different incentives. An awareness of the somewhat crude nature of quantitative scores generated based on qualitative information also influenced the decision to not display numeric cluster-scores as part of the final output of the framework.

8.4.11. Domain 5: Solution set

The solution set domain consists of two sets of solutions, namely the incentive-based solutions, and non-incentive-based solutions. The development and operationalization of both will be described in the section that follows.

8.4.11.1. Development of the solution set

This domain involves utilizing the data that was gathered throughout the framework and compiling a final set of feasible solutions for the decision-maker to consider for encouraging R&D for the specific neglected disease. This domain consists of two sets of solutions, namely a set of (i) incentive-based interventions, and (ii) a set of non-incentive-based interventions. Figure 8.18 depicts the development process of the solution set.

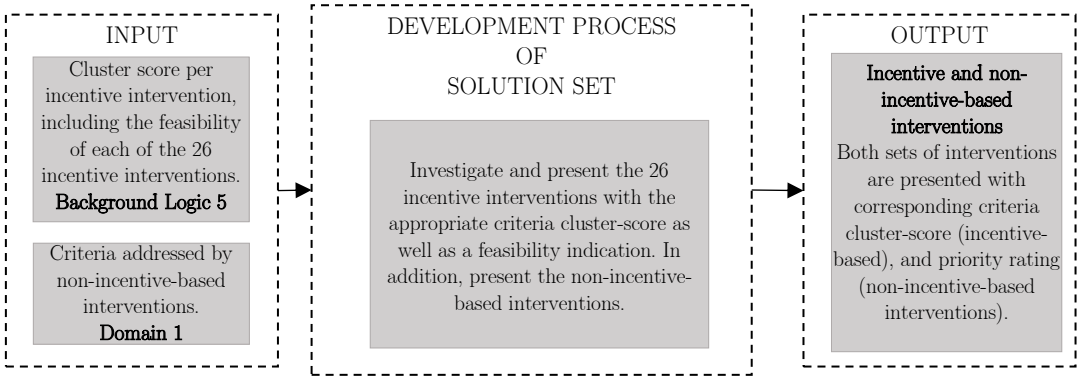


Figure 8.18: Development of the solution set.

8.4.11.2. Operationalization of the solution set domain

As mentioned, Domain 5 displays the final solution set.

(i) Input of the solution set domain

The solution set domain does not require any stakeholder input, as this is the presentation of the suggestions and derivations made by the decision-support framework. The input used to generate the solution set is sourced from the entire framework, more specifically the:

- system demarcation evaluation (provided by the enabler stakeholder in Domain 1);
- hard-coded binary evaluations of the context-specific- and context-non-specific criteria, per incentive intervention (BL 1AB);
- prioritized enabler criteria, with inclusion and exclusion criteria (provided by the enabler stakeholder in Domain 2);
- hard-coded binary evaluations of the enabler criteria, per incentive intervention (BL 2);
- prioritized innovator criteria (provided by innovator stakeholder in Domain 3); (vi) hard-coded binary evaluations of the innovator criteria, per incentive intervention (BL 3);
- prioritized consumer criteria (provided by the enabler stakeholder in Domain 4);
- hard-coded binary evaluations of the consumer criteria, per incentive intervention (BL 4); and
- evaluation of all decision criteria per criteria cluster (BL 5); and
- criteria cluster-score per criteria cluster per incentive intervention (BL 5).

(ii) Functioning of the solution set domain

The solution set domain provides the stakeholders with a tangible set of outputs. The stakeholders, in contrast to the other four domains, do not have to provide any input, however, the results need to be updated by 'pressing' a button in the MS Excel workbook (refer to Section 8.5.6 for a view of the solution set transfer media).

The solution set domain consequently interprets the ten sets of data inputs (listed above), and synthesizes and presents the outputs in readable format. The evaluation process of all the input data is processed in the background (hard-coded), without the knowledge of the user.

The scoring and prioritization of incentive-based interventions is as described in BL5. As previously mentioned, in the case where more than one stakeholder of a type exists, the priority-rating per criterion of the specific stakeholder group is replaced by the highest priority rating assigned by any of the stakeholders of one type for each criterion, with the exception of the enabler stakeholder that has the option of assigning a weight per enabler stakeholder, by which the priority rating will be a weighted average.

In the case of non-incentive-based interventions, the system element rating (on a scale of $0 - 2$), per system element that cannot be addressed by an incentive intervention, as derived from Domain 1, is assigned to the corresponding non-incentive-based interventions that aims to address that system element. The non-incentive-based interventions that are considered in the framework cover nine of the ten system element categories, described in Table 8.2. The only category not

included in the non-incentive-based interventions is the sustainability system element category, as all the criteria that relate to this category are addressed exclusively by incentive-based interventions.

(iii) Output of the solution set domain

The output of the solution set domain is split into incentive-based interventions and non-incentive-based interventions. Together these provide the stakeholders with information on a range of feasible options to pursue in order to encourage R&D for the neglected disease(s) being considered. Figure 8.19 depicts the layout of the feasible incentive interventions.

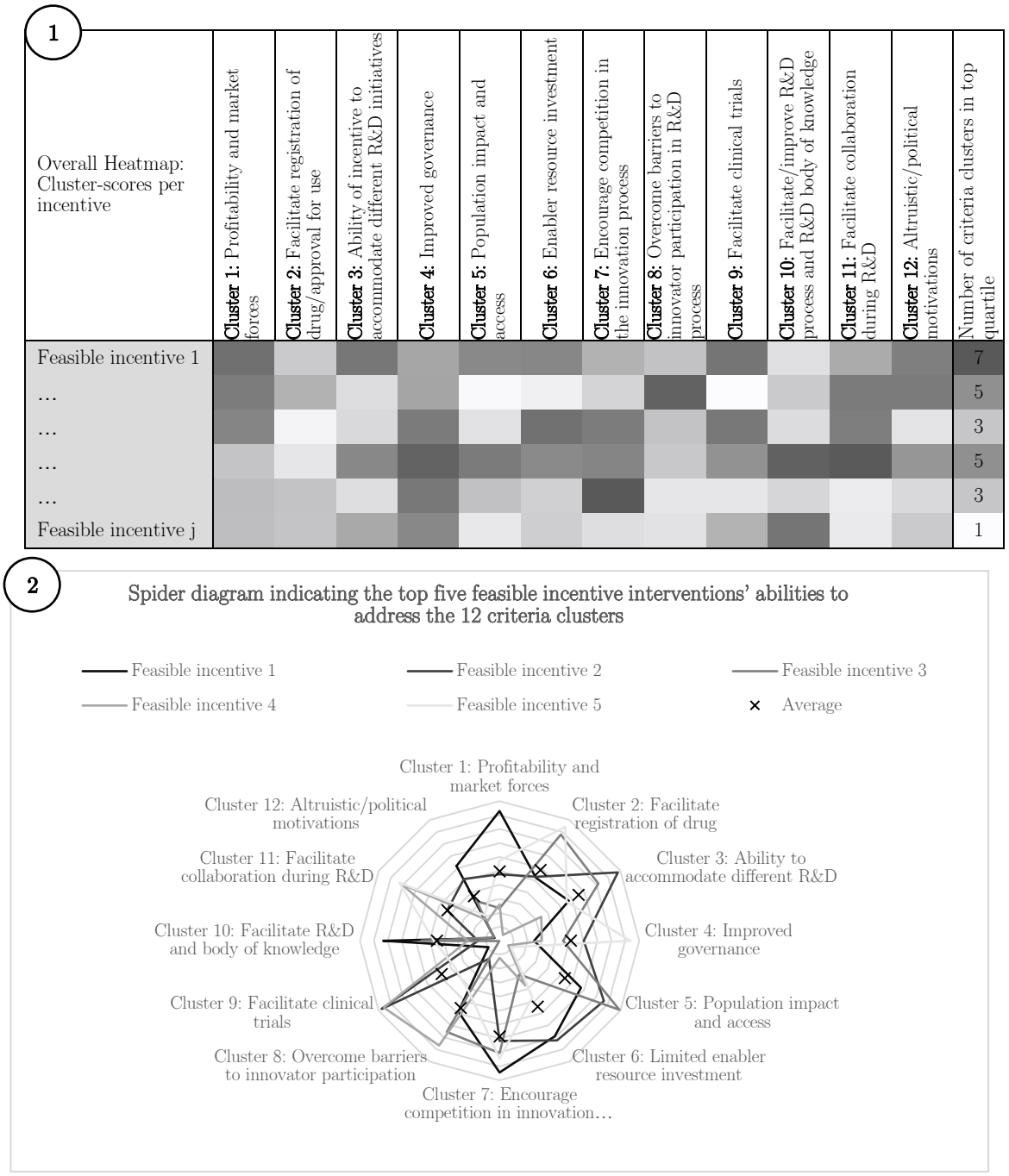


Figure 8.19: Incentive based solutions, Domain 5, overview.

As discussed, providing the incentives with an overall feasibility score would be fundamentally flawed, as this disregard the multi-criteria nature of the decision. The incentive-based solutions are, consequently, presented by means of a heatmap (Component 1 in Figure 8.19) indicating the (feasible) incentives and their corresponding cluster-scores (color scale) per criteria cluster, ranked from the incentive with the highest to the lowest number of cluster-scores (maximum of 12) that performed within the upper quartile for each criteria cluster. In addition, a spider-diagram (Component 2 in Figure 8.19) displays the top five ranked (feasible) incentives' cluster-scores for easy comparison.

In the heatmap, white indicates that an incentive has no ability to address the decision criteria, while dark red indicates strong ability to address the decision criteria. This heatmap is generated based on the cluster score per incentive (calculates using (1)). Presenting the performance in terms of each of the 12 criteria clusters, allows the users to holistically view the abilities of each incentive intervention, thus, to understand the strengths and weaknesses of each incentive intervention. This overview is intended to give users the opportunity to consider incentive interventions that have a high ability to address the criteria clusters that they view as being most important.

The incentive interventions are presented in order of their ranking, as discussed in Section 8.4.10, this ranking is based on the number of criteria clusters where the incentive intervention performs within the upper quartile. As discussed in Sections 8.1 and 8.2, the feasible set of incentive-based solutions exclude those incentives that did not address all of the exclusion criteria of the enabler stakeholder(s). In keeping with the overarching approach of providing information that supports decision-making, rather than dictating decisions, information on the performance of infeasible incentive interventions in terms of the various criteria clusters is also provided as part of the framework outputs.

The spider diagram provides the users the opportunity to view the five top performing incentives' abilities to address the 12 criteria clusters in comparison with one another. With the ability of the incentive to address the criteria cluster increasing as the distance of the series marker from the centre of the spider diagram increases. It therefore duplicates a portion of the information conveyed in the heatmap but presents this information in a substantially different format. The average ability of all the incentive interventions to address the respective clusters are also indicated as a point of reference. The rationale for limiting the number of incentive interventions that are displayed on the spider diagram to five, is that it becomes hard to interpret the information in this format if a greater amount of data is displayed.

The second main section of the solution set is the non-incentive-based interventions. These are depicted in Table 8.7 which is a preview of the complete list of the 43 non-incentive-based intervention solutions (Appendix F). These interventions are displayed in tabular format, with a description of each intervention included. These interventions are not ranked, but the priority derived from the inputs provided in Domain 1 is indicated in rightmost column. The relevance of the interventions are articulated, and intervention considerations with accompanying literature sources are listed. The aim is to provide the user with guidance on addressing the relevant aspect of the R&D system with a non-incentive-based intervention.

Table 8.7: Non-incentive-based solutions (1 of 43).

DOMAIN 5: NON-INCENTIVE-BASED SOLUTIONS			
42. Health data generation		Further reference	Priority rating
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	0/1/2
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

Apart from the incentive- and non-incentive-based interventions provided as part of the solution set; supplementary material is also included to provide the user with details regarding the incentive interventions' abilities to encourage R&D for the given scenario. The supplementary material transfer media are included in Appendix I.

Supplementary page 1 provides the user with an overview of the criteria cluster-scores per incentive intervention, with the incentive interventions grouped in the incentive strategies (i.e. push-, lego-regulatory pull, outcome-based pull, and hybrid incentive strategies). A separate spider diagram, similar to the top performing spider diagram displayed in the primary incentive-based interventions solution worksheet, is displayed for each of the four incentive strategies.

Supplementary page 2 displays the criteria-cluster score of each incentive intervention in a separate spider diagram. These diagrams allow the user to investigate the abilities of all incentive interventions to address each of the 12 criteria clusters. The average ability of all 26 incentive interventions to address each criteria cluster is also indicating, providing a reference point for comparison.

Supplementary page 3 depicts 12 spider diagrams, one for each of the criteria clusters. These diagrams indicate the ability of all the incentive interventions to address each of the criteria clusters. This allows the user to investigate the top performing incentives for the criteria clusters that they prioritize.

Supplementary page 4 depicts an enabler-focused solution set. Meaning, that the 26 incentive interventions are not evaluated on all the decision criteria (as is the case for the primary solution set) but is rather evaluated only on the decision criteria from Domains 1 and 2. Consequently, the innovator and end-consumer stakeholders' criteria prioritization are excluded when generating the cluster scores that underpin this view of the solution set. This solution set page allows the enabler stakeholder to evaluate and view the incentive interventions that addresses primarily their requirements and internal capabilities, without being influenced by the requirements and capabilities of the innovator and consumer stakeholders. The presentation of this solution set is similar to the primary solution set with the incentives classified as either feasible or infeasible, and the results displayed in a heatmap and spider diagram format.

As previously mentioned, the final framework, incorporating all the changes made during the refinement process that followed the verification and validation phases presented in Chapter 10, is presented in this section. This is done to prevent interrupting the flow of the narrative. The preliminary version of the framework (i.e. the version that was sent out as a pre-read for the phase 1 of verification and validation, as well as phase 2 of verification and validation as depicted in Chapters 9 and 10.1 and 10.2), is presented in Appendix I. The final version of the decision-support framework (including all BL functions), is depicted in Appendix G.

8.5. Decision-support framework: Transfer media

The user of the decision-support framework interacts with the framework via transfer media, as previously mentioned. Furthermore, the decision-support framework is operationalized in MS Excel, with the entire framework transformed from a paper-based system to a digital framework with transfer media that the users of the framework will interact with. The transfer media is illustrated by means of a series of screenshots taken from the MS Excel workbook, where the decision-support framework is constructed.

8.5.1. Transfer media: Landing page

The framework user's first view of the decision-support framework provides an overview of the framework domains and BL functions, this is referred to as the 'landing page'. Figure 8.20 depicts this landing page overview. The overview of the framework is also coded to allow the user to jump to a selected component. In addition to the framework layout, the stakeholder landscape is briefly introduced. The aforementioned allow the user to get an understanding of the stakeholders that are considered and involved in the decision-support framework, as well as which of the framework components needs to be completed by the respective stakeholders. The landing page of the decision-support framework also provides a brief descriptive overview of the framework, operationalization of the framework, as well as all the components within the decision-support framework (depicted by Figure 8.21).

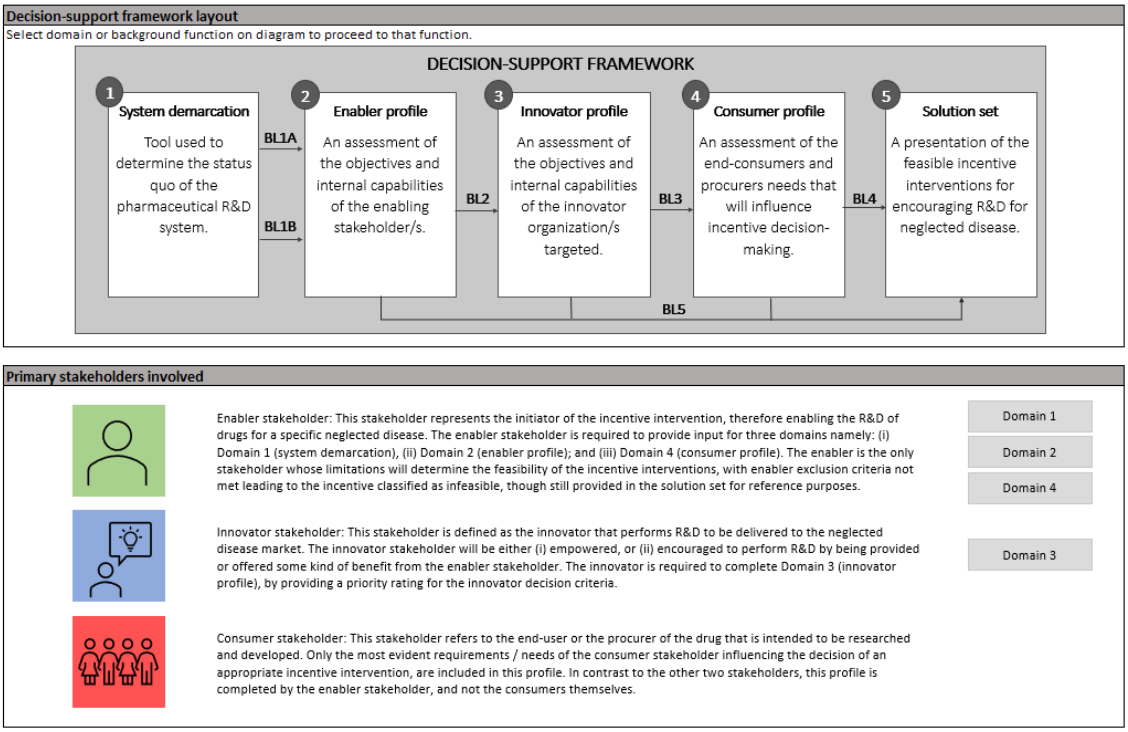


Figure 8.20: Transfer media: Decision-support framework landing page (1 of 2).

Decision-support framework: Selecting incentive interventions to encourage drug R&D of neglected diseases

INTRODUCTION

Overview of the decision-support framework

The decision-support framework aims to incentivize R&D for diseases that do not have adequate drugs available. The framework analyzes the current pharmaceutical R&D environment, receives input from the enabling, innovating and consumer stakeholders, as well as uses what literature suggests, to provide a means of enabling or simplifying the decision-making process involved in choosing an incentive intervention for encouraging R&D in drugs for neglected diseases. The framework comprises five domains and five background logic processes. The output of this framework is a proposed set of feasible incentive interventions that have been identified as being suitable to the requirements of the specific scenario, based on information gathered from literature. The presentation of the proposed set of feasible incentives highlights the ability of each incentive to address the multiple-decision criteria. The set of suggested interventions will each satisfy a different criteria cluster (focus area), or set of criteria clusters, consequently no one optimal solution exists. In addition, a set of non-incentive-based interventions that are likely to make a contribution to the scenario under consideration are also proposed.

Using this framework

The framework comprises of five domains and five background logic processes. The stakeholders and decision-makers involved are required to provide input in Domains 1 to 4. Domain 5 provides the feasible solution set, with supplementary results pages 1 to 4 providing more detailed insights. The background logic functions are included for the user to see, however, does not require any input or interaction from the stakeholders. The background logic functions are hardcoded and intended to run in the background, without the knowledge of the user.

PRIMARY COMPONENTS DESCRIPTION

Domain 1: System Demarcation

The system demarcation domain is developed to draft a holistic understanding of the pharmaceutical R&D system based on the scenario that will be investigated and consists out of 67 system elements. Each of the system elements should be ranked by the enabler stakeholder / decision-maker on a scale of [0, 1 or 2] – based on the state of the R&D system under investigation. Where 0 refer to the least ideal; and 2 refer to the ideal

Domain 2: Enabler profile

The enabler is required to complete the inquiry form, that is predefined with a short list of objectives and internal capabilities. The enabler will give each of the objectives and internal capabilities a priority rating of 0 (lowest priority), 1 or 2 (highest priority). These provide an overview of the enabler profile and give an indication of what their objectives and capacity restrictions are, this set of criteria is called the enabler criteria, being the decision criteria that is relevant to this specific enabler. It is important to note the exclusion criteria of this stakeholder, which will affect the overall feasibility of the incentive interventions.

Domain 3: Innovator profile

The innovator is required to complete the inquiry form, that is predefined with a short list of objectives and internal capabilities. The innovator will give each of the objectives and internal capabilities a priority rating of 0 (lowest priority), 1 or 2 (highest priority). These provide an overview of the innovator profile and give an indication of what their objectives and capacity restrictions are, this set of criteria is called the innovator criteria, being the decision criteria that is relevant to this specific innovator.

Domain 4: Consumer profile

The consumer profile refers to the end-user or the procurer of the drug that is intended to be researched and developed. The end-consumers are for the purpose of this study divided into two groups, namely patients and procurers. The consumer profile exists of merely the most important requirements and needs that will assist the enabler stakeholder to decide on a feasible incentive intervention type. Similar to the other two stakeholder profiles, the consumer profile consists of an 'inquiry form' with consumer requirements, and will be given a priority rating of 0 (lowest priority),1 or 2 (highest priority), by the enabler stakeholder, this set of criteria is called *consumer criteria*.

Domain 5: Solution set

The incentive-based solutions are presented by means of a heatmap indicating the 26 incentives and their corresponding cluster-scores (color scale) per criteria cluster, ranked from the incentive with the highest to the lowest number of cluster-scores that performed within the upper quartile (top 25%) range for the specific criteria cluster. In addition, a spider-diagram displays the top five incentives' cluster-scores for easy comparison, with the top five incentives being the incentives with the highest average number of criteria clusters addressed within the upper quartile. It should also be noted that the feasible incentive-based solutions exclude the incentives that did not address any of the exclusion criteria of the enabler stakeholder.
The non-incentive-based solutions are presented, with each non-incentive intervention including an articulation of alternative interventions to consider as well as the priority rating of each non0incentive based solution.

Supplementary page 1

Similar to the spider diagram in Domain 5; four spider diagrams of the cluster-score for the incentives per incentive strategy (i.e. push, outcome-based pull, lego-regulatory pull, and hybrid strategies) are displayed. This allows the decision-maker to evaluate the stregnths and weaknesses each incentive within the incentive strategies.

Supplementary page 2

A spider-diagram per incentive type, indicates the cluster-scores per incentive per cluster. This allows the decision-maker to investigate the incentives individually, and to compare the incentive capabilities with the incentive average (marked on each diagram).

Supplementary page 3

A spider diagram depicting the 12 criteria clusters, with an indication of the extent to which each of the 26 incentives addressed the speicific cluster. This allows the decision-maker to see which incentives address, or does not address the specific criteria cluster.

Supplementary page 4

The enabler stakeholder's decisions, and cluster-scores per incentive are calculated based on only the enabler criteria. Therefore, displays the most feasible incentive solutions, similar to Domain 5, this time only considering the enabler. This allows the enabler to evaluate the option that is best suited to their needs, however, is not intended to be used independently.

Figure 8.21: Transfer media: Decision-support framework landing page (2 of 2).

8.5.2. Transfer media: Domain 1

The first interaction that any stakeholder has with the decision-support framework is Domain 1, where the Enabler stakeholder evaluates the pharmaceutical R&D system in the system demarcation landscape sheet (depicted by Figure 8.22). The user is again, similar to the landing page, provided with an overview of the decision-support framework as well as a description and instructions to the completion requirements for the domain (depicted by Figure 8.23).

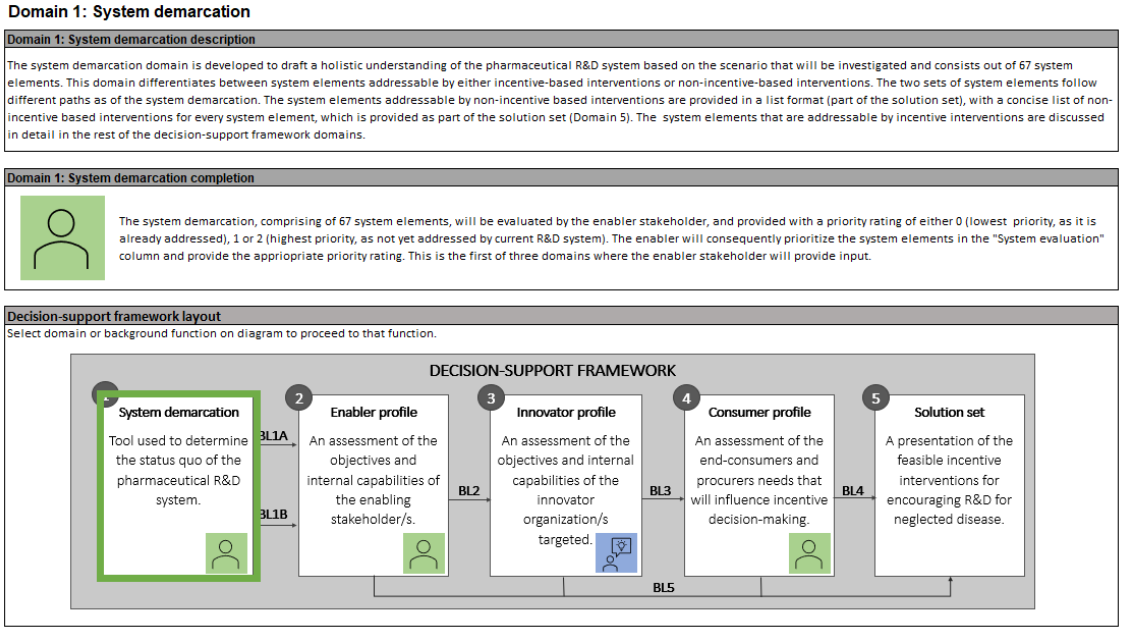


Figure 8.22: Transfer media: System demarcation landscape (1 of 2).

DOMAIN 1: SYSTEM DEMARCATION							System evaluation
	System elements	2	1	0	Aspect to address		Measure (0/1/2)
Disease setting and affected population							
1	Country economics status	Low-income	Low-to high-middle	High-income	Non-incentive-based solutions (II)		1
2	Country-wide burden of the diseases	> 35 000 DALY's (per 100 000)	DALY's: 0	0 DALY'S	4. Population impact and access		2
3	Burden fully characterized	< 40% of population within 5km of health facility	40% - 60% of population within 5km of health facility	> 60% of population within 5km of health facility	Non-incentive-based solutions (I)		0
4	Physicians per 1000 population	< 1 per 1000	1–2 physicians per 1000 population	> 2 physicians per 1000 population	Non-incentive-based solutions (I)		1
Existing drug characteristics							
5	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact		1
6	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)		0
7	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact		2
8	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)		2
9	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access		1
10	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)		1
11	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)		2
12	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)		1
13	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access		1
Service delivery							
14	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)		2
15	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)		0
16	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)		1
17	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)		1
Consumers, competitors, and suppliers							
18	Demand, size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)		0
19	The role of brand loyalty	Brand loyalty has no influence, or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)		1
20	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)		2
21	Existence of competitors	No competitors	Some competitors	Significant competition	Non-incentive-based solutions (V)		1
22	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entries	2. Implementation feasibility		2
23	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation		0
24	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation		1
Governance and leadership							
25	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)		1
26	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership		1
27	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership		0
28	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership		0
29	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)		1
30	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)		2
31	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finances some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership		1
32	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)		1
33	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)		2
Profitability and market forces							
34	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1.Profitability and market forces		1
35	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)		2
36	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)		1
37	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)		2
38	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces		0
39	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership		0
Research and development process							
40	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	3. R&D and clinical trials		2
41	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)		1
42	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)		2
43	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)		2
44	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)		2
45	Capacity and monitoring of clinical trial (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	3. R&D and clinical trials		2
46	Obstacles to initiate clinical trial (comply by FDA standards)	Obstacles to initiate clinical trials abound	Some obstacles to initiate clinical trials	Obstacles to initiate clinical trials reduced	3. R&D and clinical trials		0
47	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	3. R&D and clinical trials		2
48	Quality assurance of clinical trials (VHDPQ)	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable (National)	Good clinical trial quality (VHDPQ)	3. R&D and clinical trials		1
49	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	3. R&D and clinical trials		2
50	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)		1
51	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)		2
52	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)		2
53	Safety assessment standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)		2
54	Adaptive clinical trials occurrence	Never occurs (drugs do not survive the R&D process)	Occurrence sometimes difficult	Mostly occur	Non-incentive-based solutions (VIII)		2
55	Recruitment and retention of participants	Difficult to recruit and mostly retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)		1
56	Racial differences in participation in clinical trials	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)		0
57	Relationship between innovators and participants	No or very poor relationship (very little trust)	Relationship, mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)		0
58	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)		1
59	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)		2
60	R&D productivity	Cycle times longer than the average (12 – 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 – 15 years)	9. R&D and clinical trials		2
61	Clinical trial registration	No clinical trials performed/ are registered	Some clinical trials performed/ are registered	All clinical trials performed/ are registered	3. R&D and clinical trials		1
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)		2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)		1
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)		1
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs		2
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)		1
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)		0

Figure 8.23: Transfer media: System demarcation (2 of 2).

8.5.3. Transfer media: Domain 2

The enabler profile overview, as well as the enabler inquiry form are depicted in Figures 8.24 and 8.25 respectively.

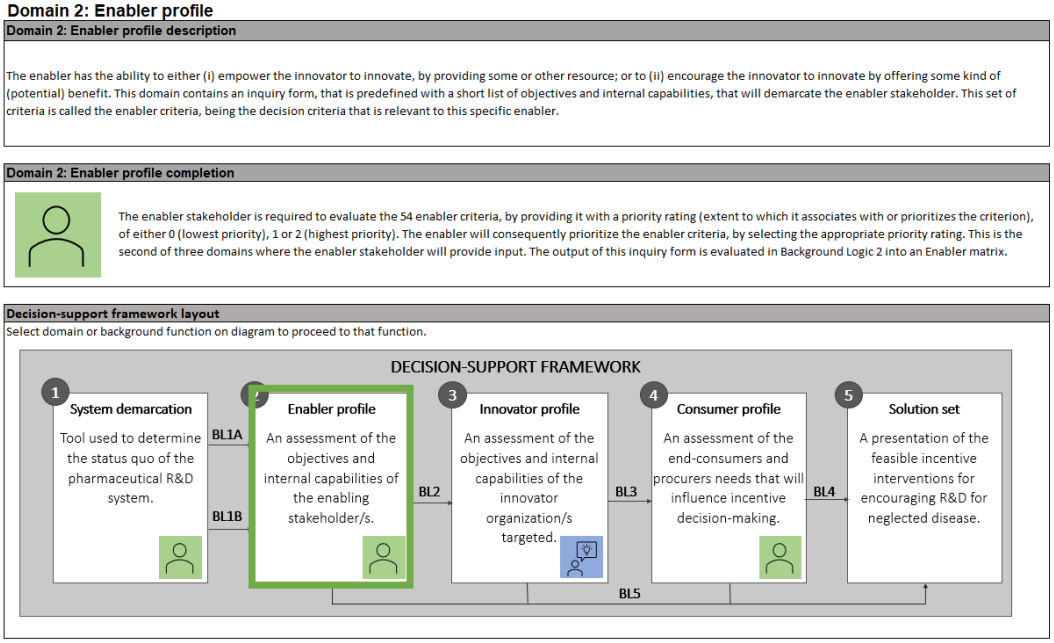


Figure 8.25: Transfer media: Enabler inquiry form (1 of 2).

DOMAIN 2: ENABLER INQUIRY FORM

OBJECTIVES		INTERNAL CAPABILITIES	
1 Goal of the incentive strategy? (Inclusion)		**1 Available funding. (Exclusion)**	
Improve the state of the R&D pipeline	1	Limited to an amount	2
Enable organizations to innovate easier	1	Full capacity	0
Gain market exclusivity over an innovation	0	No capacity	0
Advance the R&D field	2	**2 Tranches to innovators. (Inclusion)**	
Deliver affordable and accessible treatment	1	Beginning once-off	0
Convey an important message	2	End once-off	2
Fulfil corporate social responsibility	1	Once output is provided	0
Increase bandwidth and network	2	Incrementally, based on output	0
De-risk R&D process	1	Incrementally, based on timing	0
Political obligations	0	Incrementally, as innovator requires	0
2 Which innovators are targeted? (Inclusion)		**3 Ability to influence policy. (Inclusion)**	
Large pharmaceutical organizations (private)	0	Clinical trial regulation policies	0
SMEs (private)	2	Market authorization policies	0
Governmental institutions	2	Market exclusivity policies	0
Independent scientists	2	Pricing policies	0
Academic institutions	2	Tax credit policies	0
NGO organizations	2	National/international intellectual property policies	0
Everyone	1	National policies and legislation	0
3 Intention for the consumers? (Exclusion)		International trade law	0
Provide drug	1	**Access and expertise. (Inclusion)**	
Multi-purpose drug	0	**4** Access to key data	0
Play a role in improved access	1	Access to compounds	0
Implement mass drug administrations	0	Access to intellectual property	0
Deliver regime treatment	0	Technology expertise and access	1
4 Desired relationship with innovators? (Inclusion)		R&D expertise	1
Once-off occasion	2		
Limited to a number of years	0		
Milestone related	0		
Engage at given time instances	0		
Collaborate and build a partnership	0		
5 Role and Responsibility willing to play? (Exclusion)			
Fund R&D	2		
Partially fund R&D	1		
Facilitate collaboration between innovators	2		
Collaborate with innovator	1		
Facilitate in regulatory process	0		
Provide market exclusivity	0		
Adjust policies and regulations	0		
Provide market certainty	0		

Figure 8.24: Transfer media: Enabler inquiry form (2 of 2, partially filled out to aid illustration of concept).

8.5.4. Transfer media: Domain 3

The innovator inquiry form is the transfer media used by the innovator stakeholder to evaluate their objectives and internal capabilities. Figures 8.26 and 8.27 indicates the overview and the innovator inquiry forms respectively.

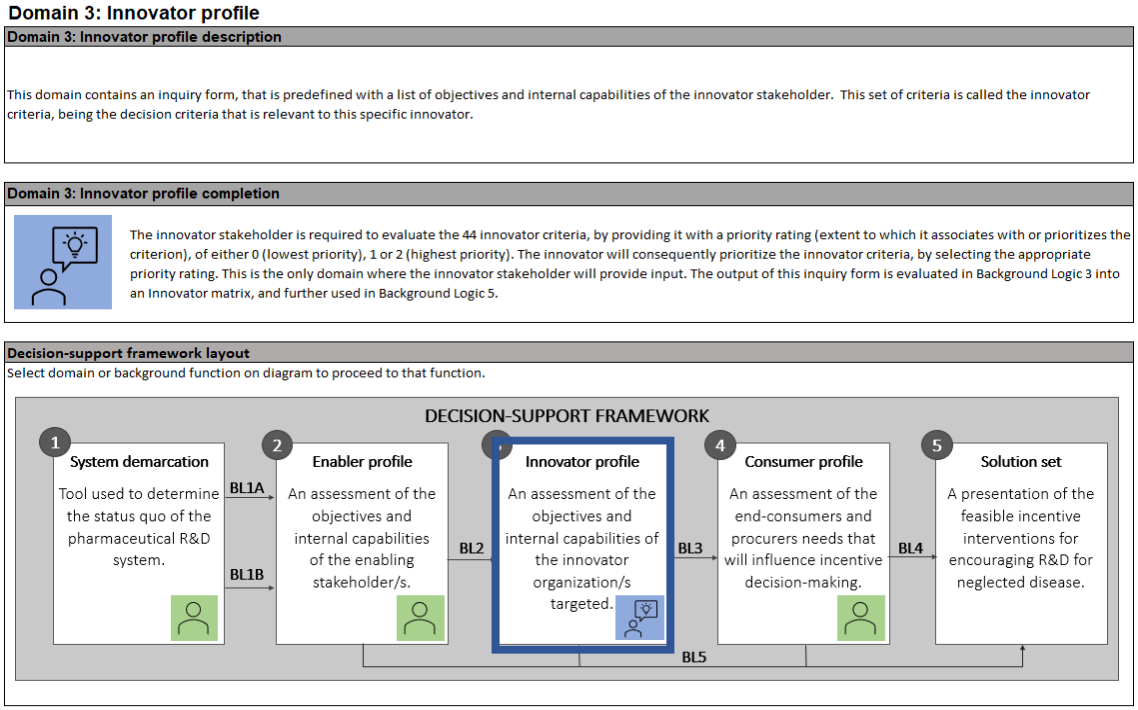


Figure 8.27: Transfer media: Innovator inquiry form (1 of 2).

OBJECTIVES			INTERNAL CAPABILITIES	
1	**Reason for performing R&D for the disease?**		1 **Nature of innovator stakeholder?**	
	Profit maximization	0	Small to medium organization (includes start-up)	2
	Corporate social responsibility	0	Large pharmaceutical organization	0
	Not for profit	1	Not-for-profit organization	2
	Profit improvement	0	Governmental institution	2
	Political obligations	0	Academic institution	2
2	**Focus area of R&D and intention for patients?**		Independent scientist (no organization linked)	2
	R&D of drug	2	2 **Capacity to provide own funding?**	
	R&D of multi-purpose drug	1	No capacity	1
	Play a role in improved access	0	Limited to an amount	1
	Drug repurposing	2	Full capacity	1
	Deliver regime treatment	0	3 **R&D limitations?**	
3	**Require from the enabler?**		Don't have research laboratory	1
	Fund all R&D costs	0	Don't have adequate equipment	1
	Partially fund R&D	2	Lack of information (knowledge) on disease	1
	Collaboration with enabler	0	Cumbersome nature of clinical trial regulations	1
	Adjust policies and regulations	0	Shortage of finances	1
	Facilitate regulatory process	0	Policies or regulatory limitations	1
	Provide market exclusivity	0	No market certainty	1
	Provide market certainty	0	4 **Authorization standards adhered to?**	
	Provide a collaboration platform	1	None	1
	Provide risk insurance or security	0	Accredited authorisation organization	2
	Improve export potential	0		
4	**Preference or required funding timing?**			
	Beginning once-off	0		
	End once-off	2		
	Incrementally based on output	0		
	Incrementally based on timing	0		
	Incrementally as required	0		
	Once output provided	0		
	Don't require any funding	0		

Figure 8.26: Transfer media: Innovator inquiry form (2 of 2, partially filled out to aid illustration of concept).

8.5.5. Transfer media: Domain 4

The consumer inquiry form is the transfer media completed by the enabler stakeholder, to evaluate the end-consumer. The overview and consumer inquiry form are depicted in Figures 8.28 and 8.29. The consumer inquiry form is made up of the consumer requirements, with contextual treatment criteria[19] included.

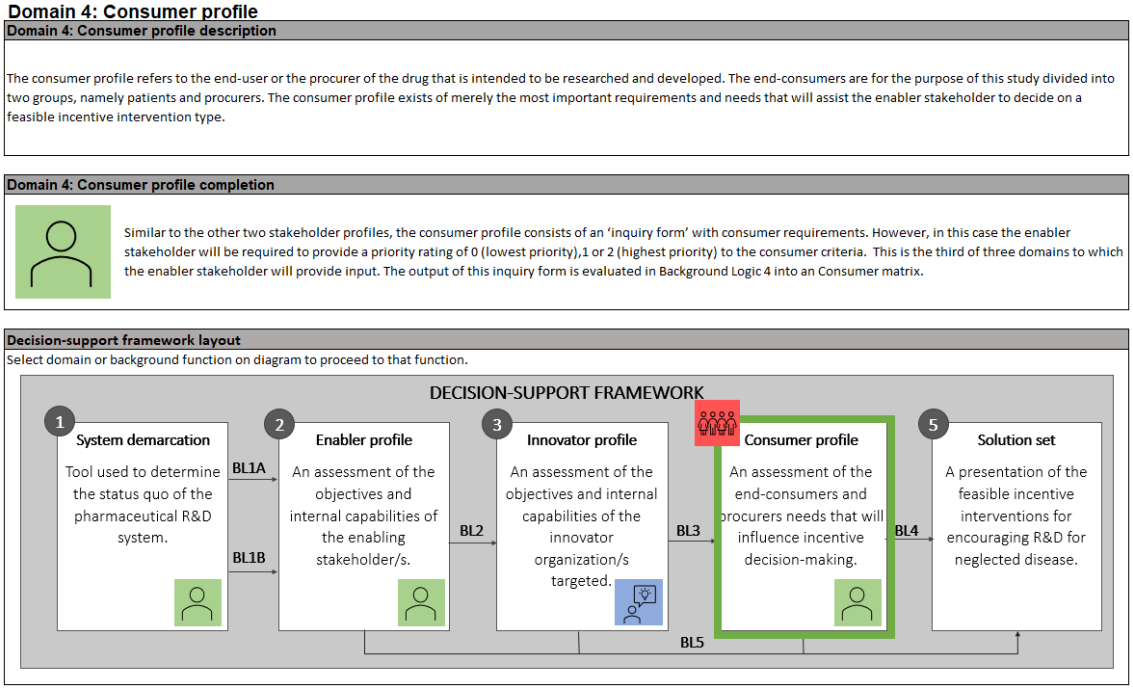


Figure 8.29 Transfer media: Consumer inquiry form (1 of 2).

DOMAIN 4: CONSUMER REQUIREMENTS	
END CONSUMER (patient)	
1 Socio-economic inequalities	
Require differential pricing	1
Must eliminate all financial risk	2
2 Contextual treatment criteria	
Accommodates contextual treatment criteria	0
PROCUREMENT: PUBLIC / PRIVATE (FOR-/ NOT FOR PROFIT)	
3 Affordability	
Require differential pricing	1
4 End-price profit margins	
Any profit margins allowed	1
Restricted profit margins	0
No profit	2
5 Availability and accessibility	
IP regulation allows procurement of drugs to target area	1
Existing drugs not allowed in target area	0
Drug status designation required	2

Figure 8.28: Transfer media: Consumer inquiry form (2 of 2, filled out to aid illustration of concept).

[19] Contextual treatment criteria of the consumer stakeholder include various aspects that the developed treatment needs to adhere to. This includes ethical considerations, clinical trial diversity requirements, type of consumer considered, drug safety, side-effects, useability, administration, advocacy, stigma consideration as well as WASH and sanitation initiatives.

8.5.6. Transfer media: Domain 5

The solution set domain transfer media is depicted in Figure 8.30 and 8.31, depicting the incentive-based and non-incentive -based interventions, respectively. Visible in Figure 8.31 is an automated button, 'Refresh results', that the user uses to update the results based on the input provided in Domains 1, 2, 3 and 4.

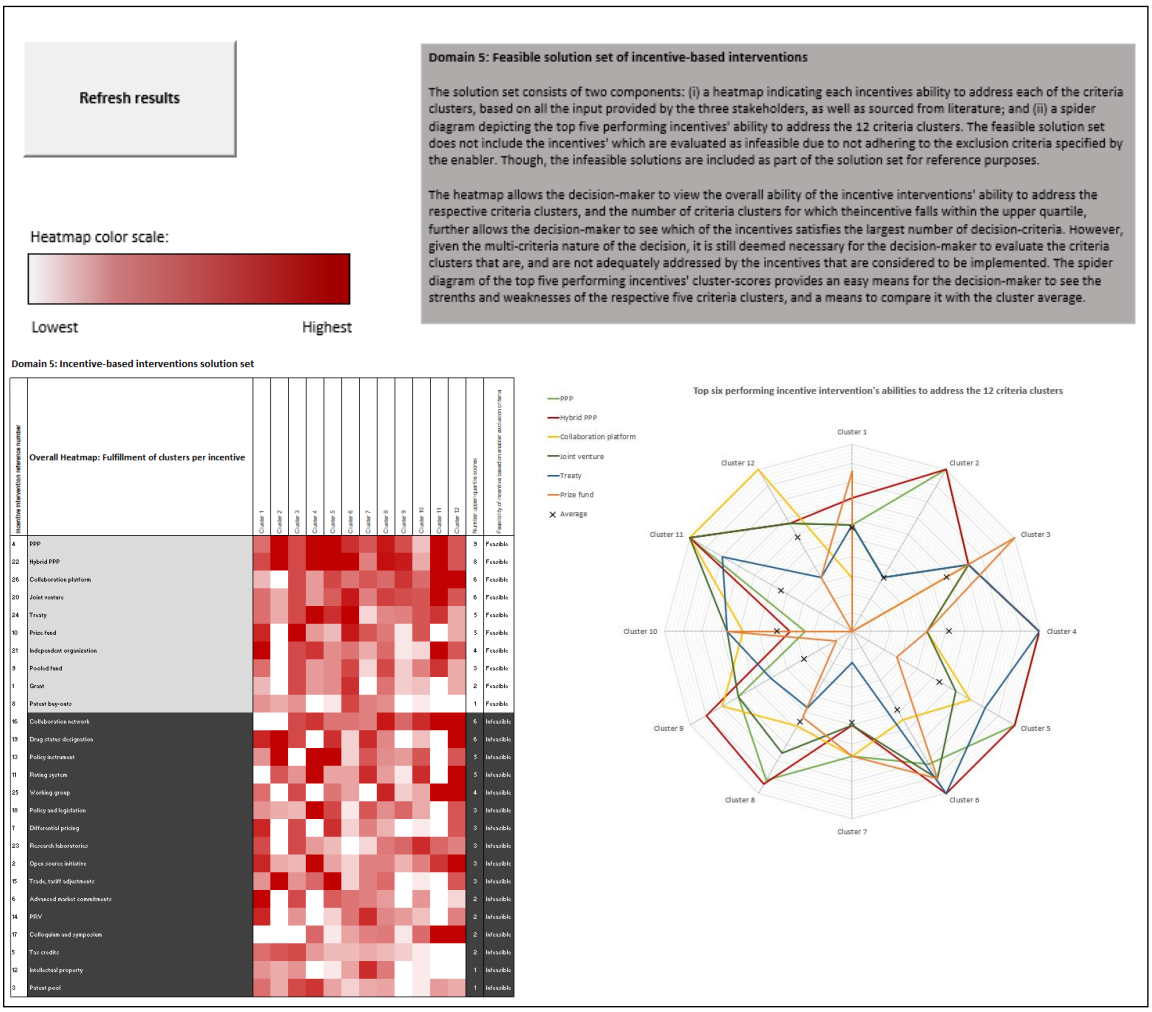


Figure 8.30: Transfer media: Solution set (1 of 2).

I. DISEASE SETTING AND AFFECTING POPULATION

1. Country economic status		For further reference	Priority rating
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błażejowski *et al.*, 2019)	1
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

2. Burden fully characterized		For further reference	
Meaning	The affected patients are diagnosed, being monitored and documented properly.	(Olmsted et al., 2006; RAND Corporation, 2007; Novak et al., 2013)	2
Relevance	Once the burden of a disease is fully characterized, consumer demand can be estimated. Consumer demand will have an influence on how profitable the perceived market is. Fully characterizing the burden also assists in the planning, distribution and implementation of control strategies.		
Intervention considerations	Diagnostic tools and technology, availability and access there of		
	Diagnostic intervention and intervention strategies		
	Availability of health facilities (option is to consider mobile health facilities)		
	Educate populations on disease side-effects, risks, and necessity of health interventions		
	Capture burden characterization data		

Figure 8.31: Transfer media: Solution set (2 of 2, extraction of full solution set for the sake of brevity).

8.6. Conclusion: Decision-support framework

The developed framework analyzes the current pharmaceutical R&D environment, receives input from the enabling, innovating and consumer stakeholders, as well as recommendations from literature, to provide a means of enabling or simplifying the decision-making process involved in choosing an incentive intervention for encouraging R&D of drugs for neglected diseases. The framework comprises five domains and five BL processes. The output of this framework is a proposed set of feasible incentive interventions that have been identified as being suitable to the requirements of the specific scenario, based on information gathered from literature. The presentation of the proposed set of feasible incentives highlights the ability of each incentive to address the multiple decision criteria, i.e. the criteria clusters. As each incentive intervention will perform differently in terms of satisfying each criteria cluster, no one optimal solution exists. In addition, a set of non-incentive-based interventions that are likely to make a contribution to the scenario under consideration are also proposed.

The aim of the decision-support framework was defined at the start of the chapter, followed by the design and operationalization of the respective framework components. Design notes, highlighting important aspects of the framework to be considered, were articulated throughout the chapter. The chapter concluded with a presentation of the final decision-support framework.

The verification of the framework is considered in the next chapter.

CHAPTER 9

Verification and refinement

The verification of the decision-support framework is presented in this chapter. The overarching purpose of this chapter is to build confidence and establish the credibility of the developed decision-support framework. Verification primarily concerns identifying inaccuracies of the design (Thacker *et al.*, 2004).

First, a thorough verification of the decision-support framework is performed. The verification step is followed by a framework refining step. The framework refinement is based on observations made during the verification process and provides insight into the actions taken in response to feedback derived from the verification process.

9.1. Verification

Verification is the process of establishing the accuracy of the proposed solution (Thacker *et al.*, 2004). In this research, the verification stage is completed after the initial framework is developed (Chapter 8). Verifying the framework ensures that it contains the required strategic content and addresses the requirements that were identified in the preceding chapters. In addition, the information gathered during the verification serves as a basis for refinement of the framework. Thus, the verification process uncovers any discrepancies, areas of improvement or changes to be made to the design before the value of the solution is confirmed by means of validation.

9.1.1. Verification methodology

The approach followed to verify the decision-support framework seeks to: (i) determine whether the specifications are satisfied by the various components of the framework; (ii) determine whether the framework components (developed based on the design requirements) are adequate and comprehensive; and (iii) identify possible omissions in the framework that should be incorporated. The decision-support framework verification is completed in two stages. Both stages of verification contribute towards confirming the adequacy of the decision-support framework components, and the framework overall.

The two verification stages are:

(i) Internal design requirement verification: Evaluate the designed solution to determine whether it adheres to the requirement specifications identified throughout the document. This stage of verification is described in Section 9.1.2.

(ii) External SME verification: Semi-structured interviews are conducted to determine the accuracy and comprehensiveness of the developed framework. This stage of verification is conducted in two phases one being on an intermediate version of the decision-support framework (Appendix I), and the other on the final decision-support framework (Appendix G). The intermediate version of the decision-support framework excluded Domains 3 and 4 as well as BL 3, 4 and 5, though it was intended from the beginning of the decision-support design process to include these components. The first phase of external SME verification involved interviewing SMEs 1 to 6, with the second phase of external verification involving SMEs 5, 7, 8, and 9. It is important to note that between these two phases of verification, changes and refinements were made to the entire framework (including Domains 1 and 2 as well as BL 1 and 2), with the feedback resulting from the first phase of external verification forming a fundamental part in the development of the Domains and BL functions added to the intermediate version of this framework. This stage of verification is discussed in Section 9.1.3.

9.1.2. Requirement specifications verification

The evaluation criteria for this stage of the verification process is design intent, measuring the extent to which the decision-support framework meets the intention of the design requirements. The verification of the requirement specifications is done by indicating the function (domain or BL function) where the individual specification is addressed in a conceptual manner or specified explicitly. The complete list of 25 requirement specifications identified in Chapters 2 - 6 includes:

- 12 functional requirements;
- 7 user requirements;
- 2 design restrictions;
- 3 attention points; and
- 1 boundary condition.

Table 9.1 contains a summary of how and where the requirement specifications (rows) are addressed by the domains and BL functions of the framework (columns). Where it is clear (from the description provided in the previous chapter) that a requirement has been addressed in a specific domain or BL function of the framework, this is simply indicated with a tick mark. Where the fulfilment of the requirement is judged to be less explicitly clear, a short explanatory note has been provided. It should be noted that the final version of the framework was used to verify the requirement specifications. Thus, the analysis shown in the table is based on the version of the framework that incorporates the final refinements which were executed based on the SME feedback received during the second stage of verification.

9.1.2.1. Purpose of verifying requirement specifications

As mentioned previously, the requirement specifications are the 'building blocks' on which the development of the framework is based. This provides the capacity to use the requirement specifications as a guideline to ensure that the research output contains all the important aspects, derived from literature and previous analysis, to be successful in achieving the desired outcome. The primary objectives of this verification step are to:

(i) Ensure all the requirement specifications are adequately addressed;

(ii) Analyse and provide reasoning for the cases where requirement specifications are not incorporated into the framework; and
(iii) Investigate which framework components do not address any of the requirement specifications, and for which the design value is therefore questionable.

9.1.2.2. Interpretation of requirement specification verification

The evaluation of the extent to which requirement specifications are met by the framework, indicates that one user requirement specification is only addressed to a certain extent in the current version of the framework. More specifically: all the functional requirements; all the design restrictions, all attention points, all the design restrictions and all the boundary conditions are adhered to and incorporated; with all, except one, user requirements being incorporated.

The user requirement specification that is only partially incorporated is considered in more detail.

> U.7 Conflicting interests of the different stakeholders, and the suggested solutions, should be taken into account and considered within the boundaries of this research. This will also bring about the necessary trade-offs to be made by the various stakeholders.

Conflicting interests of stakeholders refer to when the expectations, objectives, capabilities or needs of one stakeholder is not aligned to that of the other stakeholder(s). Ideally, the framework should incorporate the needs of the end-product consumers, with the capabilities of the innovators and, with the abilities and objectives of the enabler entities. Certain aspects of these expectations, objectives, capabilities or needs are non-negotiable, e.g. drug quality, R&D policies, or standard R&D practices. Other aspects, are, however, flexible and could be compromised on if conflicting interests are evident. These aspects can range from: (i) the funding of clinical trials; (ii) the timing of funding for R&D; (iii) pricing of developed drugs; (iv) IP agreements; or (v) data sharing agreements.

Table 9.1: Verification of requirement specifications.

		DECISION-SUPPORT FRAMEWORK DOMAINS AND FUNCTIONS						
		Domain 1: System demarcation	BL1: Criteria matrix	Domain 2: Enabler stakeholder	Domain 3: Innovator stakeholder	Domain 4: Consumer stakeholder	BL5: Criteria clusters	Domain 5: Solution set
FUNCTIONAL REQUIREMENTS								
F.1	The developed framework should provide a means to outweigh the risks and uncertainty of the R&D operation of innovating a drug with the benefits of the provided solution (or set of solutions).	The framework addresses risks and uncertainties of the R&D operation by incorporating the innovator, as well as the overarching pharmaceutical R&D industry characteristics to mitigate any unknown risks and to emphasise areas within the R&D sphere to be addressed.						
F.2	The developed framework must incorporate the occurrence of the major challenges, relevant to the scenario, that influences the R&D pipeline. Some of the top challenges include: (i) policy & regulatory issues; (ii) set-up of clinical trials; (iii) participant recruitment and retention; (iv) complexity of trials; and (v) clinical trial risk. Refer to Appendix A for the 37 factors that influence the R&D pipeline.	✓	✓	-	-	-	-	-
F.3	The framework must provide a solution set with the potential to advance the four pharmaceutical R&D pipeline trends namely: (i) improve R&D productivity; (ii) improve investment capital and ROI of the sector; (iii) increase the number of clinical trials registered; and (iv) decrease or provide means to cover the costs of clinical trials.	-	✓	-	-	-	-	✓
F.4	The designed solution must incorporate characteristics to improve the market attractiveness of the desired scenario, as well as provide a means to bridge the characteristics that reduce market attractiveness in the pharmaceutical R&D industry.	✓	✓		-	-	-	-
F.5	The designed solution must overcome disease-specific pharmaceutical drug R&D characteristics that lead to diseases becoming neglected.	✓	-	-	-	-	-	-
F.6	The designed solution must focus on improving the state of disease-specific characteristics that enhance the attractiveness of the pharmaceutical drug R&D industry.	The incorporation and ranking of the pharmaceutical R&D system characteristics in the system demarcation domain allows for the improvement of disease-specific (context-specific) characteristics of the industry.						
F.7	Provide a formal platform as a means where different incentive programs, for encouraging R&D investments, can be compared.	-	✓	✓	✓	✓	-	✓
F.8	The suggested incentive intervention should comply with context-non-specific criteria, identified in literature, as this is essential for ensuring that the incentive intervention is feasible.	-	✓	-	-	-	-	-
F.9	The designed solution must show to what extent each incentive strategy complies with the criteria that the incentive strategy must adhere to.	-	✓	✓	✓	✓	✓	✓

Table 9.1 continued on next page

Table 9.1 continued from previous page

		DECISION-SUPPORT FRAMEWORK DOMAINS AND FUNCTIONS						
		Domain 1: System demarcation	BL1: Criteria matrix	Domain 2: Enabler stakeholder	Domain 3: Innovator stakeholder	Domain 4: Consumer stakeholder	BL5: Criteria clusters	Domain 5: Solution set
F.10	The framework must include all feasible incentive interventions, this includes: (i) push; (ii) both outcome-based and lego-regulatory pull; and (iii) hybrid strategies and types.	-	✓	✓	✓	✓	✓	✓
F.11	The designed solution must not only include incentive-based interventions, but also incorporate non-incentive-based interventions.	-	-	-	-	-	-	✓
F.12	The suggested solution should allow for more than one stakeholder of a type to be incorporated.	-	-	✓	✓	✓	-	-
USER REQUIREMENTS								
U.1	The framework should select an incentive intervention that considers the patient and population as core drivers for the incentive.	✓	-	-	-	✓	-	-
U.2	The framework should provide a solution, or set of solutions, that will incorporate the outcomes and goals, as set by the WHO health care framework, namely: (i) improve access; (ii) improve coverage; (iii) improve quality of services delivered; (iv) ensure safety; (v) improve overall health (burden of disease); (vi) be responsive; (vii) provide social and financial risk protection; and (viii) improve efficiency of mitigating the disease.	The set of outcomes and goals of the WHO health care framework are addressed and incorporated in the end-consumer profile of the decision-support framework. Even though the boundaries of this research exclude addressing the implementation of an incentive or providing access to the developed drug; the consumer requirements incorporate the objectives of the end-consumers that play a role in the selection of an appropriate incentive intervention.						
U.3	The proposed solution must provide a means to alleviate the burden of disease of the consumer.	With the intention of the framework being to incentivize R&D for specific neglected diseases, a reasonable anticipation of the framework is that, if used and implemented correctly, the needed intervention will be delivered, and the burden of disease consequently reduced.						
U.4	The developed solution should address the customer requirements and unmet needs of the consumers of the developed drug.	-	-	-	-	✓	-	-
U.5	The suggested solution should accommodate stakeholder collaborations.	The decision-support system allows collaboration between the different stakeholders, including: (i) the end-consumers, innovator(s) and enabler stakeholder(s); (ii) the enabler stakeholder will collaborate with the innovator to provide some form of incentive or benefit; and (iii) the enabler and innovator stakeholders can build a partnership as part of the selected incentive intervention.						
U.6	The suggested solution should incorporate the objectives and internal capabilities of the enabler and innovator, as well as the requirements of the consumer stakeholders.	-	-	✓	✓	✓	-	✓
U.7	Conflicting interests of the different stakeholders, and the suggested solutions, should be taken into account and considered within the boundaries of this research. This will also bring about the necessary trade-offs to be made by the various stakeholders.	Conflicting interests between stakeholders is anticipated in the research. The framework does include the requirements of all three stakeholders but dealing with the conflicts of interest is not included. The reason for the aforementioned is due to the enabler stakeholder seen as the primary enabler, and therefore not being prohibited to perform their intended work, based on the impact of the other two stakeholders. (Partially addressed)						

Table 9.1 continued on next page

Table 9.1 continued from previous page

	DECISION-SUPPORT FRAMEWORK DOMAINS AND FUNCTIONS						
	Domain 1: System demarcation	BL1: Criteria matrix	Domain 2: Enabler stakeholder	Domain 3: Innovator stakeholder	Domain 4: Consumer stakeholder	BL5: Criteria clusters	Domain 5: Solution set
DESIGN RESTRICTIONS							
D.1 The designed framework should be applicable to be used either for governmental, philanthropic, and private organizations.	-	-	-	-	✓	-	-
D.2 The framework should not only provide one solution for the problem. In view of the multi-objective nature of the problem many feasible solutions exist that will provide different benefits for the respective stakeholders. Consequently, a set of feasible solutions, with different advantages and disadvantages, should be suggested instead of one 'optimal' solution.	-	-	-	-	-	✓	✓
ATTENTION POINTS							
A.1 The framework should be grounded on improving, or addressing, all six building blocks of the health care system, as described by the WHO health care systems framework, namely: (i) Leadership and governance; (ii) health care finance; (iii) health workforce; (iv) medical products; (v) information systems; and (vi) service delivery.	✓	✓	-	-	-	-	✓
A.2 The solution should take strategic uncertainties of the pharmaceutical drug R&D market into account, providing a means, within the boundaries of this research to address the strategic uncertainties applicable to this research.	✓	-	-	-	-	-	-
A.3 The proposed incentive interventions should contribute towards creating an attractive and supportive environment for investment in R&D for NDs.	It can be anticipated that the feasible set of solutions, suggested by the framework, will create a supportive R&D environment provided that the stakeholder objectives, context-specific-, and non-specific criteria are incorporated into the decision-making process.						
BOUNDARY CONDITIONS							
B.1 The framework should promote the needs of all stakeholders and consider the role of each stakeholder to ultimately provide a solution that will positively influence the patient, as well as other stakeholders involved.	The profiles of the enabler, innovator and end-consumer stakeholders incorporate the requirements and ensures the promotion of all the involved stakeholders.						

9.1.3. SME verification

The input for this stage of verification is the knowledge of SMEs, gained by means of semi-structured interviews. SMEs with extensive knowledge and experience in the following fields were approached for participation in this verification process: (i) NDs or NTDs, (ii) the pharmaceutical R&D industry, or (iii) incentive interventions. Unintentional convenience sampling occurred in the selection of SMEs to participate in this research as a result of the interviewees needing to be willing participants. Table 9.2 contains information concerning the SMEs. The identities of the SMEs are kept undisclosed to protect the privacy of the individuals. The SMEs will be referred to by the names indicated in Table 9.2.

Table 9.2: Information concerning SMEs.

Person (*Date*) *Place*	Expertise of the SME	Qualifications
SME: 1 (23 September 2019) *Skype meeting*	Senior academic at a school for tropical medicine with focus on vaccine development. Founding editor of a prominent scientific journal focused on NDs. Based in the USA.	M.D., PhD.
SME: 2 (20 September 2019) *Skype meeting*	Director at a global scientific organisation. Project lead of incentive intervention developed to promote development of affordable and accessible tuberculosis regimes. Based in Switzerland.	MB ChB, MRCP
SME: 3 (20 September 2019 and 19 August 2020) *Skype meeting*	Researcher at independent non-profit organization, focused on public health and improving pharmaceutical industry involvement in diseases that mostly affect people from LMICs. Specific interest in health policy. Based in the Netherlands.	PharmD, MPhil (Pharmacology)
SME: 4 (7 October 2019) *Phone call and questionnaire*	Medical director at a multinational pharmaceutical organizations. Extensive knowledge of the ND and pharmaceutical R&D spheres. Based in South Africa.	MB ChB
SME: 5 (19 October 2019 and 27 July 2020) *Skype meeting*	Associate director at non-profit organization, working to advance research and improve global health by forming partnerships between public and private organizations. Responsible for collaborations between different stakeholders. Based in the USA.	Ph.D. (Molecular Cell, and Developmental Biology)
SME: 6 (24 October 2019) *Email and questionnaire*	Policy specialist in health technologies, innovation, and access at a division of an intergovernmental organization responsible for, amongst other things, maintaining international peace and security. Member of a US-based law school advisory board. Based in the USA.	LLM (Law), Master (Law, Political, Economics) J.D., Law
SME: 7 (23 July 2020) *Skype meeting*	Medical advisor and clinical operations manager (Middle East and Africa region) at an international pharmaceutical organization. Based in South Africa.	MB ChB, MMED (Clinical Pharmacology)
SME: 8 (28 July 2020) *Skype meeting*	Associate professor of tropical infectious diseases biochemistry. Member of research network aimed at addressing NTDs in Africa. Based in Ethiopia.	PhD (Biochemistry)
SME: 9 (7 August 2020) *Skype meeting*	NTD program officer at non-profit organization championing action that reforms public health across Africa. Works with partners to coordinate campaigns for NTD control and elimination campaigns. Based in Senegal.	MPhil (Public health), BSc

As indicated in Table 9.2, SME 6 completed a questionnaire form in contrast to the rest of the SMEs with whom interviews were conducted. SME 6 requested this as their busy schedule did not allow time for a meeting. As a result, SME 6 evaluated the research only based on the pre-read document and discussions via email. The reason why a deviation from the standard interview procedure of the verification of the framework was accommodated in this case, is because the input of SME 6, provided their background knowledge and expertise, is considered to be valuable, both for refining the framework and for contributing to the credibility of the research.

9.1.3.1. Purpose of the SME interviews

Before further discussing the SME verification process, attention should be devoted to clearly accentuating the rationale behind the verification interviews. Establishing the desired output of the verification interviews allows for the maximum value to be extracted from both the interviews, as well as the interpretation of the data analysis of the interview comments and critique. The objectives of this step of the research is as follows:

(i) Establish whether the framework accurately performs its intended purpose;
(ii) Verify whether all the decision-support framework components are comprehensive and credible;
(iii) Analyse SME critique to identify concepts that are not included in the framework (gaps and omissions); and
(iv) Analyse and interpret SME critique to find valuable themes and patterns to incorporate into the framework.

The formulation of interview questions, the selection of the SMEs, as well as the interpretation of the SME critique are grounded in meeting the four abovementioned SME verification objectives.

9.1.3.2. Interview questionnaire for verification

The interview questions are formulated to: (i) evaluate the input used to develop the framework; (ii) evaluate the thoroughness of the decision-support framework components; as well as (iii) ensure that each framework component is accurate and sufficiently comprehensive in performing its intended function.

Of the nine SMEs, six were interviewed in 2019 and five interviewed in 2020 (SMEs 2 and 5 were interviewed in both rounds). The reason for two phases of verification to be performed, is as mentioned in Section 9.1.1, to firstly identify major requirement specifications that the framework did not address after the initial version of the decision-support framework, and to evaluate the perceived correctness of the decision-support framework, before the final version of the framework was developed. This resulted in the second round of interviews including interview questions, not included in the first round, to verify the added decision-support framework components. With three of the first round interview questions (2.2, 2.4 and 3.4) omitted in the second round of interviews due to four main reasons being: (i) to allow enough time for all the interview questions; (ii) Question 2.2 is based on literature; (iii) Question 2.4 is partially already incorporated in Question 2.3; and (iv) Question 3.4 referring to the decision-support framework focus areas, is replaced with Question 3.5 with different terminology and additional 'focus areas' included after changes made to the framework. Both the SME verification interview rounds are discussed in this section, with all the feedback received in the interviews further analysed in Sections 9.1.4 and

9.1.5, and all the framework refinements discussed in Section 9.2, regardless the time instance in which the suggested feedback was given. The aforementioned is done to simplify and improve the readability of this research.

The verification questions asked to the SMEs (Table 9.3), are divided into three parts.

Table 9.3: SME verification questionnaire.

No.	Verification questions	SMEs
Part 1: System demarcation verification		
1.1	To what extent is the system demarcation effective to determine the status quo of an R&D environment?	1 - 9
1.2	Does the system demarcation contain all the applicable context-specific element categories and system elements (frequently experienced challenges) to assist in understanding the need that the pharmaceutical R&D environment might have for an incentive intervention? If not, could you provide any guidance on additional elements that should be considered for inclusion?	1 - 9
1.3	To what extent do you agree that incentive-based interventions cannot address all the pharmaceutical R&D system demarcation elements?	1 - 9
Part 2: Incentive-based interventions and incentive-based-intervention criteria		
2.1	Can you think of any category of incentive-based intervention not included in the list of 26 incentive types?	1 - 9
2.2	Are the definitions of the incentive interventions adequate in providing a brief introduction to the meaning of the interventions?	1 - 6
2.3	Do you think the CLIC is sufficient in depicting the most critical requirements that an incentive-based intervention must adhere to (criteria matrix columns)? If these are not sufficient, could you provide any guidance on additional elements that should be considered for inclusion?	1 - 9
2.4	Do all the CLIC and CLIC categories included, affect the consideration of incentive interventions?	1 - 6
Part 3: Stakeholder profiles, focus areas and criteria		
3.1	Can you think of any objective or internal capability, in the enabler inquiry form, that is absent and might play a crucial role in the solution decision?	1 - 9
3.2	Can you think of any objective or internal capability, in the innovator inquiry form, that is absent and might play a crucial role in the solution decision?	2, 5, 7 - 9
3.3	Do you think the consumer requirements and objectives is sufficient to depict the most salient requirements of the consumers that should be considered when selecting an incentive intervention?	2, 5, 7 - 9
3.4	Do you think all the focus areas that play a role in decision-making of an appropriate incentive intervention are included in the framework? If not, could you provide any guidance on additional focus areas that should be considered for inclusion?	1 - 6
3.5	Do you think the criteria clusters of the solution set are effective and comprehensive in depicting the different incentives' abilities?	2, 5, 7 - 9
3.6	To what extent do you agree that the format of the decision-support framework solutions are being presented in a manner that provides insight into the relative strengths of incentives per criteria cluster? Thus, providing the decision-maker with an objective overview of the multi-criteria decision.	2, 5, 7 - 9

Table 9.3 also shows what questions were asked to which of the SMEs. Though, given the semi-structured nature of the interviews, additional questions were discussed. Some of the questions in

the questionnaire are linked to a Likert rating scale, whereas other questions are open-ended. With the permission of each SME, a voice recording of the interviews were made, enabling the author to revisit the discussion and ensure that no details of the interview are overlooked in the documentation of the feedback received.

9.1.3.3. Interview protocol

Prior to the scheduled interview, a pre-read document was sent to the SMEs (refer to Appendix I for the first round of interviews version and Appendix J for the latest version). The pre-read informed the SMEs on the developed framework, and the operationalization thereof by providing the most salient information necessary to understand the crux of the research output. The interview then followed along the lines of the following procedure:

(i) The author presents the purpose and a brief overview of the decision-support framework to the SME (the SMEs were given the option to skip this step). Appendix L and M depicts the MS PowerPoint presentations delivered in rounds 1 and 2 respectively.
(ii) The author gives a live demonstration of the decision-support framework in MS Excel.
(iii) An introduction question was asked to find out more about the SME's occupation and knowledge on fields that are applicable to this research.
(iv) The questions, shown in Table 9.3 and Table 9.14, were discussed. The interviewer provided insight into the questions where needed and answered any questions raised by the SMEs.
(v) In some cases, questions, directly linked to work that the SME has done, were asked to gain more knowledge based on their expertise and experiences in the neglected disease sphere.
(vi) In two of the cases, the SMEs were asked about their input regarding the changes made to the framework based on feedback received during the first round of verification interviews.

Given the semi-structured nature of the interviews, the interviewer or SME could, at any point in time, deviate from the intended protocol, to ask questions and/or provide insight.

9.1.4. Verification interview data analysis

In order to comprehensively analyse and present the data gathered from the interviews, a qualitative data analysis process, suggested by Creswell (2014) is followed. Figure 9.1 depicts the six-step process. The interview data is transcribed. This is followed by categorizing the data of the respective interview questions into parts. As a result, the data from each interview adheres to the same structured layout, which facilitates the data analysis process.

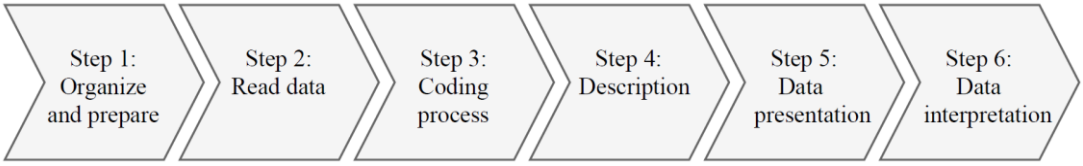


Figure 9.1: Qualitative data analysis process (produced from Creswell (2014)).

The first step of the six step qualitative data analysis process entails investigating the input from the interviewees by analysing and organizing all the interview transcript data. The transcription of the data also forms part of this data preparation and organization step. The data preparation leads to differentiating between the different sets of comments. Where comments are divided as: (i) relevant and feasible to incorporate into the framework; (ii) not relevant or out of the scope of this research; (iii) already incorporated into the framework; (iv) agreed but did not implement; (v) nice-to-have aspect; or (vi) something that should be taken note of but not necessarily incorporated. The data preparation also established the sets of comments where, the interviewee: (vii) disagreed with something in the framework; (viii) did not provide any comment; or lastly responded with 'indifferent' due to the SME (ix) not understanding; or (x) not having the knowledge or insight required to answer adequately. The second step of the data analysis process is completed by reading through all the different sections of transcript data.

The next step is the coding process. Where coding refers to the process of organizing the data into different parts or segments and providing a name that represents those data segments, consequently leading to a summarized, condensed and/or reduced data set (Creswell, 2014). According to Saldana (2009) various methods of coding exists, with qualitative data coding entailing the formulation of interpretations by a researcher. The fundamental aims of the interpretations are to categorize the data and to detect patterns. According to Saldana (2009) patterns in data can be recognized by one of the following: (i) similarity; (ii) difference; (iii) frequency; (iv) sequence; (v) correspondence; or (vi) causation.

Although coding does not have a "*specific formula to follow*", Saldana (2009) does state that it is usually a "*cyclical act*" (Saldana, 2009, p. 7, 8). Therefore, each iterative cycle breaks the data apart in analytically relevant ways in order to lead to further questions about the data. The effect of 'coding filters', where the manner in which the data is interpreted depends on either (i) the researcher's analytic lens, or (ii) on the type of filter that covers that lens, should also be considered. The aforementioned lenses affect the way in which the researcher perceives, documents and codes the data (Saldana, 2009).

Coding is an exploratory problem-solving technique, described by Saldana (2009) to be not just concerned with labelling, but also with linking data. The aim of the coding process as applied in this dissertation, is to summarize and interpret the themes, categories, and patterns that exist in the SME interview data. *ATLAS.ti*, one of the preferred electronic ways in which data can be coded suggested by Saldana (2009), was utilised in this research.

The coding for this research is completed in three coding cycles. Figure 9.2 depicts the three coding cycles and the primary activities completed for each cycle. The first cycle focuses on evaluating the input provided by the SMEs and identifying what statements, comments and critique are applicable to which component of the decision-support framework. The second coding cycle focuses on investigating the themes evident per framework component. The third, and final, coding cycle investigates deeper insights into the data by yielding overhead themes of the interview data. The derivations and findings made in each of the coding cycles are subsequently discussed.

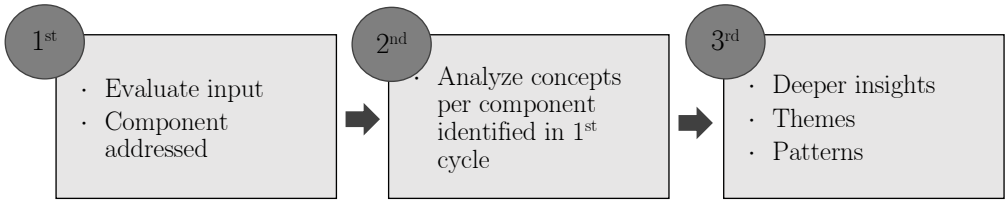


Figure 9.2: Coding cycles completed part of verification data analysis.

9.1.5. Verification data analysis results

The three coding cycles, (step 3) of the qualitative data analysis process, as well as the description, presentation and interpretation (step 4 - 6) of the interview data are depicted in this section.

9.1.5.1. First coding cycle

The purpose of the first coding cycle is primarily to start processing and categorizing the concepts suggested by the SMEs to: (i) determine whether all the framework domains are adequately discussed and agreed on; and (ii) structure the data in a way that will facilitate the data analysis in the coding cycles that follow. The open-ended nature of most of the semi-structured interview questions resulted in the interviewees deviating from the question. Even though the interviewer made an effort to guide the discussion into the direction of the question, deviation seemed to be inevitable. The topic deviation of SMEs provoked interesting discussions leading to core concepts that should be included in the framework, but also resulted in some framework components being discussed in more detail, compared to others. Consequently, this coding cycle analyses the interview data, followed by allocating codes to each comment made by relating it to one of the primary framework components.

Although the interviews had a fixed set of questions discussed, the time spent, and amount of critique given for the respective components differed noticeably. The interview data was coded in such a way that the number of comments made on each framework concept was recorded. Comments in this section are defined as any statement made discussing one concept or providing one argument that relates to the operation or content of the framework. The comment occurrence for the different framework components are presented in Figure 9.3. Depicting the occurrence of comments made per component provides insight into (i) whether the component was thoroughly discussed; (ii) where SMEs have significant knowledge, and (iii) where a number of improvement suggestions were made.

The framework components are listed in sequence, where the number in brackets indicates the domain where the component is addressed. It should be noted that the numbering of the domains in the first round of verification interviews were different from the numbering of the domains in the latest version of the framework. To minimize confusion, all the domains are referred to as they are in the current version of the decision-support framework, refer to Chapter 8 for the overview of the decision-support framework domains.

It should also be noted that the number of comments made are not restricted to one comment per SME.

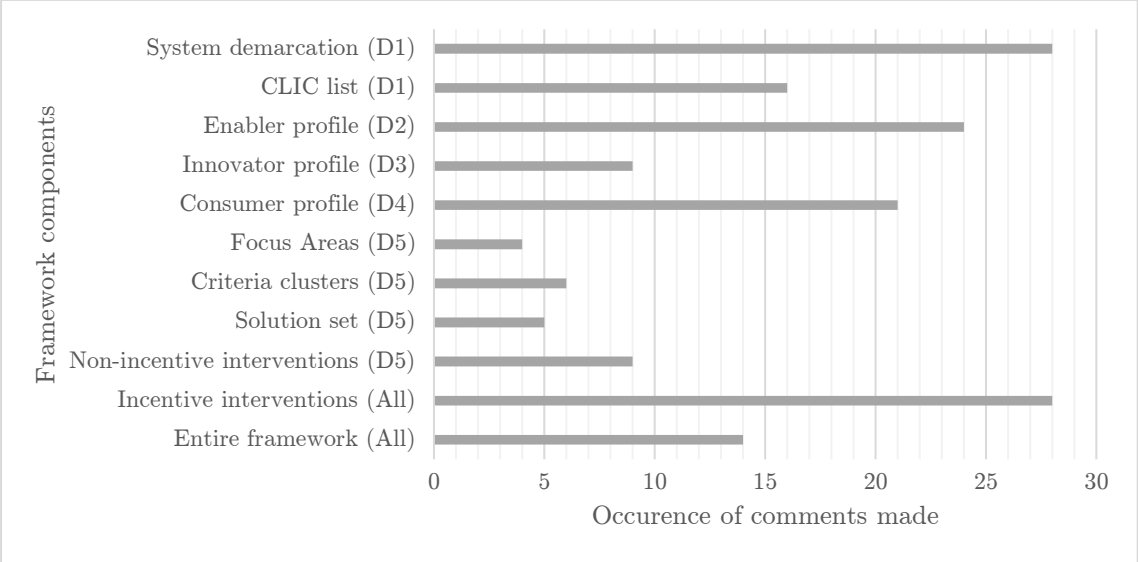


Figure 9.3: Occurrence of comments made per framework component.

The interviews resulted in a general consensus amongst the experts agreeing to the accuracy and usefulness for all the domains. Evident in the interview data was that the different SMEs, with their versatile backgrounds and knowledge, provided insight into the distinct research components that are relevant to their field of expertise. Although the SMEs convened for this research were from a variety of backgrounds, all of their expertise were focused on health, health access, pharmaceutical organizations, drug development, education, health policy and drug incentives.

The two components discussed most are the incentive interventions, the enabler and the consumer profiles. This is ascribed to the fact that all of the SMEs have insight and knowledge in these three components of the framework. It is also worth mentioning that the focus areas (phase 1), as well as the innovator profile, consumer profile, and the criteria cluster domains (phase 2), were only questioned in the one phase of the verification interviews. With the rest of the components included in the questions for both phases of verification interviews.

9.1.5.2. Second coding cycle

The purpose of the second coding cycle is to investigate which framework concepts are verified, and to identify any omissions, further refinement or additional concepts that should be added to the framework. The verification objectives fulfilled by this cycle, include numbers two and three listed in Section 9.1.3.1, namely aiming to: (ii) verify whether all the framework components are comprehensive and credible; and (iii) identify omissions and concepts that are not included in the framework.

This coding cycle adopts two lenses derived from analysing the interview data. These lenses appeared throughout the interview discussions, and again when all the interview data was investigated. The two lenses that are adopted for this cycle are listed in Table 9.4. These lenses improve the ability to analyse the data into relevant segments, and to identify similarity between the concepts suggested, evaluated and omissions identified by the SMEs. The lenses were applied when reading through the interview data to gather information regarding each lens.

Table 9.4: Adopted lenses in second coding cycle.

Adopted lenses	Description of lens
Conceptual	These refer to new insights and ideas regarding the theories, aspects, and views already incorporated in the framework.
Structural	Structural concepts are suggestions and understandings of the complexity, design, format, need or overall observations of the framework.

The primary components of the framework (established in coding cycle one) formed the basis of identifying omissions and additional concepts to add to the framework. The findings of the second coding cycle are summarized in Table 9.5. For each of the framework components (rows), the following are identified and discussed: (i) topics confirmed and agreed on by the SMEs (VC); (ii) omissions or disagreements with the framework (DG); (iii) additional concepts to add or consider in the framework (AD); and (iv) observations regarding the two lenses, where applicable. The concepts discussed in Table 9.5 are mostly derived from the interview data directly, by using in vivo coding (direct words of SMEs) to formulate the arguments listed. Each concept made by SMEs, listed in Table 9.5, is allocated a reference number to make the referencing and traceability of the concepts easier. The relevant additional concepts and refinements suggested in Table 9.5 are further discussed in Section 9.2.

Domain 1: System demarcation and CLIC

The system demarcation section includes all concepts that relate to Domain 1 of the framework. All the SMEs were unanimous in stating that Domain 1 is effective in determining the status-quo of the R&D environment. The domain is described as "very effective" (SME 5), and that it provides "a good landscape" (SME 3). The SMEs similarly confirmed that the context-specific-elements list is "very comprehensive" (SME 7 and 8), with specific suggestions made on aspects to be considered for inclusion further discussed in Section 9.2.

The most predominant disagreement responses of this section relate to either (i) service delivery, or (ii) the drug treatment appropriateness. Service delivery embodies a particularly large scope of activities within the pharmaceutical industry, ranging from the accountability of the system to basic delivery logistics. Although acknowledging the importance of all service delivery dimensions (refer to Section 3.1.3), all aspects thereof are not relevant to the pharmaceutical R&D system. This research does not investigate the ground logistics on providing treatment to end-consumers but does discuss certain aspects thereof in the non-incentive-based intervention solution set. The second disagreement mainly relates to characteristics of the treatment being developed. These characteristics are regarded in more detail in the enabler, and consumer inquiry forms.

SME 1 discussed a "fundamental flaw" of all studies on R&D investment as not providing a differentiation between drug and vaccine R&D sufficiently. Though, SME 1, an ambassador for neglected disease vaccines, also states that "most of the literature does not recognize", and "most of the incentives are not designed to incentivize vaccines". The difference between the R&D processes for drugs and vaccines are also highlighted by SME 5, stating that "the economics and R&D processes of drugs and vaccines differs without a doubt".

Table 9.5: Summary of the second coding cycle findings.

Section		Verified concepts (VC)	Disagree and gaps (DG)	Additional insight (AD)
Domain 1:	System demarcation	VC.1 Adequate to determine pharmaceutical status-quo	DG.1 Complex to have so many topics in one diagram	AD.1 Difficulty in being comprehensive for so many topics
		VC.2 Good, comprehensive, landscape of R&D properties	DG.2 Appropriateness of drugs; also wording might be confusing	AD.2 WHOPQ quality assurance practices
		VC.3 Very effective in investigating the environment	DG.3 Instability of drugs; thermostability of products, existing and required	AD.3 End price profit margins set by donors not countries
		VC.4 Provides a list of all the important aspects to consider	DG.4 Acceptability of drugs	AD.4 Impact of donors on drug consumption
			DG.5 Pill burden appropriateness	AD.5 Difference between small molecule & vaccine R&D
			DG.6 Complexity of manufacturing, maybe rename to "Qualified manufacturing"	AD.6 Some pharmaceutical organizations don't solely want to make ROI, but just break-even
			DG.7 Human resources (trained personnel to population ratios)	AD.7 Insufficient exclusivity in governance is not negative
			DG.8 Potentially split quality and efficacy of drugs	AD.8 Capacity building of the context-specific requirements
			DG.9 Clinical trial diversity (include more diversity than just racial)	AD.9 Drug donations might de-incentivize pharmaceutical R&D
			DG.10 Health system elements of service delivery	AD.10 DALYs might put NTDs as a low priority
	CLIC	VC.5 Some CLIC are more important/ have more weight than others	DG.11 Payoff to innovators based on cost-effectiveness rather performance	AD.11 Conservation of resources versus yield of the process
		VC.6 CLIC covers the scale of depicting most critical elements that incentive should adhere	DG.12 The political situation in the country.	AD.12 Payoff based on cost-plus model. Reward above profit margin
		VC.7 No CLIC element is redundant, all affects incentive consideration	DG.13 Country ownership and leadership used in the 2030 NTD roadmap, consider using their terminology.	AD.13 Bandwidth of participating in incentive, might be a motive
		VC.8 Very comprehensive list	DG.14 'Reduce clinical trial risk involved' is more like an outcome, rephrase	AD.14 Context-specific factors might still surface after implementation
Domain 2:	Enabler Profile	VC.9 Sufficient enabler objectives and internal capabilities	DG.15 Different partners 'enablers' have different roles	AD.15 Different types of data sharing: Full, partial, closed data sharing
		VC.10 Very comprehensive list, especially market authorization and clinical trial regulations	DG.16 Tiered-pricing, intuitive pricing, or based on income-brackets	AD.16 Data sharing part of funding agreements
			DG.17 Affordability and access as part of the goal	AD.17 Collaboration component for the case of regime development
			DG.18 Donors and procurement	AD.18 Possibly technology and expertise as part of enabler capabilities
			DG.19 Regime development, combination of drugs	AD.19 Split of the market when no consensus of agreements
			DG.20 Data sharing between collaborators	AD.20 Corporate social responsibility
			DG.21 Connection to the consumer seems missing.	AD.21 Public reputation and building marketability/brand image.
			DG.22 Access to data, compounds& IP	AD.22 Network partners, to offer distribution as part of agreement.
			DG.23 De-risking can be a goal of enabler	
Domain 3:	Innovator Profile	VC.11 Sufficient innovator objectives and internal capabilities	DG.24 Public reputation and brand image, subtle but still present.	AD.23 Might be tricky to get innovator to participate
		VC.12 Comprehensive list of innovator characteristics	DG.25 Manufacturing capacity required from the enabler stakeholder.	AD.24 Incorporating economic viability for innovators concept
			DG.26 Enabler might link the innovator with their network.	
Domain 4:	Consumer Profile	VC.13 Sufficiently included the treatment, social and economic aspects	DG.27 Ethical considerations within the treatment	AD.25 Considering stigma around NTDs and taking drugs
		VC.14 Comprehensive and sufficient list of consumer criteria	DG.28 Clinical trial diversity (ethnic groups, sex, age group, pregnant women)	AD.26 WASH and sanitation initiatives and how they can be incorporated)
			DG.29 The type of consumer to make sure the drug is appropriate	AD.27 Preventative versus reactive treatment
			DG.30 Drug registration in a country	
			DG.31 Contextual treatment criteria seem like a catch-all phrase, expected to see drug safety, side effects, use-ability, administration and advocacy.	

Table 9.5 continued on next page

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Section		Verified concepts (VC)	Disagree and gaps (DG)	Additional insight (AD)
Domain 5:	Criteria clusters	VC.15 It is a comprehensive list VC.16 Agree that the clusters are useful and has value in this framework	DG.32 Considering countries that don't prioritize NTD, maybe difficult to launch drugs in that country.	AD.28 The 'abilities' might not be measured at this stage of the research. AD.29 Consider removing 'enabler' from cluster 6, just general limited investment in resources
	Solution set	VC.17 Strongly agree that it provides the decision-maker with a good overview of the multi-criteria decision. VC.18 The format of the framework provides insights into the strengths and weaknesses of the incentives per criteria cluster. VC.19 This framework informs the stakeholders of incentives available and how to select it so that it is mutually beneficial to everybody	DG.33 The binary evaluation of the incentives might provide a biased result, where a 5-tier scale might provide better insight into the incentives abilities	AD.30 Allows stakeholders to see the incentives by their prioritized clusters, as well as when all clusters are prioritized
	Focus area	VC.20 All focus area plays a role in decision-making of appropriate incentives VC.21 Comprehensive list of focus areas	DG.34 Considers R&D environment in isolation of R&D system at large, such as more profitable diseases	AD.31 The impact of risk to the incentives AD.32 Public perception (reference to vaccine debacle)
Overall Framework	Non-incentive	VC.22 Agree/Strongly agree that non-incentive-based interventions are comprehensive VC.23 Incentive-based interventions cannot address all the pharmaceutical R&D demarcation elements.		AD.33 Consider rewording this to: Interventions outside scope of pharmaceutical R&D industry AD.34 The neglected disease issue is complex and varies, so no one solution is possible, but a series of interventions must be considered.
	Incentive interventions	VC.24 Incentives are the areas where organizations are most responsive to VC.25 A (this) system to easily facilitate incentives is important VC.26 Types of incentive-based interventions are comprehensive VC.27 Accurate and adequate definitions of incentive interventions VC.28 Types of incentives are well defined VC.29 Agree to vaccine incentives being excluded, with economics and processes being so different	DG.35 Definitions of open source, PPPs, TRIPS, PRVs DG.36 Risk in saying 96 interventions, rather non-exhaustive list DG.37 Data sharing DG.38 Private capital being venture capital investment funding DG.39 Incentive interventions: SABIN; EDCDP; MPP; WIPO; IPM; TB Drug accelerator; IAVI; TB Alliance; BRICS network DG.40 Working group description is extraordinarily broad, so might lead to misinterpretation.	AD.35 No mechanism for regional disease importance AD.36 Public or philanthropic funding resulting in public-available data AD.37 Some incentives only funds operational research AD.38 The motive behind investment/ collaboration might be to get a message across (e.g IP not bad) AD.39 Differential pricing seems like a mechanism to increase access and not necessarily encourage R&D AD.40 Consider looking into subscription-model, used in antibiotic research, very novel AD.41 Maybe including behaviour change incentives, but this is more aimed at the consumer

Consensus among SMEs exist that the CLIC is sufficient and comprehensive, with SME 3 stating that the list "overall covers the scale of depicting the most critical elements that incentives should have". A comment was made that the 'sustainability and green' category is less important than some of the other categories, this can however be justified with the priority score of the CLIC elements already built-in to this domain.

Domain 2: Enabler profile

The SME feedback for this domain was quite diverse. With specific reference to SME 1, who did not discuss this section due to lack of knowledge of the domain. Although most SMEs agreed that the profile is comprehensive, various suggestions were made to incorporate additional concepts that could add value.

Some of the major omissions highlighted, and insights gained in this domain included the following: First, the development of drugs as regimes. Considering that some drugs already exist for most NDs, regime development could drastically improve the effective intervention of diseases. Second, and linking to the interaction between enablers, is the concept of data sharing between collaborators. Data sharing is evident in collaborations, with certain agreements compelling stakeholders to share certain data. The third major insight highlighted by the SMEs is that certain enablers use certain incentives as a method to de-risk their efforts to improve or advance the R&D of a neglected disease treatment.

Domain 3: Innovator profile

Two domains were added to the decision-support framework, after the initial round of verification interviews were conducted. The innovator profile is one of them. This led to only the second round of subject matter expert interviews, having the opportunity to verify this domain.

The SME feedback for this domain, was again unanimous in stating that the list of innovator objectives and internal capabilities is "sufficient" and "comprehensive", according to SMEs 8 and 9 respectively.

Two omissions highlighted include, firstly, the subtle but still evident objective, mentioned by SME 7, of performing R&D for a neglected disease that might include "public reputation and brand image". According to SME 7, performing R&D for a neglected disease, can be seen as a 'marketing strategy', where the organization might be awarded or recognized for its 'philanthropic' services to public health. Second, the type of manufacturing required, and the intricacy of the specific manufacturing method, according to SME 3, might play a role in the ability of the innovator to perform R&D for a specific drug.

Domain 4: Consumer profile

The consumer profile, similar to the innovator profile, was added to the framework after the initial verification interview round. Therefore, once again, this profile was only verified during the second round of subject matter experts interviews, though many suggestions and comments were made in the first round of verification interviews regarding the consumer stakeholder.

The SMEs agreed that the consumer criteria list was comprehensive and sufficient in depicting the most important requirements of the consumer stakeholder, with SME 8 highlighting that the framework "sufficiently includes the treatment, social and economic aspects of the consumer stakeholder". Some of the major omissions and additional insights highlighted in terms of this profile, relate to context-specific considerations of the consumer stakeholders, such as: (i) ethical considerations; (ii) type of consumer that will be consuming the drugs; and (iii) whether the consumers requires a preventative or reactive treatment. In the development of the consumer stakeholder, these context-specific considerations of the consumer stakeholder were considered and attempted to be included by adding the consumer requirement: 'Context-specific treatment criteria'.

Domain 5: Criteria clusters, solution set and focus areas

Another major change that was incorporated into the framework after the first round of verification interviews, is the alteration and refinements to the solution set domain. Though the

changes made to the solution set are highlighted in more detail in Section 9.2, something to take note of is that the solution set focus areas (verified in verification round 1), are replaced with the more encompassing criteria clusters. This section, consequently, includes the verification discussions of both the focus areas as well as the criteria clusters. This approach is taken as the inputs on the focus areas that were gained in the first round of verification interviews is still valid for the current version of the framework (even though the focus areas are not explicitly stated in the manner that they were in the initial decision-support framework design).

Very brief feedback was provided for the focus area section of the framework, with the aspects established during verification including that: (i) all focus areas play a role in the selection of appropriate incentives; and that (ii) the focus areas are comprehensive.

The SMEs were in general agreement that articulating the feasible set of incentives by means of the criteria cluster-scores increases the quality of the decision-support framework output significantly. SMEs 7, 8 and 9 agree that the criteria clusters list is "comprehensive", with SME 5 agreeing to the criteria clusters being "useful and adding value to the decision-support framework".

The following key aspects of the overall solution set content and design were verified, namely: (i) it provides the decision-maker with a good overview of the multi-criteria decision (SMEs 5 and 8); (ii) the output format provides insights into the strengths and weaknesses of the incentives per criteria cluster (SMEs 7 and 9); and (iii) the framework informs the decision-makers of the available incentives to select from, and which decision(s) might be beneficial to all the involved stakeholders (based on the framework input). Some additional insight from SME 5 also highlights the ability of the solution set to provide the decision-maker with the means to see what the incentive options are regarding the prioritized criteria clusters.

Overall framework: The incentive- and non-incentive-based interventions

In the first round of verification interviews, the response of three of the five SMEs emphasised that the set of incentive intervention instances is not complete. In hindsight, this is an indication of a poorly formulated question, rather than an indication that not all incentive instances are listed. The question should not have asked whether the set of incentive intervention instances is complete, as it is known that the list is not exhaustive and serves as examples of interventions for reference purposes. A better formulation of the question would be to ask whether the 26 incentive types are exhaustive, which was adapted accordingly in the second verification round.

In line with the intention of the domain, all SMEs agreed that the list of 26 incentive types are comprehensive. Private capital was initially included as one of the incentive strategies, in line with a proposal by Renwick *et al.* (2016). Based on feedback from SMEs it has, however, been removed throughout the document as it is deemed to be a means to enable incentive interventions, rather than an incentive strategy in itself. One and two of the incentive type definitions were respectively mentioned by SMEs 2 and 3 to be outdated, or the wording thereof slightly misleading. The suggested changes to the list of incentive intervention instances, as well as the three definitions, were added to the framework, as outlined in Section 9.2.

Another major adjustment made to the framework between the two verification rounds, is removing all the incentives aimed at encouraging vaccine R&D. Refer to Section 9.2.1.1 for an elaborated explanation.

The SMEs did not provide extensive feedback on the non-incentive-based interventions, other than stating that the non-incentive-based intervention list is comprehensive. The second attribute mentioned, is that incentive-based interventions alone cannot address all the system elements of the pharmaceutical R&D system, thus supporting the framework's design that includes non-incentive-based interventions.

Additional concepts

All the additional concepts to be incorporated or deemed as not feasible that are mentioned in Table 9.5, and/or the discussion of this coding cycle, are briefly mentioned and incorporated into the framework in Section 9.2

9.1.5.3. Third coding cycle

The purpose of this coding cycle is to yield themes and deeper insights into the interview data. The SME interview objectives realised in this coding cycle are: (i) establish whether framework is accurate to perform its intended purpose; and (iv) analyse and interpret SME critique to find valuable themes and deeper insights to incorporate. These derivations build on the outcomes of, primarily, the second coding cycle where certain topics featured continuously. The most frequently occurring features and concepts are grouped together as themes and deeper insights to be considered for meeting the objectives of the SME verification.

Seven overarching themes emerge from the data namely: (i) stakeholder characteristics; (ii) collaboration; (iii) perception and responsibility; (iv) manufacturing considerations; (v) incentive implementation; (vi) incentives; and (vii) overall framework concepts. Where themes (i) – (v) relate mostly to the conceptual lens discussed in coding cycle two, and themes (vi) – (vii) more to the structural lens. Each theme will be discussed separately, to provide deeper insight into the relevance of the theme to this research and the impact that the theme might have on the stakeholders, interaction of stakeholders, or the feasibility of the suggested incentive intervention.

(i) Stakeholder characteristics

The stakeholders are recognized as one of the most integral parts of a successful incentive intervention, given the need to: (i) come to agreement; (ii) the willingness to cooperate; and (iii) the ability to innovate in developing the desired treatment. The stakeholder characteristic themes mentioned by the SMEs, range over all three stakeholders and relate to various aspects of each. Table 9.6 depicts the three stakeholder profiles (sub-categories), relevant sub-themes and deeper insights yielded through SME interviews. Only two of the most prevalent case sub-themes will be discussed in detail.

Table 9.6: Stakeholder profiles' relevant sub-themes and deeper insights.

	Sub-themes	Theme attributes and deeper insights
Consumer profile	Treatment access	All access components were brought up by SMEs, namely that the framework should encourage: (i) appropriate; (ii) affordable; (iii) accessible; and (iv) acceptable treatments. The quality assurance and different quality standards acceptable by different procurers are also evident to drug acceptability standards.
	Burden of disease	DALYs is not always the most accurate estimate of disease burden, though it is the most widely accepted one. A critique of DALYs is that a significant portion of disease burden amongst poor populations living in developed countries is not recognized.
	Context-specific requirements	Specific requirements that consumer stakeholders might have, including the type of consumer targeted, potential consumer stigma and consumer ethics, are highlighted by SMEs to be important for considering in the selection of an incentive intervention.
	Alternative interventions	A well-known preventative intervention widely implemented to reduce the occurrence of NTDs is water, sanitation and hygiene (a.k.a. WASH) initiatives. Though this framework focuses on implementing an R&D incentive, consideration should be given to curbing the disease with alternative interventions.
Enabler profile	Internal capabilities	Enablers have technological-, facility- and expertise capacity, and also have possible objectives to increase internal bandwidth, improve the reach and quality of networks, as well as portray a certain 'message' of importance.
	Payoff to innovators	Payoff to innovators does not necessarily depend on cost-effectiveness, but rather as a result of drug performance and attributes that the drug meets. Payoff methods also include the cost-plus method.
	Risk and de-risking	Risk, being a major contributor to the poor state of R&D pipelines, should be more evident in the framework. With a possible objective of the enablers being to de-risk.
Innovator R&D	Drug versus vaccine R&D	The R&D of vaccines is entirely different from R&D of small molecule drugs. Areas of difference include upfront investments being larger, time horizons being longer, level of investment higher, risk higher but also a higher public health impact, with the financial returns remaining modest.
	Regime development	Combining drug treatments offer improved treatments. Where combining the various drug compounds results in various complexities that should be clinically tested.
	Adaptive R&D	Adaptive R&D is often performed to improve the use of compound information.
	Diversity in clinical trials	Diversity in clinical trials needs to be considered in terms of ethnicity, sex, age, as well as pregnant and lactating women. Though this can also be seen as a consumer requirement in defining the identity of the consumer, it should be taken into account in the R&D process of the innovating stakeholders.

The first significant theme evident through all the SME interviews, is the five dimensions of access to medicines that are not adequately included in the initial version of the decision-support framework. In response to the SMEs' feedback, all five access dimensions of the consumer profile are taken into account in the final version of the decision-support framework (Chapter 8).

The second important theme is the payoff to innovators. One CLIC criterion states 'payoff to innovators based on cost-effectiveness', where SME 2 disagreed with this statement. In their experience, cost-effectiveness is not necessarily something that should be looked at, where drug performance is a much better criteria to base payoff to innovators on. The cost-effectiveness payoff has been included in the framework as it has been identified as a requirement for successful antibiotic research incentives by Granville and Trushin (2010).

The third important theme is the difference between vaccine and drug R&D. As previously mentioned, in Sections 9.1.5.2, SME 1 highlights the importance of differentiating between the R&D of drugs and vaccines, and consequently also the incentive interventions that encourage research for the respective products. As a result of the major difference, this research only focusses on incentives for encouraging R&D for drugs, and not vaccines. The drugs can be either preventative or treatment medications.

(ii) Collaboration

The collaboration aspects that were evident in the interview data are primarily the collaborating interaction between different stakeholders, cooperation with policies and agreements, and the effect that different collaborations might have on the treatment developed, and access thereto. Table 9.7 depicts the sub-themes and insights that emerged from this overarching theme.

Table 9.7: Collaboration sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Promoting collaboration	The collaboration between two or more innovators or enablers is important. The means of the framework to allow more than one entity per stakeholder to collaborate, and the means to collaborate, should be explored.
Data sharing	Data between stakeholders, as well as making certain data available to the public is required to a certain extent as part of certain funding agreements or policies. All stakeholders should be aware of these agreements before commencing collaboration. Various types, e.g. open source, full, partial and closed data sharing, exists.
Stakeholder participation	Difficulty in getting the different stakeholders to buy-in and assist with the completion of the decision-support framework might occur. With specific focus on the innovator stakeholder who might be concerned with completing the innovator profile if they do not understand the benefit to their organization.
Donors and procurement	Donors often procure drugs on behalf of the government. Consequently, they might have different criteria with regard to drug quality. Also impact on access, because donors are willing (or have the means) to pay much more than what governments (in most cases) do. The former has an impact on end price profit margins and drug access.
Drug donations	The donation of drugs is widely accepted from especially large pharmaceutical organizations in the ND sphere. Incentivizing R&D for a specific ND might be difficult as drugs are already being donated for NDs.
Market exclusivity	Market exclusivity, in this case grouped under collaboration, because of the discrepancy between different stakeholders' views on IP agreements. Where exclusivity in the neglected sphere is often seen as negative given the potential impact on access; whereby other stakeholders market exclusivity is a big incentive with regard to encouraging innovation and to ensure a profitable outcome.

The two most significant themes emerging from this overarching theme are: the collaboration of stakeholders; and the sharing of data. Within the context and operation of this framework, 'promoting collaboration' can imply two possible meanings. First, collaboration between the different stakeholders. This refers to the way in which stakeholders communicate, engage or make agreements. SME 2 mentioned the possibility of a "split in the market", that might occur as a result of stakeholders not reaching agreement on certain aspects, or terms. Second, 'promoting

collaboration' can refer to collaboration facilitation work done by a third party, such as WIPO Re:Search[20].

Reflecting on the role that WIPO plays, it can be derived that this framework might need a facilitator, or the input of a collaboration network, to serve as a communication and engagement platform on which the stakeholders present in the scenario can collaborate. The role of a facilitator was also deemed valuable by SME 7. The final observation with regard to facilitating collaboration, is the ongoing follow-up between stakeholders, to make sure that both parties are fulfilling and meeting their ends of the agreement. The aforementioned can, however, be viewed as part of the operationalisation of the incentive intervention chosen, as opposed to an aspect of the selection of an appropriate incentive.

Data sharing also has more than one meaning in the context of this research. First, it refers to the sharing of important data to facilitate the R&D process. Second, data should be shared after successful R&D. As stated, "there is an increasing awareness that any public or philanthropic financing has to result in publicly available product, which is data". (SME 2).

(iii) Perception and responsibility

The third overarching theme identified, linking to the stakeholder profiles, as well as the collaboration of the stakeholders involved, is the perceptions and responsibilities of the various stakeholders. With perception referring to ideas and thoughts of the specific stakeholder with regard to treatments, the disease, and R&D for those diseases. Responsibilities refer to the matters and actions for which the different stakeholders will be held accountable. Table 9.8 summarizes the sub-themes that emerged from this overarching theme.

Table 9.8: Perception and responsibility sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Public perception	The perception of the public on certain diseases, treatments or organizations might play a major role in the success of any health intervention. The public perception of specifically vaccines and vaccine safety has put immense pressure on vaccine development, negatively affecting the commencement of vaccine R&D.
Corporate social responsibility (CSR)	A lot of pharmaceutical organisations perform R&D for NDs, as part of their CSR-portfolios. CSR play a major role in organizations to pursue R&D, or to fund NDs.
Brand image and public reputation	It was argued that some stakeholders might be incentivized to perform R&D or to be involved in incentivizing R&D for NDs, for the sake of public reputation concerning social responsibility to public health.
Misconception of responsibility	The public puts significant emphasis and pressure on pharmaceutical organizations to be the 'saviours' to address all neglected disease challenges, but it should not be placed solely on one stakeholder.

CSR is found to greatly affect the amount of R&D performed, as well as resources invested for NTD treatment and interventions. Where CSR is applicable to not only the innovating organizations performing the R&D, but also to the enablers, including private and philanthropic organizations, who might be funding the R&D. In addition to CSR, SME 7 highlighted the

[20] The role of the World Intellectual Property Organization (WIPO) Re:Search organization is to engage with different innovating organizations, to find out what exactly their needs are, and who they can contact to meet those needs, therefore, to facilitate partnerships to develop new medicines for NTD, TB and Malaria. (SME 5)

influence that improving their brand image or public reputation regarding philanthropic work, may have on incentivizing an innovating organization. SME 7 also mentioned that, though the aforementioned aspect might be "un-mentioned and subtle", it is still worth considering.

(iv) Manufacturing considerations

Manufacturing of the drugs, resulting from R&D encouraged by the selected incentive, though not fundamentally part of the aim of the decision-support framework (Section 1.3), is mentioned by SME 3 as a generally experienced influencing factor in the selection of an appropriate incentive intervention. Table 9.9 depicts sub-themes that surfaced relating to manufacturing considerations.

Table 9.9: Manufacturing considerations sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Manufacturing complexity	The difficulty of manufacturing different drugs differs, with regard to the type of compound of drug considered for R&D.
Manufacturing capacity as incentive	Small-and-medium R&D organizations might not be able to manufacture drugs for companies outside of high-income countries and might be incentivized by agreements allowing manufacturing to be outsourced.

The two sub-themes mentioned in Table 9.9, link to one another as both the sub-themes relate to the ability of the innovators to include the manufacturing of the drug as part of the incentive R&D agreement. The first sub-theme also refers to the innovator not being able to perform specified R&D, and that the innovator will not be incentivized to perform R&D for a specified ND, regardless of the incentive intervention that is selected. The second sub-theme can further be related to the first sub-theme, and be interpreted as a response, or solution for the lack of manufacturing ability that the innovator might have. What is meant by this, is that in the case where an incentive intervention targets small-and-medium R&D organizations, or other innovating organizations with certain R&D or manufacturing limitations; it can be considered to offer, as part of the incentive agreement, the certainty to provide a means to manufacture or develop the innovated drug. The aforementioned will subsequently aid in incentivizing the innovator and ensure the actual manufacturing of the drug.

(v) Incentive implementation

The fourth overarching theme relates more to the implementation of an incentive intervention. Though the implementation of the incentive is not included within the scope of the research, the aspects discussed in this section, are considered due to the emphasis placed on this by the SMEs and the role that the implementation considerations might play in the selection of an appropriate incentive intervention. Table 9.10 depicts themes that surfaced relating to the incentive implementation theme evident in the decision-support framework.

Table 9.10: Incentive implementation sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Drug registration	The registration of a drug in a country should be considered, as different countries have different policies in place. This aspect also links with authorizing a drug in the country of sale.
Political situation and government willingness	The political atmosphere in a country often influences the ability to implement an incentive intervention. Some countries might not prioritize NTD treatment and control, leading to a lot of red tape.

The incentive implementation considerations primarily refer to the ability of the incentive to be implemented within the context of the desired country. As mentioned by SME 7, the "political atmosphere" in a country might affect the ability of the incentive to be successfully launched, as some governments might not support certain incentive interventions. In addition, SME 9, highlighted that national budget and government buy-in that is not in line with the enabling organization's buy-in, often results in difficulties in launching incentives.

(vi) Incentives

This is the first of the themes that emerged that relates mainly to structural concepts and patterns of the developed framework. Incentive interventions, referring to both the non-exhaustive list of 96 incentive instances, as well as the 26 types. Table 9.11 depicts themes that surfaced relating to the incentive interventions evident in the decision-support framework. Both themes resulted from the questions asked regarding the comprehensiveness of the incentives list, and the accuracy of the incentive definitions.

Table 9.11: Incentive interventions sub-themes and deeper insights

Sub-themes	Theme attributes and deeper insights
Incentive intervention instances	Various adjustments should be made to the list of 96 incentive intervention instances.
Incentive type definition	The definitions of the incentive types intend to provide an overview of the different intervention types. With the definition of the incentive types providing a brief introduction of what exactly the intervention entails.

(vii) Overall framework

The sixth and final overarching theme, resulting from the SME verification data, is overall feedback on the framework. The sub-themes surfaced in this section refer to the characteristics of the framework, and potential role that the framework might play. Table 9.12 depicts the sub-themes.

Table 9.12: Overall framework sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Framework complexity	The framework is comprehensive, which results in becoming complex to cover and address all the aspects in the level of detail required.
Qualities of framework	The framework provides a good landscape, it has a very broad scope, targeting a comprehensive number of topics and different areas. This framework might also be handy for enablers to determine their value proposition, from a business perspective.
Value of framework	A system that can more easily facilitate the decisions regarding incentive interventions of R&D in NDs, is important. This framework is also deemed as useful and comprehensive.
Capacity building	Selecting an incentive for a specific R&D system, with specified stakeholders might lead to context-specific characteristics not being included in the framework. The option of expanding the framework, thus building the capacity of the framework, as the specific scenario might demand, will allow for a better fit of the selected incentive intervention.
Presentation of results	Expressing the feasible incentive interventions in terms of their ability to address the respective criteria clusters, allows the stakeholders to get an objective overview of the strengths and priority focus areas of each incentive intervention.

The main qualities that were mentioned by SMEs include the complexity of the framework, referring to the comprehensiveness but also difficulty of addressing the various concepts (SME 3), as well as the expected contribution of the framework in facilitating decision-making regarding

interventions for R&D of drugs for NDs (SME 5). The decision-support framework, as elaborated in Section 8.4, though recognizing the dynamic atmosphere of selecting an incentive intervention, does not allow the users of the framework to explicitly change the requirements considered in the decision-making process. The reason for the aforementioned, is that the framework is developed by taking requirements into consideration that are stated in literature to have an effect on the selection of an appropriate incentive intervention. Another reason includes that, for the framework to be expanded, extensive knowledge and research must be done to complete the BL functions and evaluate the abilities of the incentives to address the newly added framework components or requirements. As a result, the framework does not allow for "capacity building", meaning that the users of the framework cannot add context-specific objectives, system requirements or capabilities to the framework.

The presentation of the decision-support framework results is recognized by SMEs to add significant value to the ability of the framework to assist with selecting an incentive intervention. SME 5 highlights the ability of the criteria cluster categorization to provide the decision-maker with the opportunity to recognize in which focus areas one incentive performs better than its counterparts. Thus, the criteria clusters allow the user to objectively compare the strengths and weaknesses of the feasible solutions.

9.2. Framework refinement

As mentioned earlier, part of the aim of verifying the decision-support framework, is to refine the framework by revisiting and iterating the design process. Based on the comments made by the SMEs, various aspects were found to be lacking and needed to be incorporated into the framework. Aspects to be considered in the design of the framework are discussed in Section 9.2.1 All the suggestions made by the SMEs are considered and evaluated to identify whether it should be included. The suggestions that fall outside of the scope of the research, are incorporated elsewhere or found to not be feasible within the context of the research, are not included in the refinements and are discussed in Section 9.2.2, whereas the suggestions that are incorporated are discussed in Section 9.2.1. Lastly, suggestions not incorporated into the framework, but still deemed important, are discussed in Section 9.2.3.

9.2.1. Changes incorporated into the framework

The incorporated changes mentioned in this section, differ in terms of the significance of the impact that each change has on the decision-support framework, and the feasible solution set output that the framework provides. In Section 9.2.1.1, some of the major incorporated changes are discussed in greater detail to highlight the conceptual effect on the framework of the changes made. The smaller and less significant changes that are incorporated, are briefly discussed, and listed in Section 9.2.1.2. The incorporated changes resulted in requirement specifications (that were not addressed in the first phase of verification) to be addressed, as further discussed in Section 9.1.2.3.

9.2.1.1. Major changes incorporated into the framework

The analysis of the SME feedback, as elaborated in Section 9.1.5, led to great insights into the omissions and conceptual voids from the perspective of the SMEs. The in-depth analysis of the

SME feedback, further led to the realization that some suggestions that should be incorporated into the framework, will have a more significant impact on the final solution set of feasible incentive interventions, compared to other suggestions. With some suggestions being less significant, and even though adding value, not a critical concern or determining factor of the framework's ability to successfully evaluate the pharmaceutical R&D system and its relevant stakeholders to suggest a feasible set of solutions. This section elaborates on the three major framework changes that were incorporated as a result of SME input, namely: (i) inclusion of innovator and consumer stakeholders; (ii) exclusion of vaccine R&D; and (iii) criteria cluster presentation of the final solution set.

(i) Consumer and innovator profile inclusion

The process of selecting an appropriate incentive intervention, as highlighted in Section 6.2, depends on a variety of factors. Even though the enabling stakeholder will play the primary role in the selection, realization and implementation of the selected incentive, it should not be omitted to take the other relevant stakeholders into account in the decision that is being made. In the case where the relevant stakeholders are not taken into account in a decision being made; the risk exists for the incentive to be a 'misfit', or for the incentive to not deliver the intended results. SME 6 mentioned that the exclusion of the consumer causes the framework to not be "mature in capturing the patient R&D nuances".

In response to the aforementioned, the objectives and internal capabilities of the innovator and consumer stakeholders are included as part of the decision criteria in the selection of an appropriate incentive intervention. The incorporation of these stakeholders, consequently, minimize and reduce the risks involved in omitting important consideration factors for the selection of the appropriate incentive.

(ii) Exclusion of vaccine R&D

The processes of vaccine and drug R&D, "though not always explicitly stated in literature does differ significantly" (SME 1). Some of the major differences, according to NTD vaccine ambassador SME 1, include "upfront funding investments for vaccine R&D being much higher than drug R&D, and the time horizons for development of vaccines to be much longer than drugs". SME 1 also stated that "even though the investment and risk associated with vaccine R&D is higher, the public health impact has the potential to be greater though the financial returns remains quite modest".

Based on the aforementioned statement made by SME 1 as well as on the differences acknowledged in literature between incentives for drug versus vaccine R&D (Berman and Giffin, 2004; Beutels *et al.*, 2008; Régnier and Huels, 2013), the feasible set of 26 incentive interventions that are considered as solutions by the decision-support framework exclude all incentives suggested and implemented exclusively to encourage vaccine R&D.

(iii) Criteria cluster presentation of solution set

The selection of an incentive intervention for encouraging R&D as defined in Section 6.5, is a multi-criteria decision. In the initial version of the decision-support framework, though multiple sets of decision criteria were considered for determining the feasible solution set, the overall feasibility of the 26 incentive interventions was not expressed by means of their ability to satisfy

the different sets of decision criteria. In the final version of the framework, the solution set is presented in a way that articulates the abilities of the incentive interventions with regard to the different criteria clusters. With the criteria clusters representing the different objectives that the incentives can potentially fulfil.

9.2.1.2. Smaller changes and alterations incorporated in the decision-support framework

All the aspects suggested by SMEs to be incorporated in the decision-support framework are listed in Table 9.13. The table defines each concept, followed by describing the change made to the framework. The applicable domain and a reference to both the SME suggesting the change and the relevant concept number (from coding cycle two), are also given. It should be noted that Table 9.13 does not include the omissions and suggestions that will not be incorporated into the framework.

Table 9.13: Changes incorporated into the decision-support framework.

	Aspect to incorporate	Changes made to framework	Domain	Reference
1.	Trained personnel	Add system element to see the ratio between population and trained staff	Domain 1	DG.7 (SME 4)
2.	Complexity of manufacturing	Add 'Qualified' to manufacturing system element	Domain 1	DG.6 (SME 3)
3.	Drug quality and efficacy	Include drug efficacy in quality description	Domain 1	DG.8 (SME 3)
4.	Clinical trial diversity (racial)	Change wording to incorporate other forms of diversity	Domain 1	DG.9 (SME 3)
5.	Country ownership and leadership	Incorporate wording of NTD 2030 roadmap in governance and leadership	Domain 1	DG.13 (SME 9)
6.	Payoff of innovators	Adjust enabler profile	Domain 1	DG.11, AD.12 (SME 2)
7.	Bandwidth as motivator	Add to goal of enabler that motivator to be part of incentive is to increase their bandwidth	Domain 1	AD.13 (SME 5)
8.	WHOPQ quality assurance	Add quality assurance to system elements, with the WHOPQ ensuring unified quality, safety and efficacy standards	Domain 1	AD.2 (SME 2)
9.	Treatment attributes	Add as part of enabler objectives that developed drugs should adhere to access and affordability	Domain 2	DG.17 (SME 1 - 6)
10.	Regime development	Enabler goal to develop regimes and not only single treatments	Domain 2	DG.19 (SME 2)
11.	De-risk as objective	De-risking of the enabler is an objective for collaborating and partaking in incentives	Domain 2	DG.23 (SME 5)
12.	Data sharing types	Add to enabler profile	Domain 2	DG.20,37 & AD.15, 16 (SME 2)
13.	Technology and expertise ability	Add to enabler capabilities	Domain 2	AD.18 (SME 4)
14.	CSR compliance	CSR part of enabler motivator	Domain 2	AD.20 (SME 5)
15.	Access to data, IP, compounds & network	Add to enabler profile	Domain 2	DG.22 & AD.22 (SME 6)
16.	Public reputation and brand image	Mention as sub-objective of enabler stakeholder	Domain 2	AD.21 (SME 7)
17.	Public reputation and brand image	Mention as sub-objective of innovator stakeholder	Domain 3	DG.24 (SME 7)
18.	Manufacturing capacity required	Elaborate on supplementary agreement including manufacturing capacity	Domain 3	DG.25 (SME 3)
19.	Innovator requiring network exposure	Elaborate on supplementary agreement including network exposure	Domain 3	DG.26 (SME 3)
20.	Clinical trial diversity	Mention clinical trial diversity as part of requirement in contextual criteria	Domain 4	DG.28 (SME 3)

Table 9.13 continue on next page

Table 9.13 continued from previous page

	Aspect to incorporate	Changes made to framework	Domain	Reference
21.	Drug registration in a country	Change wording of 'drug registration' criteria	Domain 4	DG.30 (SME 9)
22.	Contextual treatment criteria	Insert clause to include all contextual treatment criteria mentioned.	Domain 4	DG.27, 29, 31 & AD.25, 26 (SME 3, 7, 8 & 9)
23.	Tiered pricing	Include require differential pricing	Domain 4	DG. 16 (SME 2)
24.	Political resistance	Include political resistance in government and leadership category of criteria clusters	Domain 5	DG.32 (SME 9)
25.	Enabler limited resources	Change wording to 'limited investment in resources'	Domain 5	AD.29 (SME 9)
26.	Binary evaluation biased	Mention the limitation in the framework of the scale used	Domain 5	DG.33 (SME 3)
27.	Wording of non-incentive-based interventions	Include the wording: 'out-of-scope'	Domain 5	AD.33 (SME 3, 4)
28.	Messaging	Objective of enabler to portray a 'message'	Overall	AD.39 (SME 5)
29.	Working group description	Add specific boundaries to the definition of working group	Overall	DG.40 (SME 9)
30.	Differential pricing as an incentive	Add clause establishing why differential pricing is included	Overall	AD. 39 (SME 3)
31.	Adjust incentives	Change all incentives, as suggested	Overall	DG.39 (SME 2, 3)
32.	Non-exhaustive list	State nature of incentive list	Overall	DG.36 (SME 3)
33.	Inaccurate definitions	Adapt definitions	Overall	DG.35 (SME 2,3,6)

As previously mentioned, the final version of the framework, incorporating the changes outlined in this section, is presented in Chapter 8. The majority of changes incorporated were additions to Domains 1 and 3, thus to the system demarcation and the enabler profiles.

9.2.1.3. Requirement specifications addressed as a result of the changes incorporated

As mentioned in Section 9.1.1, two phases of verification were performed. The first phase of verification was an intermediate verification process, that led to a number of insights with regards to the decision-support framework. The first phase of verification also fundamentally informed the expansion of the decision-support framework, with the internal verification (i.e. Section 9.1.2) being the evaluation of the decision-support framework to address the identified requirement specifications, performing a critical part in the expansion and final development of the decision-support framework.

It is necessary to provide a clear view of the requirement specifications that were not addressed, or partially addressed in the initial version of the decision-support framework. Table 9.14, consequently, indicates the requirement specifications that were not addressed or were partially addressed (column 1), and links it with the changes incorporated into the framework that led to the requirement specification to now be addressed (column 2). The changes incorporated, are sourced from Sections 9.2.1.1 and 9.2.1.2.

From Table 9.14 it can be concluded that the incorporation of the innovator, and end-consumer profiles were two of the biggest changes incorporated after the initial version into the final version of the decision-support framework.

Table 9.14: Requirement specifications addressed after first phase of verification.

	Requirement specification not-, or partially-addressed	Status after phase 1 of verification	Changes made to the framework after the first round of verification
U.1	The framework should select an incentive intervention that considers the patient and population as core drivers for the incentive.	Partially addressed	Incorporate end-consumer stakeholder profile (i.e., Domain 4).
U.2	The framework should provide a solution, or set of solutions, that will incorporate the outcomes and goals, as set by the WHO health care framework, namely: (i) improve access; (ii) improve coverage; (iii) improve quality of services delivered; (iv) ensure safety; (v) improve overall health (burden of disease); (vi) be responsive; (vii) provide social and financial risk protection; and (viii) improve efficiency of mitigating the disease.	Partially addressed	The set of outcomes and goals of the WHO health care framework are addressed and incorporated in the end-consumer profile of the decision-support framework (i.e., Domain 4).
U.3	The proposed solution must provide a means to alleviate the burden of disease of the consumer.	Partially addressed	Incorporate end-consumer stakeholder profile (i.e., Domain 4).
U.4	The developed solution should address the customer requirements and unmet needs of the consumers of the developed drug.	Not addressed	Incorporate end-consumer stakeholder profile (i.e., Domain 4).
B.1	The framework should promote the needs of all stakeholders and consider the role of each stakeholder to ultimately provide a solution that will positively influence the patient, as well as other stakeholders involved.	Partially addressed	Incorporate innovator and end-consumer profiles (i.e., Domains 3 and 4)

9.2.2. Changes not incorporated into the framework

Some suggestions of SMEs are not incorporated into the design of the decision-support framework. These concepts and suggested changes are either deemed irrelevant, out-of-scope, or already addressed in a different section of the framework. These suggestions are referred to as 'unviable suggestions' in the context of this research. Table 9.15 depicts the concepts suggested by SMEs that are not included in the framework and provides the reasoning for omitting the concepts.

Four of the SME suggestions, listed in Table 9.15, are already incorporated into the framework (aspects no. 1, 5, 7 and 8). Major design changes such as changing the scope of the framework, as well as the complexity of the framework are omitted as this would affect the entire research product and is not feasible. In designing the framework, an effort was made to strike a balance between: taking sufficient information into consideration in order to provide in-depth insight into the selection of an appropriate incentive intervention; and limiting the effort required to use the framework to that which could reasonably be expected from a stakeholder. The aforementioned increases the complexity whilst the latter reduces it. Thus, effort was made to proactively manage the complexity of the framework.

Table 9.15: Suggested concepts not included in the framework.

	Aspect to omit	Reason for omitting	Reference
1.	Conservation of resources versus the yield of process	Sustainable R&D is incorporated in the system demarcation domain, and the CLIC	AD.11 (SME 3)
2.	Making framework scope smaller	Not feasible at this stage of research	AD.1 (SME 3)
3.	Complex to have so many topics	The comprehensiveness of the framework is seen as a strength	DG.1 (SME 3)
4.	Private capital as incentive	Private capital is a means to incentivize rather than an incentive in itself	DG.38 (SME 1)
5.	Different enablers have different roles	More than one enabler can exist, and play different roles	DG.15 (SME 3)
6.	Capacity building	Expanding the context-specific elements, would not be possible, because of hardcoded background processes.	AD.8 & AD.14 (SME 5, 7)
7.	DALYs as measure	DALYs used for context, and DALYs high priority burden low enough to include NTDs.	AD.10 (SME 3)
8.	Economic viability	Already incorporated in innovator profile	AD.24 (SME 7)
9.	Innovator participation	Aim of incentive is to encourage innovator participation, therefore an indirect consequence.	AD.23 (SME 5)
10	Subscription-based model	Incentive only in beginning stages for antibiotic research	AD.40 (SME 3)
11.	Public perception	Referring to consumer consumption of drugs, is outside of the scope of this research	AD.32 (SME 1)
12.	Behaviour change incentives	These incentives are aimed at consumer participation and buy-in.	AD.41 (SME 9)

9.2.3. Important concepts omitted

Six concepts suggested by the SMEs are not included in the refinement of the framework, but still viewed as important to be incorporated or considered when implementing the framework. This set of concepts are summarised in Table 9.16.

Table 9.16: Feasible changes not incorporated into the framework.

	Conceptual concept description	Reference
1.	Impact of donors on drug consumption, R&D willingness, and end-price profit margins for countries	AD.3,4 & 9
2.	Collaboration component for the case of regime development	AD.17
3.	Split of the market possible when no consensus of agreements	AD.19
4.	The impact of risk to the incentives	AD.31
5.	Considers the R&D environment in isolation of R&D system at large, such as more profitable diseases	DG.34
6.	Elaborated context-specific requirements of the treatments as well as service delivery, as part of the consumer stakeholder	DG.10 & 31

The concepts listed in Table 9.16 are further discussed as future work of this research.

9.3. Conclusion: Verification and refinement

The objective of this chapter was to verify the framework to ensure its accuracy and credibility. The verification phase of this research firstly, established whether the requirement specifications (identified throughout the research) are met by the various components of the framework, and secondly, whether experts in the fields of NDs, incentive interventions and the pharmaceutical R&D industry agree that the framework constitutes a realistic, legitimate mechanism to propose a suitable set of interventions for the scenario at hand.

Based on the internal verification stage, 24 of the requirement specifications were positively verified to be fulfilled by at least one of the framework components, while 1 of the specifications were only partially fulfilled A detailed discussion of the requirement that were partially fulfilled was presented, and as discussed, the fulfilment of this requirement is proposed as future work. The SME interviews underlined various aspects that should be considered in the design of the framework. Both the internal and external verification of the requirement specifications and design of the framework, confirmed that the design of the framework is adequate to perform its intended purpose.
The aspects identified by the SMEs that are not addressed by the current decision-support framework are briefly discussed and either incorporated, omitted, or omitted but considered as potential future work.

CHAPTER 10

Validation

Validation determines the degree to which a developed solution is an accurate, reasonable representation of the real-world (Thacker *et al.*, 2004). The validation presented in this chapter also deals with the evaluation of the research product to determine whether the proposed solution is fit for its intended purpose. This chapter first describes the validation approach that is followed in this research. Second, validation through subject matter expert interviews is discussed. Lastly, three case studies are performed, and the results are synthesized.

10.1. Validation approach

Validating the decision-support framework aims to fulfill three primary objectives, as described in the section below. The validation methodology employed in this research is described in Section 10.1.2.

10.1.1. Purpose of validation

In contrast to the verification process depicted in Chapter 9, the objectives of the validation are to establish:

(i) Whether the framework is applicable, useful and adds value to the real-world;
(ii) Whether SMEs perceive the decision-support framework as a feasible solution to the problem at hand; and
(iii) Whether the outputs of the decision-support framework provide valid solutions to the problem that it aims to address.

In support of objectives (i) and (iii), the following sub-objectives must be achieved in the case study application, namely, to establish: (i) internal validity (integrity of the specific case study); (ii) external validity (generalizability of the case study to other situations not part of the original study); (iii) construct validity; and (iv) reliability.

These objectives and sub-objectives are elaborated on in the remainder of this chapter.

10.1.2. Validation methodology

Various validation techniques exist to evaluate a proposed solution. However, given the complex nature of the developed framework, an in-depth understanding of the pharmaceutical-, neglected disease- and incentives spheres is required to validate the framework's integrity. Consequently, the framework could not be validated by the mass market through, for example, a broad questionnaire or survey. Instead, subject matter experts were required to validate the research.

A validation technique, such as a practical implementation, is not feasible for this research given the nature of the study, where a practical implementation would require the buy-in of various stakeholders, the availability of sufficient funding, and a sufficient period of time for implementation. Practical implementation of this framework could also be simulated by means of an illustrative case study application. Application to a case study is deemed to hold significant value, as it can reveal strategic weaknesses and insights into the decision-support framework that cannot be identified otherwise. A case study, requiring an in-depth investigation of the R&D environment and relevant policies applicable to the case study scenario, will provide detailed insights into the implementation of the decision-support framework.

Two validation techniques are selected to use for the validation of this study. The first is to conduct one-on-one (semi-structured) interviews with subject matter experts. One-on-one interviews provide a platform for the validators to ask questions, and for the author of the research to provide clarity on the framework and its functions, where required. The interviews are semi-structured, providing the opportunity to maximize the insight gained from the SMEs. The same experts who performed verification of the framework, were asked to provide their opinion on the value of the decision-support framework and its applicability to the problem at hand, as well to provide feedback on the likely feasibility of implementing the framework. These questions were posed during the same interview session as those used for the SME verification of the framework. Also similar to the external verification, the validation interviews were conducted in two phases. The reason for this, is the same as for the external verification, being that a preliminary version of the framework was verified and validated, with the intent of gaining insights to apply with the design, development and refinement of the final decision-support framework. The preliminary version validated excluded Domains 3, 4 and BL functions 3, 4, and 5.

The second technique selected for validating the decision-support framework is by means of cumulative retrospective case studies. As elaborated in Section 2.3, the retrospective case study format is selected due to its ability to retrospectively consider an incentive intervention that was selected, and to provide insights into the ability of the decision-support framework to take a set of information and propose a feasible set of incentives to pursue. It can subsequently be established whether the framework suggested the incentive intervention that was in fact selected, therefore confirming that: the relevant information on which to base the selection of an incentive is gathered in Domains 1 to 4; and the solution(s) that are proposed based on this information are accurate.

10.2. Validation through SME engagement

The input for the SME validation phase is the knowledge of the SMEs and their perception of the research output, as derived from the pre-read documents (Appendix I and J) and from the presentations by the author (Appendix K and L), at the beginning of each interview. The expert interview details are the same as presented in Table 8.2, and the SMEs will be referred to with the same abbreviated name.

10.2.1. Purpose of the SME validation interviews

As defined in Section 10.1.1, the purpose of validation can be summarized as three primary objectives. The SME validation phase is intended to achieve objective (ii) of the validation

objectives, namely, to establish whether the SMEs perceive the decision-support framework as a feasible solution to the problem at hand.

10.2.2. Interview questionnaire for validation

As opposed to the verification questions, the validation questions are not concerned with the theoretical correctness of the research product. The validation seeks to investigate to what extent the SMEs agree that the framework is adequate and valuable in serving the intended purpose. A total of seven validation questions are asked to all the SMEs. With the questions being divided into two parts and the numbering continuing from the questions asked in the verification phase of the research (Table 9.3). The only 5-scale Likert rating question asked for validation is Question 4.1, with the rest of the questions being open-ended.

Table 10.1: Validation interview questions.

No	Validation questions
Part 4: Adequacy of the framework	
4.1	To what extent do you agree that the framework is a logical and holistic approach to find an applicable set of incentive interventions for encouraging R&D?
4.2	Does this framework exclude any major components that you believe should be included?
Part 5: Investigation of the framework value	
5.1	What do you view as the key strengths of the decision-support framework?
5.2	What do you view as the key weaknesses of the decision-support framework?
5.3	Based on your experience and what you perceive from the framework, if the framework were to fail, what do you think would be the most likely cause of this failure?
5.4	Are you aware of any other approach that will lead to a similar or superior solution to the one delivered by framework presented in this document?
5.5	Do you have any additional comments or critique?

10.2.3. Validation interview data analysis

Similar to the handling of the verification data, Creswell's (2014) qualitative data analysis process (depicted in Figure 9.1) is applied to analyse the validation data. In the interest of brevity, the implementation of the analysis process to the validation data is not described in as much detail as the verification data. This is because the data analysis process followed is conceptually similar.

The first two steps off the qualitative data analysis process are followed as described in Section 9.1.4. This is followed by step three, thus the coding process, which differs from the verification coding process structure as a result of the validation data nature. More specifically, the two coding processes differ because of the validation data that cannot be attributed to a specific framework component as it refers to the overall frameworks' abilities and value. The coding cycles for the verification data analysis (Section 9.1.4) and the validation data analysis consequently differ with regard to the number of coding cycles applied to the data sets, as well as the type of information derived from the coding cycles.

The coding for the SME validation data in this research is, therefore, completed in two coding cycles (refer to Section 10.2.4). The first coding cycle focuses on evaluating the input provided by

the SMEs and investigating themes that resulted from the type of questions that were discussed. The second, and final, coding cycle investigates deeper insights by yielding overarching themes and sub-themes of the interview data.

10.2.4. Validation data analysis results

The two coding cycles, (Step 3) of the qualitative data analysis process, as well as the description, presentation and interpretation (Steps 4 - 6) of the interview data are depicted in this section.

10.2.4.1. First coding cycle

The purpose of this coding cycle is to process the validation data into concepts validated by the SMEs. The response to the validation interview questions varied, and similar to the verification questions, the background knowledge and experience of each SME is apparent in the answers provided to the questions. The following section investigates the responses of the SMEs, with the intention to quantify the value of the framework as well as identify further opportunities for future work.

The interview data are organised into five categories, namely: (i) strengths; (ii) weaknesses and limitations; (iii) points of vulnerability; (iv) implementation difficulty; and (v) framework novelty. Table 10.2 depicts all the categories with the respective concepts validated and derived from the interview data of specific SMEs indicated. Note that these are not an indication of SMEs agreeing (on a Likert scale) to the respective concepts, but rather a depiction of concepts raised by the SMEs themselves in response to the questions (Table 10.1) discussed.

(i) Framework strengths and robustness

The greatest framework strength is found to be the comprehensiveness of the decision-support framework, together with the number of influencing attributes that it considers in recommending the most feasible set of solutions. This framework is deemed as "certainly helpful, being a very valuable means for the different people looking for ways in which they can drive change", (SME 2). The framework also succeeds in: (i) being useful, valuable, and helpful to solve the problem at hand; (ii) providing a sufficient overview of the necessary concepts and factors to consider for the problem at hand; (iii) being logically and holistically designed and comprehended; and (iv) quantifying by means of a score-based system to provide the most feasible solution.

Furthermore, the framework is said to be: (v) a good starting point for initiating collaboration; with the (vi) incorporation of multiple stakeholders ensuring that all the relevant decision criteria are considered for selecting an incentive intervention; and lastly (vii) all the SMEs (exception SME 6, emphasising in the first validation round that the consumer profile should be included) agreed that the framework does not "exclude any major components". It can be concluded that the framework strengths primarily relate to the in-depth and exhaustive nature by which the framework identifies influencing factors, analyses the status-quo, quantifies the appropriateness of solutions, and proposes feasible interventions to pursue.

(ii) Framework weaknesses and points of vulnerability

The weaknesses, limitations and points of vulnerability pointed out by SMEs are diverse in nature, highlighting both the different exposure and knowledge of the SMEs, as well as facets of the framework that can still be improved. Most of the weaknesses were only mentioned once, as

opposed to the strengths being mentioned on average three to five times. Various weaknesses that were already identified in the verification process were repeated. The major weaknesses and possible points of failure of the framework are, first, the binary scale (used to evaluate incentive intervention in two matrices) that might overlook important details of the interventions; however, this was seen as both a strength and weakness as it can aid in quick decision-making.

Table 10.2: Concepts derived from interviewing respective SMEs.

Overarching concept	Description and attributes	SME reference								
		1	2	3	4	5	6	7	8	9
Strengths										
1. Comprehensive	The framework manages to encompass all relevant concepts.	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Useful, helpful and valuable	The framework can improve- and make a valuable contribution to current problem.	✓		✓		✓		✓		✓
3. Logical and holistic	The framework logically approaches the problem and solves it holistically.				✓	✓		✓	✓	✓
4. Ambitious	The study is very ambitious, given the extent of the problem targeted.			✓						
5. Provides overview	All incentives, concepts and tools provided in one framework solution.		✓	✓		✓	✓	✓	✓	
6. Robust	The framework is robust, and unlikely to fail in solving problem at hand.				✓					
7. Score-based design	Strategically, the score-based design makes the framework very strong.			✓		✓				
8. Collaboration	Starting point for initiating collaboration.					✓				
9. Multiple stakeholders	The inclusion of multiple stakeholders, as opposed to only the enabler.			✓				✓		✓
10. Does not exclude major components	The framework does not exclude any major components.	✓	✓	✓	✓	✓		✓	✓	✓
11. Output presentation	Synthesis of data, with the graphic output, is easy to understand.							✓		✓
Weakness and limitations										
12. Maintain, start cost	All incentives require starting and maintenance funding.		✓							
13. Isolated R&D view	Looks at neglected R&D efforts in isolation from rest of R&D.						✓			
14. Engagement	Entities might not know how to use the framework without education.		✓					✓		
15. Capacity building	The ability of the users to expand the framework as needed.					✓				
16. Consumer context	The consumer treatment criteria not included sufficiently.			✓						✓
Points of vulnerability										
17. Vaccine R&D	Not effectively addressing R&D of vaccines and incentives	✓								
18. Incorrect assumptions	If initial steps of framework are done incorrectly, might affect outcome.					✓			✓	
19. External nuances	External nuances might affect the ability of the framework to be successful.								✓	
20. Binary score allocation	Leads to quick and clear road to decision-making. Conversely, leaves room for omitting details, but non-binary would make differentiation difficult.			✓		✓				
21. Scale and scope of study	Good to incorporate so many variables but might open way to a weakness if not being as comprehensive as might be required			✓						
Implementation difficulty										
22 Creating awareness	Need a strategy to make people aware of this framework.					✓				
23. Users	The usage and facilitation of the framework should be clarified		✓	✓		✓				
24. Relationship management	Relationship and alliance management, how will it be maintained.					✓				
25. Reluctance	Enablers might be reluctant to adopt a new strategy.			✓						
26. Education	Requires education from your side, to effectively use the framework.		✓							
27. Innovators to buy in	Getting the innovators to buy into the incentive.		✓							
28. Complexity	Difficult to understand the framework completely from the beginning.			✓				✓	✓	
Framework novelty										
29. Novel solution	Not aware of similar approach to solve the problem at hand.	✓	✓	✓	✓	✓	✓	✓	✓	✓

The second major weakness identified, is that a capacity building aspect is not included in this framework. This refers to the ability of framework users to add requirements to the system

demarcation domain and stakeholder profiles, as they identify more context-specific characteristics that are relevant to that specific scenario being applied to the framework. As mentioned in Table 9.14, capacity building of the framework would require changes to be made to the BL processes, where the users of the framework do not necessarily have adequate knowledge or expertise to do so.

The third major weakness identified, is that the framework does not incorporate consumer context-specific treatment criteria, regarding the specific drug that is required. Though important to consider for the potential impact that the product will have on the target population, it does not necessarily play a major role in the selection of an appropriate incentive intervention. Given the maturity of the research, the weaknesses identified in this phase of the research are not addressed, but rather considered as potential future work to be completed.

Two framework weaknesses that were addressed after the initial phase of validation interviews include firstly, the inclusion of the consumer and innovator profiles as described in Section 9.2.1.1. The framework is also adapted to secondly, provide a means for the different stakeholders to collaborate in incentivizing R&D. The aforementioned weaknesses were overcome by (i) allowing for more than one stakeholder of a types' needs to be taken into consideration by completing a stakeholder profile per participating stakeholder; (ii) application of a case study (Section 10.5) to investigate the difficulties around framework usability; and (iii) the second phase of validation interviews.

(iii) Implementation

Difficulty to implement, although grouped as a separate category, is a potential weakness of the framework. SMEs 2, 3 and 5 mentioned in the first phase of validation that there is a lack of clarity on the facilitation of implementing the framework. The aforementioned is addressed by operationalizing the framework into a decision-support system, with automated navigation. This reduces the perceived complexity and the ability of the users to easily identify the points of interaction with the system and the input required.

Another aspect that might prevent the implementation is a lack of awareness of the framework's existence. Awareness of the framework should form part of the marketing strategy to introduce the advantages of applying the framework.

(iv) Framework novelty

Lastly, the novelty of this framework is investigated with Question 5.4. It is found that no current strategy exists to evaluate the pharmaceutical R&D sphere, its stakeholders and incentive interventions in the way that this framework approaches it. All SMEs agreed that they are not aware of any similar effort or study that investigates and provides the oversight and insight into the neglected disease R&D- and incentive intervention landscape that this research does. As a result it is concluded, based on the feedback from a number of individuals with significant experience in the field, that the developed framework represents a novel approach to the neglected disease field. This conclusion aligns with the finding of the structured literature search presented in Section 1.4.

10.2.4.2. Second coding cycle

The purpose of the second coding cycle is to yield themes and deeper insights into the validation data. These derivations build on the outcomes of the first coding cycle, where certain characteristics of the framework featured continuously.

Five overarching themes emerge from the data namely: (i) output value to decision-makers; (ii) qualities of framework content; (iii) collaboration and alliance building; (iv) framework operationalization; and (v) fundamental design concepts.

(i) Output value to decision-makers

The decision-support framework, and the operationalization thereof as a decision-support system provides the decision-maker with a means to a make an informed decision. Deeper insights into the output value of the feasible set of solutions provided by the decision-support framework, are depicted in Table 10.3.

Table 10.3: Output value to decision-makers sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Means to achieve the decision-makers' goal	The decision-support framework incorporates context-specific and non-specific criteria, evaluates the incentives in a quantitative manner, and presents the results to the decision-maker, thus achieving the goal of providing a feasible set of incentives to consider.
Presentation of results	Data synthesis and graphic presentation of the results allows the decision-maker to see which incentive interventions have the ability to adequately address the criteria clusters that are prioritized by the decision-maker.
Improves knowledge on available incentives	Literature does not give an overview of all the incentive intervention approaches available to encourage R&D for neglected diseases. This research output provides the decision-makers with overall knowledge on existing incentives.
Provides decision-makers with options	The framework does not merely propose one solution to the problem at hand but evaluates each of the incentive interventions' abilities to address the 12 criteria clusters.
All aspects considered in one place	The incentives are evaluated according to all the aspects, regarding context-specific, non-specific and stakeholder decision criteria. Provides a feasibility overview of the incentives, with all aspects considered. This is especially good for more inexperienced decision-makers.

The first significant theme that surfaced in the SME validation of the decision-support framework is the presentation of results in a format that allows the decision-maker to achieve their objective, being to get an overview of the feasible incentive interventions to consider for encouraging R&D for a specific ND. Another major theme commended by the SMEs is that the output of the decision-support framework considers a wide variety of aspects in evaluating the feasibility of the incentive interventions. This theme is supported by the qualities sub-themes discussed in the following section.

(ii) Qualities of framework content

The second overarching theme that surfaced in the SME validation interviews is the qualities and characteristics of the decision-support framework. This theme links with the output value provided by the decision-support framework, though indicates more specifically the framework features highlighted by SMEs. Table 10.4 depicts deeper insights into the qualities of the framework content.

Table 10.4: Qualities of the framework sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Comprehensive and logical	The framework considers aspects ranging across the Health systems framework suggested by the WHO. This provides the decision-maker with a lot of insight into the R&D of NDs, incentive interventions and participating stakeholders by means of a logical approach. Covers a lot of material from a lot of angles.
Robust	Robust design, with logical systematic approach followed to develop it.
Ambitious	The framework is ambitious in everything that it incorporates, the scale and the level of detail of topics covered.
Unique and novel	The framework is unique, and the only of its sort. The framework provides a novel perspective on incentive interventions and the factors that influences its success.

The most evident aspects highlighted by the SMEs include the framework's comprehensiveness in analysing the pharmaceutical R&D system. The framework novelty also links with the comprehensiveness attribute in that no other solution, as stated by SMEs, provide such a broad overview of incentives, or the factors that influences the selection or successful implementation of incentive interventions.

(iii) Collaboration and alliance building

Collaboration among stakeholders is a theme that continuously surfaced in this research. As depicted in Chapter 7, as well as derived from the SME verification interviews in Section 9.1.5, the collaboration of stakeholders is an important consideration when selecting and implementing an incentive intervention. Table 10.5 depicts the sub-themes and deeper insights associated with the collaboration and alliance building theme.

Table 10.5: Collaboration and alliance building sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Multiple stakeholders as users	The research considers the three relevant stakeholders, takes their objectives and limitations into account, which is often omitted in real-life.
Alliance management	Alliance management is often a complicated and difficult task. This is because some stakeholders are not always willing to cooperate in terms of communication response.
Relationship building	Linking to alliance management, stakeholders often lose interest and grit for projects if good relationships are not established.
Starting point for initiating collaboration	The framework provides the stakeholders with a clear starting point. Especially in government-aligned organizations, it is often difficult to effectively start and initiate a project without any guidelines and context.

The collaboration and alliance building theme highlighted in this section of the research refers primarily to the ability of the framework to allow for more than one stakeholder to collaborate with stakeholders of the same type and to engage with other types of stakeholders. Establishing, maintaining and managing relationships with other stakeholders is another important sub-theme that surfaced regarding stakeholder collaboration. This attribute is highlighted especially by SME 5 with vast experience in collaboration between stakeholders for specifically ensuring partnership alliance and management.

(iv) Framework operationalization

The fourth major theme that surfaced in the SME validation interviews is operationalization characteristics of the decision-support framework. Table 10.6 depicts sub-themes and deeper insights into the framework operationalization theme.

Table 10.6: Framework operationalization sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Adoption reluctance	The decision-makers often have set ways in which they make decisions. This may result in reluctance to adopt a new strategy.
Stakeholder buy-in	The participation of all stakeholders, especially the innovating stakeholders, is important for the framework to be successful. Measures should be considered to engage with each of the stakeholders to ensure buy-in.
Using the framework	Engaging with the framework is important for it to function correctly. Using the framework incorrectly might lead to incorrect results. Less mature decision-makers might also mis-interpret the outputs of the framework if they do not understand the results correctly.

The sub-themes identified regarding framework operationalization, refer primarily to the usability of the framework, and the practicality of adopting the decision-support framework as a means to find a suitable incentive intervention. The successful operationalization of the decision-support framework requires stakeholder participation, and buy-in. Without the aforementioned stakeholder buy-in, the results presented by the decision-support framework will not be pursued, resulting in a waste of resources and effort.

(v) Fundamental design concepts

The final theme that emerged from the validation interviews is fundamental design concepts. Table 10.7 depicts the sub-themes and deeper insights of the fundamental design concepts theme.

Table 10.7: Fundamental concept design sub-themes and deeper insights.

Sub-themes	Theme attributes and deeper insights
Score and binary rating system	The binary score used to evaluate the incentive interventions adds strengths and weaknesses to the decision-support framework. With the decision-making ability being improved, the risk exists that some incentives might be rated higher or lower than what they should.
Scale and scope	The scope of the topics and considerations incorporated into this framework is vast. If the scale were to be narrowed, a less informative decision would have been made, though a narrowed scope would lead to more in-depth investigations of the existing research scope.
Capacity building	The idea of having the ability to expand the requirements considered in the decision-support framework, given that no system is static, but rather dynamic.
Complexity	The complexity of the framework might decrease the usability, and the practicality of implementing the framework. The complexity is reduced by operationalizing the framework into a decision-support system.
External nuances	External factors and nuances might affect the ability of the framework to suggest a feasible set of solutions, or the success of an incentive when implemented. There will always be factors that are unaccounted for.

The fundamental design concept theme is associated with design considerations that are mentioned by SMEs to be either beneficial or important to consider, ensuring that the framework fulfils its intended purpose. Two deeper insights worth elaborating on include, firstly, the complexity of the framework. The complexity of the framework links with the score and binary rating system used to evaluate the incentives considered in this research. The decision-support

framework is found by most SMEs to be difficult to understand from the introduction documents provided. Though the binary scale used to evaluate the incentive interventions, and the operationalization of the framework into a decision-support system, reduces the perceived framework complexity, alternative interventions should be considered to reduce the framework's complexity even more. This is further discussed in the future work (Section 11.4). Second, even though the framework aims to incorporate as many topics as possible and influencing factors into the decision of selecting an incentive intervention, external nuances and factors will always surface and be present in the real-world.

10.2.5. SME validation interpretation

The primary objectives of the SME validation, as described in Section 10.2.1, is to establish whether, from a practical point of view, the strengths of the framework outweigh the weaknesses and whether the decision-support framework is a feasible solution to the problem at hand. Through analysing the SME feedback, derivations regarding the SMEs' understanding of the decision-support framework were made, which led to deeper insights with respect to the framework's ability to perform its intended function. The themes identified in the SME validation interviews were described in detail in Section 10.2.4. However, the following three insights are worth mentioning again in concluding the discussion of the SME validation interviews. Firstly, it was found that the decision-support framework provides a comprehensive overview of factors to consider and the incentive interventions that are available, to encourage R&D for neglected diseases with all but one SME stating that the framework does not exclude any major components[21].

Second, implementing the framework is a point of vulnerability highlighted by the SMEs, due to the perceived complexity of the framework, the number of stakeholders involved, as well as the fact that a facilitator will not necessarily be present when the framework is implemented. Third, collaboration and alliance management surfaced as an important consideration for ensuring success of the framework. Stakeholder collaboration is essential for guaranteeing that the decision-support framework is 'completed' correctly, thus for all the decision-criteria to be an actual representation of the scenario being investigated. Even though specific attention was given to ensuring that collaboration between stakeholders is considered and incorporated in the operationalization of the decision-support framework, future work could focus on initiatives to even further support easy, sustainable and effective collaboration between all the stakeholders involved in the selection of an incentive intervention.

It can, therefore, be concluded that the SME validation interviews provided sufficient insights into the decision-support framework's ability to act as a means to select an incentive intervention for encouraging R&D for neglected diseases. The framework strengths are deemed by SMEs to outweigh the weaknesses, in it being highlighted that no major components are excluded in the framework's design. Lastly, the SME interviews validated that the decision-support framework is a feasible solution to the problem at hand.

[21] The aspect highlighted by this SME was incorporated into the framework after the first phase of SME interviews.

10.3. Case study validation

A case study is a systematic way of looking at an instance, analyzing the output information, and reporting on the results (Becker *et al.*, 2012). Case studies are fundamentally focused on gaining an in-depth understanding of the particular instance (Hayes *et al.,* 2015), though the level of detail considered in the case will vary based on the case study type applied as well as the objective of performing the case study. Applying case studies to this research aims to achieve objectives (i), and (iii) of validation (mentioned in Section 10.1). Thus, the aim is to: establish whether the framework is applicable, practicable and adds value to the real-world; and whether the output of the decision-support framework provides valid solutions for the problem that it aims to address. This will be elaborated on in the remainder of this section.

10.3.1. Introduction to case studies and case study types

From the perspective of Hayes *et al.* (2015), case studies are a form of observational studies, focused on collecting data from either a single or multiple cases of a phenomenon. Case studies are also used to gather data from one or more sites at a single or multiple time instances. Lastly, the general aim of applying a case study is to increase the understanding of a specific phenomenon, whether it is in the context of a specific case instance or generalized (Hayes *et al.*, 2015).

Case studies are performed to serve a number of specified research goals (Maxwell, 2005), with three of the most common goals being case or concept description, theory testing, and theory generation (Eisenhardt, 1989). The selection of a case study type is influenced by the goal that the researcher(s) is seeking to achieve in conducting a case study. Furthermore, Hayes *et al.* (2015) recognise that the fundamental aim of applying a case study is to focus on gathering data to use with the aim of: (i) presenting it to others in detail; (ii) gaining a deeper understanding of a topic; and/or (iii) enabling generalized conclusions over a population. Different sources identify different types of case studies (Morland *et al.*, 1992; Nelson and Martin, 2013). For the purpose of this research, the six case study types cited by Marshall (1984), Davey (1991) and Hayes *et al.* (2015) are considered, namely: (i) illustrative; (ii) exploratory; (iii) critical instance; (iv) program implementation; (v) program effects; and (vi) cumulative case studies. Each of the case study types are further explored in Table 10.8.

As seen in Table 10.8, each case study, though serving the same goal of gaining in-depth insight into a single, or multiple events, differs significantly in terms of the applicable goal and design considerations.

Illustrative- and exploratory case studies are similar in their aim of describing a phenomenon. With illustrative case studies describing a single in-depth case in a simplistic manner, and exploratory case studies describing multiple high-level cases. The critical instance case study type's goal relates to generating a theory about a single case. This type of case study typically examines one case in extensive detail with the output focused on the unique case (Becker *et al.*, 2012). A more rare version of a critical instance case study is to serve as a critical test of an assertion about a program, problem, or strategy (Marshall, 1984; Davey, 1991).

The program implementation- and program effects case study types are similar in that the goal of both is to test a theory. Program implementation is useful when concerns regarding implementing a program exist, as it aims to identify the difficulties that might be faced during the implementation process (Hayes *et al.*, 2015). The program effects case study determines the impact of a theory or program and allows the researcher to maximize their understanding, examine causality, and gain inference of the failures and successes of the specific program (Hayes *et al.*, 2015).

Table 10.8: Case study type investigation.

Case study type	Description	Goal	Design
Illustrative	Used to describe a case or phenomenon, what is happening and why it is happening (Hayes *et al.*, 2015).	Bridge the gap between understanding the topic and informs the audience of the topic (Hayes *et al.*, 2015).	Require presentation of in-depth information of all the elements involved in case (Davey, 1991). Number of cases should be kept small (Davey, 1991).
Exploratory	Used to derive an educated initial perception of what is going on in a case (Hayes *et al.*, 2015).	Can improve confidence in an understanding of a problem. Also used to justify and design a large-scale investigation (Becker *et al.*, 2012).	Exploratory studies are meant to be short and small-scale case studies (Hayes *et al.*, 2015).
Critical instance	Performed to examine a specific event or case, focusing on only one site (Becker *et al.*, 2012).	An examination of a particular instance that is not highly generalizable, or of a particular instance, to question a highly generalized or universal assertion (Hayes *et al.*, 2015).	Focus on typically one, or very few cases. Method suited for answering cause-and-effect questions (Hayes *et al.*, 2015).
Program implementation	Discern whether implementation is in compliance with its intent (Davey, 1991).	Provide extensive, large scale generalization about difficulties being faced during implementation (Hayes *et al.*, 2015).	Usually require a team to work through large amount of data and resources. Large sample of cases needed compared to other types(Hayes *et al.*, 2015).
Program effects	Used to determine the effects of specific case (already undertaken) and provide inference about reasons for success or failure (Davey, 1991).	To provide inference on an implemented phenomenon (Davey, 1991).	Conduct case study/studies in sites chosen for representatives, then verify these findings through examination or surveys. Or, best used in conjunction with prior reports and data collections (Hayes *et al.*, 2015).
Cumulative (retrospective or prospective)	Aggregate information from several sites collected at different times of a specific case (Davey, 1991). Case can be retrospective or prospective (Davey, 1991; Hayes *et al.*, 2015).	Provide a greater generalization of the results of multiple case studies that have been conducted at different times and locations (Hayes *et al.*, 2015).	Data typically in the form of previously conducted case studies and contain information that can be aggregated into a single study for a useful purpose (Hayes *et al.*, 2015).

Lastly, the cumulative case study can be classified as being either retrospective (focused on case studies that have been completed in the past) or prospective (focused on case studies that will be conducted in the future). The overall focus is on aggregating information from several sites, collected at different times (most often previously conducted case studies) (Becker *et al.*, 2012), enabling generalization of findings (Hayes *et al.*, 2015). Two features of the cumulative case study are the case survey method (used as a means to aggregate findings), as well as backfill techniques

(used as a means to obtain information from authors that permits use of otherwise insufficiently detailed case studies).

10.3.2. Applying a case study within the context of this research

The goal of applying a case study for this research is multifaceted. Most importantly, the overarching intent of applying a case study is to validate the decision-support framework. To elaborate, and relating to the four objectives mentioned in Section 10.3.1, this research aims to validate the decision-support framework by achieving the goals of both: (i) describing how the framework will operate once implemented (linking to the descriptive goal of Eisenhardt (1989)), as well as (ii) testing the decision-support framework, and determining whether or not it can be successfully implemented (linking to the theory testing goal of Eisenhardt (1989)). A more detailed description of the relevance and intent of applying a case study as well as a description of the case study type that is selected to be applied in this research, is presented in the sections that follow.

10.3.2.1. Case studies and philosophical perspective

According to Løkke and Sørensen (2014), a case study can be conducted from a positivist or an interpretivist philosophical perspective (representing the two extremes). It can follow a deductive or an inductive approach. It can rely on either qualitative data or quantitative data. Lastly, it can also employ a mix of these philosophical perspectives, research strategies and approaches. As clarified in Section 2.1, this research adopts a pragmatic philosophical perspective. This perspective recognizes that there are many different ways of interpreting the world (and undertaking research), and that no single point of view can give the entire picture (Saunders *et al.*, 2009).

In support of Løkke and Sørensen's (2014) aforementioned statement, a case study involving a mixed methods approach implementing both deductive and inductive approaches can be appropriately implemented within the boundaries of the pragmatic research perspective (as defined in Section 2.1). The pragmatic perspective, therefore, views a case study as a means to interpret and test research (the developed decision-support framework), and recognizes that the case studies conducted in this research represent a limited number of perspectives on the efficacy of the work completed.

10.3.2.2. Intent of performing a case study

As stated previously, the case study application aims to achieve objectives (i), and (iii) of validation (mentioned in Section 10.1). Thus, the aim is to: establish whether the framework is applicable, useful and adds value to the real-world; and whether the output of the decision-support framework provides valid solutions for the problem that it aims to address. In support of the aforementioned two objectives, the following sub-objectives (defined in Section 10.1) must be achieved in the case study application, namely, to establish: (i) internal validity (integrity of the specific case study); (ii) external validity (generalizability of the case study to other situations not part of the original study); (iii) construct validity; and (iv) reliability.

In summary therefore, the intent of applying a case study in this research is to gather data to gain a deeper understanding of: the applicability of the decision-support framework in the real-

world; whether the framework is fit for its intended purpose; and whether the decision-support framework is applicable to scenarios outside of the context of this case study, i.e. to interrogate theoretical inference.

10.3.2.3. Selecting a case study type

The case study type applied in this research, namely a cumulative, retrospective case study, is selected based on its feasibility and ability to fulfil the aforementioned purpose of a case study in this research. In the case of this research, cumulative retrospective case studies allow the researcher to aggregate information from more than one source as well as to compare the incentive interventions selected in real-life historical cases with those proposed by the decision-support framework (Davey, 1991). Applying more than one retrospective case study also allows the researcher the opportunity to infer greater generalizations on the ability, transferability, and applicability of the decision-support framework in different scenarios (Hayes *et al.*, 2015).

Given the scale of completing a case study for evaluating the incentive intervention for encouraging R&D for NTDs, it was deemed that three thorough case studies would suffice to demonstrate the applicability and value of the decision-support framework developed in this research study.

10.4. Case study design

Becker *et al.* (2012) argue that due to the diverse nature of, and topics covered by case studies, a universal method or design for conducting a case study does not exist. However, basic components of research design do exist, and include considerations such as: (i) what questions to study; (ii) what data are relevant; (iii) what data to collect; and (iv) how to analyze the data (Becker *et al.*, 2012). The case study design can further be tailored based on the purpose of the study as well as the fundamental logic of applying a case study (Nelson and Martin, 2013). In response, this section explores the following design considerations: (i) desired case study environment; (ii) case study rationale; (iii) single or multiple case study method; (iv) data collection methods; (v) data interpretation and desired output variables; and lastly (vi) case study validity. The 'case study quality checklist' defined by USAID (2013), was used as a guideline in constructing the case study design for this research.

10.4.1. Case study environment

The decision-support framework seeks to support the selection of incentive mechanisms for pharmaceutical R&D for a neglected disease or set of neglected diseases. The selection of an incentive for encouraging R&D of a neglected disease can be either local (with a focus on one country, or area within a country), or globally focused (targeted at being launched in more than one country, and/or with global organizations involved). In the case of a local focus, the framework will most likely be applied to identify solutions for incentivizing R&D that target LMIC settings, where neglected diseases are most prevalent.

As defined in Section 7.1, the framework is intended to include inputs from three primary stakeholders namely the enabler, the innovator and the consumer stakeholders. The enabler stakeholder, being the entity initiating the research seeks to encourage R&D and can be a public-

(including governments), or private (for-/not-for- profit) organization. The innovator stakeholder is the entity that is being incentivized to perform R&D. With the consumer stakeholder being either the end-product user, or any public / private procurers.

10.4.2. Case study rationale

The purpose of applying a case study in this research, as well as the rationale for selecting a cumulative, retrospective case study type comprising three cases, was set out in Section 10.3. Translating this to a lower level of abstraction, the intention in executing the case studies is to establish, amongst other points, whether the framework is able to accurately capture the objectives and limitations, where applicable, of real-world stakeholders. The intention in executing the case studies is also to establish whether the framework can be applied to different scenarios, including cases with more than one stakeholder of a specific type (e.g. more than one enabling stakeholder). Finally, the intention in executing the case studies is to evaluate whether the outputs generated by the framework are both accurate and useful by comparing the outputs to the incentive interventions that were implemented in each of the retrospective case studies, and by asking SMEs to reflect on the usefulness of the results that were generated.

10.4.3. Case study execution and data collection

The case studies are executed by interviewing an individual(s) that represents the perspective of the enabling stakeholder(s) involved in each of the cases. Based on this interview, derivations are made regarding the R&D system environment (Domain 1), the enabler stakeholder(s) (Domain 2), the innovator (Domain 3), and the end-consumer stakeholders (Domain 4). Subsequent to the interviews with the respective stakeholders, interpretations and conclusions are made.

The next step involves determining the validity of the case studies. According to Yin (2014), four concepts relating to the validity of a case study should be considered, namely the: (i) internal validity (integrity of the specific case study); (ii) external validity (generalizability of the case study to other situations not part of the original study); (iii) construct validity; and (iv) reliability. These four aspects are further elaborated in Section 10.8. The validity of the case studies is established through a questionnaire that is sent out to the participants. The questionnaires are subsequently interpreted, and key insights gained from applying case studies are outlined in Section 10.8.

10.5. Case study application 1: Prize fund

In this section, two SMEs that each represent the perspective of an enabling stakeholder, are approached and questioned on the objectives, limitations, considerations, and approach taken before the commencement of a Prize fund targeted at incentivizing NTD R&D. The idea behind this case study is to investigate the stakeholders and pharmaceutical R&D system as defined by the actual case, followed by simulating the decision-support framework, to populate results based on the input provided. As a result, derivations regarding feasible incentive interventions that are proposed for implementation can be investigated compared to the incentive intervention that was actually pursued.

The five domains of the decision-support framework is consequently applied to this case study. The case study is firstly contextualized by providing background information and details regarding the stakeholders involved. Their primary aims as well as innovation boundaries are also defined. Second, the five decision-support framework domains are discussed by referring to the: (i) input and context, (ii) assumptions and considerations; and (iii) output of the domains, by applying the input provided by the enabler stakeholders. For the sake of brevity, only key operationalization context and results of the case study application will be included in this section of the document. A detailed account of the Prize fund case study's content is included in Appendix M. Lastly, the case study's results are interpreted, with the key insights gained highlighted and case study limitations stated.

10.5.1. Contextualization: Prize fund case study

A Prize fund incentive intervention is defined as a monetary reward, mostly provided by governments or donor organizations, to a pharmaceutical organization when the organization successfully delivers an innovation subscribed to a certain set of criteria (Mueller-Langer, 2013a). Prize funds are also often awarded for milestones met by the pharmaceutical organizations (Mueller-Langer, 2013a).

The primary enabler stakeholder in the case study is a private not-for-profit organization that identified a need for R&D to expand the NTD body of knowledge. The enabler organization had the capability to provide a defined monetary reward and partnered with a second enabling organization (private for-profit) also willing to allocate some funding towards an R&D innovation targeting NTDs. In other words, the two enabling stakeholders partnered to provide a prize reward to any innovator with a proposal for an innovation in the field of NTDs, with a third organization acting as a platform provider for the prize to be awarded. The Prize fund offered pre-defined monetary rewards to the three most feasible research proposals for an innovation for NTDs.

The enabler stakeholders in the case study aim to encourage R&D in the entire NTD sphere, with the exception of snakebite infection innovations. Thus innovations in this case study are not confined to a specific outcome, with any innovation targeted at mitigating, diagnosing, or treating NTDs considered within the scope of the incentive. The innovations targeted to be incentivized are also not confined to a specific country, with no geographical boundaries set in terms of either the innovators or the population groups affected by NTDs that are targeted. The only condition for innovators to be eligible for consideration of the incentive intervention is that the innovator needs to have an established relationship with a research centre or institution in NTDs, and can therefore not be an independent scientist working in isolation.

For the Prize fund incentive intervention, the sources of input used included primarily two SMEs, described in Table 10.9. The identities of the SMEs are kept undisclosed to protect the privacy of the individuals. Both SMEs were involved in the incentive intervention that is the subject of this retrospective case study in a professional capacity. For the purpose of the case study, SME 10 was asked to represent the perspective of the primary enabler organization involved in commencing the Prize fund incentive, while SME 11 was asked to represent the perspective of the secondary enabling organization. Based on the nature of their professional experience, both SMEs

were also asked to represent the innovator stakeholders. Finally, one SME provided inputs from the perspective of the consumer stakeholders.

Table 10.9: Information concerning SMEs.

Person (*Date*) *Place*	Expertise of the SME	Perspective	Qualifications	Experience
SME: 10 (19 October 2019) *Skype meeting*	Director of Research and Innovation at private not-for-profit organization. Subject areas of knowledge: Incentive interventions for encouraging drug R&D, neglected disease R&D, and involvement in existing incentive intervention for encouraging R&D. Based in UK.	Enabler perspective	PhD M.Sc B.Sc	10 years
SME: 11 (28 October 2019) *Skype meeting*	Senior Global Program Clinical Head at multi-national pharmaceutical company. Subject areas of knowledge: Incentive interventions for encouraging drug R&D, neglected disease R&D, operational research for drugs and clinical R&D. Based in USA.	Enabler and innovator perspectives	M.B.A, PhD. M.Pharm, B.Pharm	20 years

10.5.2. Domain 1: System demarcation

The system demarcation evaluates the status quo of the neglected disease environment that is targeted by the two enabler stakeholders through the Prize fund intervention.

10.5.2.1. Domain 1: Input and context

As discussed previously, the pharmaceutical R&D system targeted by the Prize fund is defined as the global pharmaceutical environment for researching and developing any innovation targeted at NTDs, with the exception of snakebite infection. The completion of Domain 1 of the decision-support framework commenced with SME 10 and SME 11 providing separate sets of input regarding the R&D system status quo, with inputs of the SMEs based on the system element categories namely the: (i) existing drug characteristics; (ii) consumers, competitors and suppliers; (iii) governance and leadership; (iv) profitability and market forces; and (v) research and development process. The detailed input provided by SMEs 10 and 11 in completion of Domain 1 is depicted in Appendix M. In addition, the completion of Domain 1 also relied on research done outside of the interviews with the SMEs, in order to depict the general system demarcation of NTDs globally.

10.5.2.2. Domain 1: Assumptions and considerations

A primary consideration that occurred in this case study, is that the lack of boundaries defined for this incentive intervention resulted in difficulties to accurately describe the status quo of the elements in the targeted R&D system. (As discussed in Section 8.4.1.4, the status quo of the R&D system for which an incentive is being selected, is described by selecting one of three predefined state descriptors for each of the 67 state elements that comprise Domain 1.) The reason for the aforementioned is that in many cases, each of the three predefined state descriptors could be accurate for at least one of the countries / scenarios that make up the global NTD landscape. Consequently, in this case study where a large spectrum of NTDs and innovators are targeted,

some system elements were described based on a general interpretation of the global pharmaceutical R&D system.

10.5.2.3. Domain 1: Output

Linking to the aim of Domain 1 (thus, to articulate an understanding of the R&D system status quo in the context being targeted by the incentive), the output of Domain 1 highlights the existing discrepancies, opportunities, and gaps in the pharmaceutical R&D system for NTDs. In addition, it draws attention to the key aspects of the NTD R&D system that should be addressed by the selected incentive intervention.

The key insights gained through the completion of Domain 1 can be summarized as follow:

(i) The existence of medicines to address NTDs globally is inadequate, with existing treatments for some NTDs, but breakthrough drugs not existing for the majority of the NTDs. Furthermore, breakthrough drugs that do exist for NTDs are not readily available for all who require these.

(ii) There is insufficient access to treatments for NTDs (links with aforementioned key insight). While the access to treatments can be addressed by means of public mass drug administration efforts, this does not hold true for all NTDs.

(iii) There is a large number of clinical trial barriers for NTD R&D. This can be attributed to the amount of research done, and the size of the body of knowledge of NTD R&D that is small compared to other areas of research.

(iv) Generalizations regarding government involvement in countries cannot be made, as each country has varying domestic policies and health agendas for NTD resource allocation. However, the WHO has been particularly active in promoting the mitigation of NTDs and prioritizing it on their health agenda, through for example the construction of the 2030 NTD Roadmap[22].

(v) Quality assurance of clinical trials is somewhat questionable in certain circumstances as the investigators and hospitals do not always participate in the trials correctly, leading to concerns over data accuracy.

(vi) NTD R&D of treatments has insufficient market potential and efforts should be made to address this. This links to the product export potential of certain products to countries, which might limit the access of the NTD population groups to treatments.

(vii) The risk associated with clinical trials for NTD R&D treatments as well as vaccines, is deemed higher than average. This is due to the limited basic R&D that has been done for most of the NTDs. This might link to the observation that activating clinical trials for NTDs is perceived to be more difficult than activating clinical trials for other conditions .

(viii) Though most clinical trials are registered, some of the regulatory bodies that monitor these trials do not maintain the same level of standards as other regulatory bodies.

(ix) In LMIC settings where many NTDs occur, it is sometimes the case that, though domestic policies for eradicating NTDs are in place, these are not functioning optimally as required for attaining the goal of eradication.

[22] The 2030 NTD Roadmap sets global targets and milestones to prevent, control and eliminate NTDs (WHO, 2020c)

The insights gained regarding the status quo of the pharmaceutical R&D environment as it relates to the NTD Prize fund case study, again reiterate that the R&D body of knowledge for NTDs still experience a lack of priority, even while the WHO is in the process of prioritizing NTD mitigation. This highlights the need for an incentive intervention that allows researchers to add to the body of knowledge.

10.5.3. Domain 2: Enabler profile analysis

The enabler profile domain aims to pinpoint and investigate the objectives, limitations and internal capabilities of the enabler, thus the stakeholder that wants to encourage innovator stakeholders to perform R&D in the NTD sphere.

10.5.3.1. Domain 2: Input and context

The enabler inquiry is intended be completed by each of the enabler stakeholders that are involved, so that the objectives, limitation, and internal capabilities of each enabler stakeholder can be accurately captured. As discussed previously, in this case study there are two enabler stakeholders, namely the primary (not-for-profit private) entity, as well as the secondary (for-profit private) entity. SMEs 10 and 11 were requested to each represent the perspective of one of the enabler stakeholders, and they completed the enable inquiry form separately The completed enabler inquiry forms are included in Appendix M.

10.5.3.2. Domain 2: Assumptions and considerations

An important consideration for the enabler profiles is that SMEs 10 and 11 were asked to complete the enable inquiry form based on their general perception of the objectives, limitations, and internal capabilities of the relevant enabler stakeholder. Though both SMEs were actively involved in the initiation and commencement of the Prize fund that is the subject of this retrospective case study, it is plausible they may not personally have insight into every aspect of the decision-making that took place in relation to the initiation of the incentive. The level of insight into the enabler stakeholders that the SMEs were able to provide is, however, deemed sufficient for the purpose of this case study.

Another consideration that is applicable to this case study, is the appropriate integration of the perspectives of the two enabler stakeholders in the framework. As discussed in Section 8.4.11, the feasible set of incentive interventions suggested (i.e. the solution set) can either be (i) calculated by using a weighted average per enabler of the decision-criteria completed, with the weights per enabler stakeholder defined by the primary enabler stakeholder(s) involved; or (ii) determined by assigning the highest priority rating (given by any of the enabler stakeholders) to the specific enabler criterion. The second approach was applied in this case study.

10.5.3.3. Domain 2: Output

The key insights derived based on the information provided for each of the enabler stakeholders is discussed separately:

(i) Private not-for-profit organization:

This enabler's aim is to not only encourage innovation of treatments and drugs, but to incentivize any innovation (including diagnostic equipment and immunizations) aimed at significantly improving the body of knowledge on NTDs. For this not-for-profit organization, corporate social responsibility is not a motivating factor in the initiation of the incentive intervention.

The innovators targeted range over all types of organizations, with the only pre-requisite being that the innovators need to be linked to or work in collaboration with an established NTD organization. It was, however, mentioned that large pharmaceutical innovators might not find the Prize fund attractive, as the monetary reward on offer may be viewed as relatively small by such organizations. Nonetheless, though big pharmaceutical innovators were not expected to participate, nothing would prevent them from doing so.

(ii) Private for-profit organization:

The objectives and limitations of the second enabling organization that partakes in the Prize fund incentive, are slightly different from the objectives and limitations of the primary enabling organization, namely: to expand the existing R&D network; as well as to advance the R&D body of knowledge. More specifically, the goal of this enabler stakeholder was articulated as creating "*an ecosystem so that there is a stable R&D army in the future who constantly think of NTDs*". The incentive offers this enabling stakeholder the opportunity to fund basic research. Though the enabler organization also performs research, their research focus is not the R&D of treatment drugs. A second motivation in pursuing the incentive, is that it may offer this enabler organization the opportunity to collaborate with drug innovators, though this collaboration is not a requirement. Thus, it is envisioned that such collaboration will only occur if it is mutually beneficial to the stakeholders. The desired relationship with the innovator is once-off.

In terms of the enabling stakeholders' ability to influence policy. It was evident from the inputs provided that no single enabling organization working in isolation can change or influence policy. Policy change requires industry-wide influence, with a consortium of enabling or pharmaceutical organizations required to collaborate in establishing policies that benefit the enablers, the innovators as well as the consumers.

10.5.4. Domain 3: Innovator profile analysis

The innovator profile domain aims to pinpoint and investigate the objectives, limitations and internal capabilities of the innovators that are targeted by the incentive.

10.5.4.1. Domain 3: Input and context

The innovator inquiry form consists of 45 questions that relate to the objectives and limitations of the innovator organization, and the form should ideally be completed by (some of) the innovating organizations that the enabler(s) would like to target. As discussed previously, in this case study both SMEs were asked to complete the innovator inquiry form, based on their professional experience in drug R&D. In completing the innovator inquiry form, the most likely objectives and capabilities of innovators that were targeted in this retrospective case study are borne in mind, instead of focusing on a specific innovator stakeholder. The detailed innovator inquiry forms, as completed for this case study, are included in Appendix M.

10.5.4.2. Domain 3: Assumptions and considerations

Though SMEs 10 and 11 are considered to have significant insight into the objectives and limitations of the innovator stakeholders that were being targeted in this retrospective case study, it is considered a limitation that some of the innovator stakeholders themselves did not complete the innovator inquiry form. More specifically, it is acknowledged that the enabling stakeholders might have a biased view of the innovators that they are hoping to incentivize. Nonetheless, it was judged that the information on potential innovators that could be provided by the SMEs was sufficiently accurate for the purpose of the case study.

10.5.4.3. Domain 3: Output

The key insights gained regarding the innovator stakeholders through the completion of Domain 3 can be summarized as follows:

(i) A likely motivation for innovator stakeholders to complete R&D for NTDs includes to expand the body of knowledge, and to address the disease. The framework considers the aforementioned as a result of the incentive being implemented, but not necessarily as the intrinsic reason why innovators embark on research in the field.

(ii) Political obligations and CSR do not influence the innovators targeted by the Prize fund. The innovators targeted are primarily from academic institutions where a lack of funding to launch or advance an innovative R&D concept, that might contribute to the body of NTD knowledge, exists.

(iii) The research focus area of the innovators targeted by the Prize fund (based on proposals received) is not limited to innovations in the treatment of NTDs, but also includes, diagnostic and equipment innovations that should be considered for mitigating NTDs globally.

(iv) The innovators, though most likely requiring more funding, applied for the Prize fund knowing that it was confined to a limited amount. Though this was not mentioned explicitly, the innovators can also request additional funding from the enablers.

(v) Some innovators might have the ability to fund R&D and use the Prize fund platform for additional funding or exposure to research.

(vi) Most of the innovators do not have major R&D limitations, other than that they require more funding to successfully launch the innovation that they propose.

(vii) Finally, the innovators that participate need to be registered at an acceptable authorization body. All innovators are required to submit a letter of approval proving their compliance to the applicable authorization body.

10.5.5. Domain 4: Consumer profile analysis

Domain 4 aims to establish the needs of both the end-user of the product as well as the potential procurers of the final product.

10.5.5.1. Domain 4: Input and context

Though both SMEs were requested to complete the consumer profile inquiry form, only SME 10 deemed this to be feasible in the case of this retrospective case study. The case study participants indicated that they perceived the consumer stakeholder profile to be different from the enabler and innovator profiles in it being "*far removed*" from the primary aim of the incentive intervention. The SMEs indicated that in the retrospective case study, the perspective of the consumer stakeholder was not viewed as a determining factor in the selection of an incentive intervention. As a result, the case study participant that did complete the consumer profile, requested to not complete all the questions listed, as some of the questions were perceived as not being relevant to the case study. The detailed completed consumer inquiry form is depicted in Appendix M.

10.5.5.2. Domain 4: Assumptions and considerations

The completion of the consumer stakeholder by SMEs 10, highlighted the following attention point that should be considered in more detail.

Attention point: The consumer is too far removed from the incentive intervention objective.

Interpretation: The consumer stakeholder, though being the ultimate target group of any innovation research and development for NTDs, is not always considered in the initial phases of basic research. Questions that further surface as a result of this argument, include whether (i) attention should be given in incentive interventions to focus more on the actual end-consumers, and (ii) whether such efforts will improve the potential of R&D efforts to be more effective in mitigating the targeted disease. This consideration is further explored in the discussion of potential future work based on this research.

10.5.5.3. Domain 4: Output

The following key insights are derived, in terms of both the i) end-consumer, being the patient; and the (ii) potential drug procurers the consumer stakeholder:

(i) End-consumer (patient) stakeholder:

The incentive intervention should aim to eliminate all financial risk for the population groups affected by NTDs. This attribute again highlights that NTD patients do not necessarily have the financial means to procure the drugs required for treatment. By eliminating the financial risk of the innovations, aimed at mitigating the disease, access to the innovation will immediately improve, which in turn will result in improved disease mitigation results. The innovations that are developed in response to the incentive, must accommodate contextual treatment criteria, such as clinical trial diversity requirements, type of consumer considered, drug administration, and stigma considerations. No progress can be made in terms of innovation uptake with the consumer stakeholder population, without adhering to the contextual treatment criteria of the NTD consumer stakeholder. Therefore, these criteria is critical to

facilitating effective disease mitigation, regardless the innovation discovered and developed for NTDs.

(ii) Drug procurer stakeholder:
A criterion that was indicated as important from the perspective of drug procurers, is that the end-price should contain no profit margins.

The SME that completed the consumer profile, mentioned that it was not as easy to complete as the other stakeholder profiles. Further investigations regarding the consumer stakeholder and the inclusion thereof in the decision-support framework is discussed in the future work of this research study in Chapter 11.

10.5.6. Domain 5: Solution set

The solution set of the decision-support framework combines the data from Domains 1 to 4 to ultimately propose a feasible set of incentive interventions for the enablers to consider.

10.5.6.1. Domain 5: Input and context

As elaborated in Section 8.4.11, the solution set consists of 26 incentive interventions that are evaluated based on their ability to address a defined set of decision criteria. The decision criteria are categorized into 12 criteria clusters, with a corresponding criteria cluster score calculated, as per Equation (1) depicted in Section 8.4.10.

10.5.6.2. Domain 5: Output

An overview of the framework outputs is provided in this section, while a detailed presentation of the case study results is given in Appendix M. An analysis of the results is presented in Section 10.5.7. The recommendations provided by the decision support framework can be divided into two categories namely the (i) incentive-based interventions, as well as the (ii) non-incentive-based interventions.

(i) Incentive-based interventions

The results provided by the decision-support framework are depicted by Figures 10.1 and 10.2. With Figure 10.1 depicting an overall heatmap, indicating the degree to which the 26 incentive interventions address the 12 criteria clusters. As discussed in Section 8.4.10, the incentive intervention criteria cluster scores are depicted relative to one another utilising a colour scale instead of providing quantitative scores, as such scores could potentially be misleading.

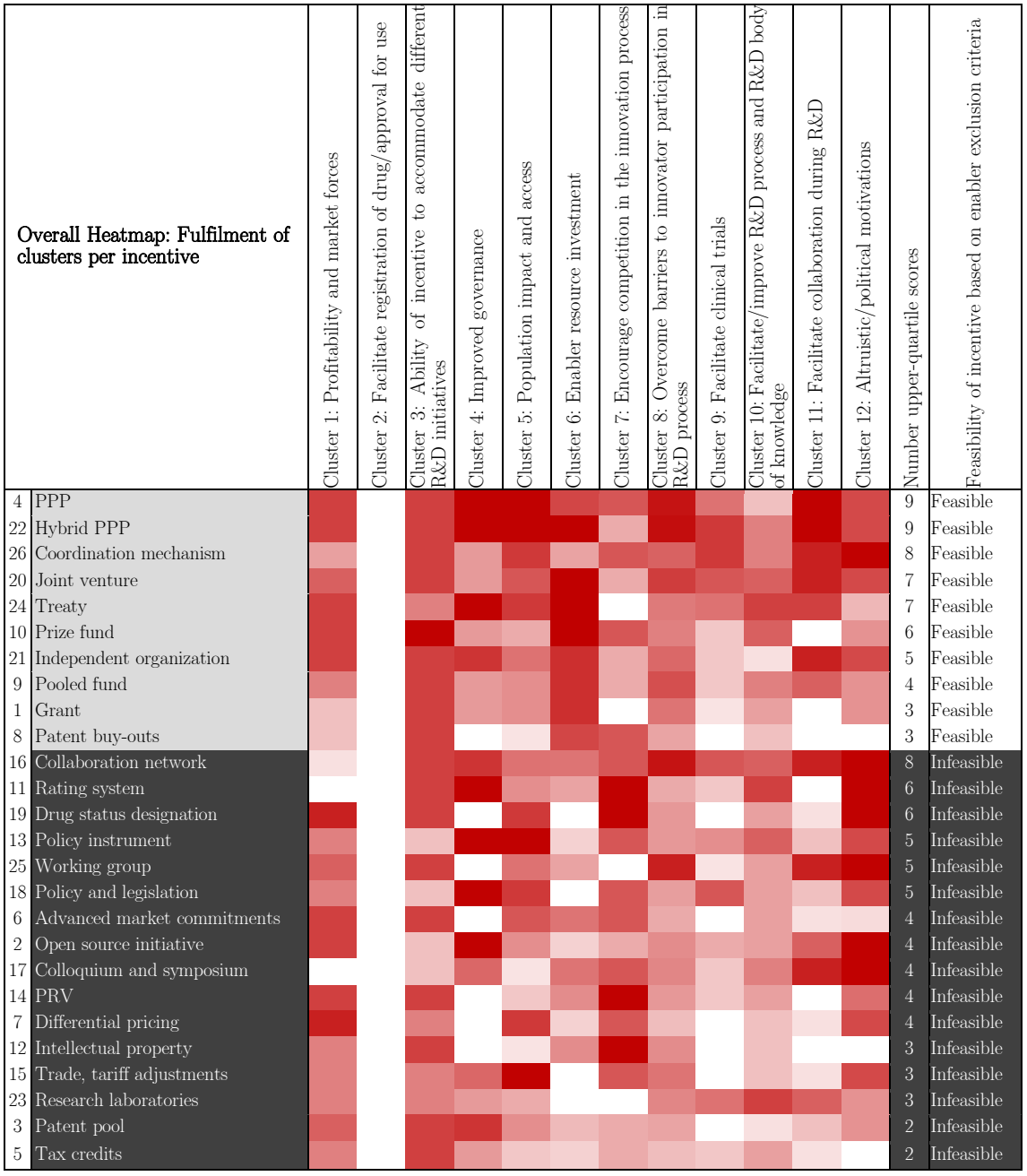


Figure 10.1: Solution set heatmap indicating the extent to which the 26 incentive interventions address the 12 criteria clusters, based on the input provided by SMEs 10 and 11 for the Prize fund case study.

As indicated in Figure 10.1, ten of the 26 incentive interventions are deemed feasible interventions to encourage R&D for NTDs, based on the enabler stakeholder exclusion criteria. Of these ten feasible incentive interventions, the top six incentive interventions achieved a criteria cluster score that fell in the upper quartile in 50% or more of the criteria clusters. These six top performing incentive interventions include: (i) PPP's, (ii) hybrid PPP's, (iii) coordination mechanism; (iv) joint venture; (v) treaty; and (vi) prize fund. Also visible in Figure 10.1, is that Criteria Cluster

2 (i.e. 'Facilitate registration of drug/approval for use'), is not addressed by any of the incentive interventions. Further interpretation of the solution set is provided in Section 10.5.7.

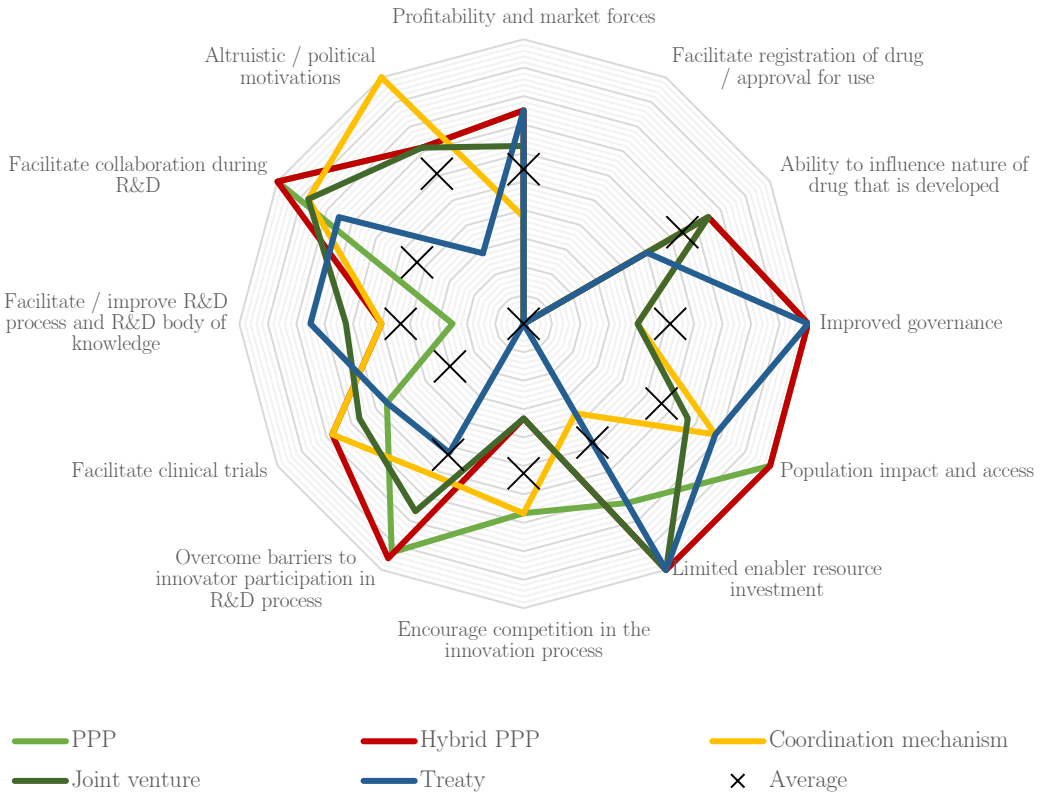


Figure 10.2 Spider diagram indicating the top five feasible incentive interventions' abilities to address the 12 criteria clusters.

Figure 10.2 depicts a detailed overview of the top five performing incentive interventions, and their respective abilities to address the 12 criteria clusters by means of a spider diagram. From Figure 10.2 it can be derived that though they perform well in many criteria clusters, some incentive interventions perform below average in addressing other criteria clusters. For the sake of brevity, a spider diagram for all 12 criteria clusters is not included in this section of the dissertation, though it is included as part of a supplementary solution set in Appendix M.

To depict the value of reviewing these sets of output, however, spider diagrams are included for two of the 12 criteria cluster in Figures 10.5 and 10.6. From Figures 10.5 and 10.6 it is visible that the Prize fund incentive intervention performed the best of all incentive interventions in Criteria Cluster 3, with PPP and hybrid PPP outperforming the rest of the incentive interventions in Criteria Cluster 11.

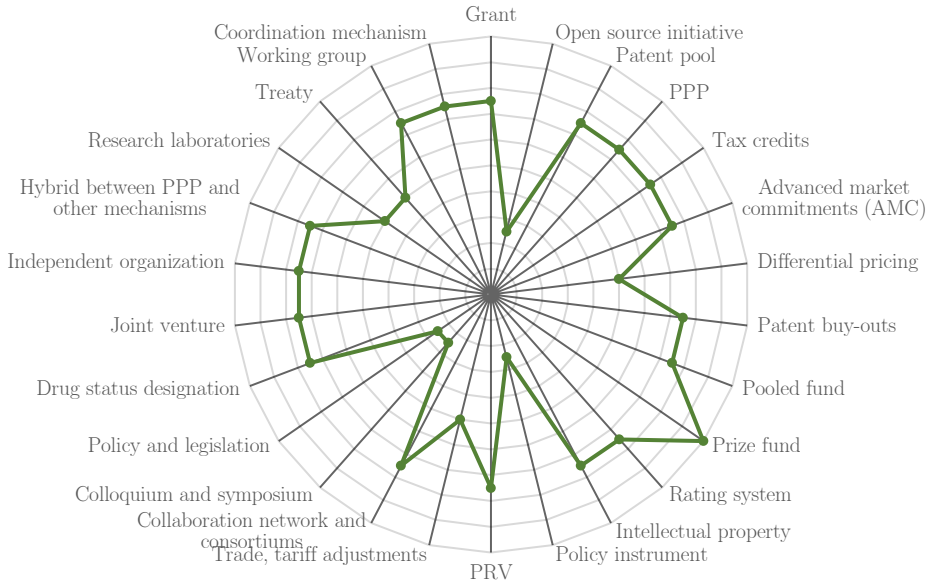


Figure 10.4: Spider diagram indicating the ability of the 26 incentives to accommodate different R&D initiatives (Criteria Cluster 11).

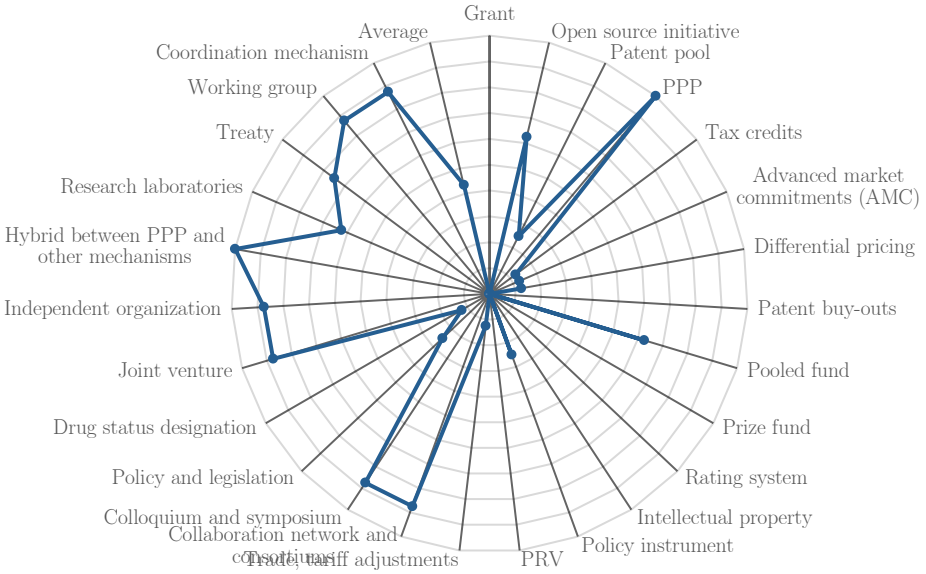


Figure 10.3: Spider diagram indicating the ability of the 26 incentive interventions to facilitate collaboration during R&D (Criteria Cluster 3).

(ii) Non-incentive-based interventions

For the sake of brevity only the non-incentive-based interventions that are deemed a high priority by the decision-support system for the Prize fund case study are listed in Table 10.10. The full set of non-incentive-based interventions recommended for this case study are included in Appendix M.

Table 10.10: High priority non-incentive-based interventions resulting from Prize fund case study.

6. Affordability of current drugs to desired population		*Further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	2
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

9. Comprehensiveness of services delivered		*Further reference*	
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004, WHO, 2010)	2
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.		
Intervention considerations	Education of prevention measures.		
	Address root-cause of disease (e.g. water and sanitation)		
	Investigate the needs of the affected population group		
	Address social needs of patients		
	Repeat prevention or mass drug administration interventions, if necessary.		

10. Continuity of patients' access to health services		*Further reference*	
Meaning	For health interventions where once-off treatment is not adequate, follow-up treatments must be scheduled and adhered to.	(Jackson, 2018, Holt, Gillam and Ngondi, 2012, Stevens, 2004)	2
Relevance	If follow-up treatments are not provided, then patient health might not improve as desired.		
Intervention considerations	Scheduling of follow-up interventions		
	Mobile health facilities		
	Track patient health records and data		
	Monitor and track patients		

16. Existence of competitors		*Further reference*	
Meaning	Competitors refer to other pharmaceutical innovators completing R&D in the same field, thus, targeting the same disease.	(Thakor and Lo, 2018, Whiteside, 2016)	2
Relevance	Strong competition exists because of intellectual property rights that are gained for new chemical entities innovated.		
Intervention considerations	Explore and compare for similar drugs being marketed as different products.		
	Competition is not always a bad thing (speeds up discovery)		
	Collaboration and open innovation		

20. Adequate supply of the health service		*Further reference*	
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Jacobs et al., 2012, RAND Corporation, 2007)	2
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

Table 10.10 continue on next page

Table 10.10 continued from previous page

22. Current investment capital and returns		*Further reference*	
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Vischer et al., 2017, (Bates et al., 2015, Ho, Zarrinpar and Chow, 2016, Payne et al., 2015)	2
Relevance	This factor refers to the current ROI being profitable or not, if not then more investment in a similar research area is not likely.		
Intervention considerations	Financial analysis		
	Cost analysis of activities		
	Reduce indirect and operational costs		

34. Recruitment and retention of participants		*Further reference*	
Meaning	Clinical trials require participants to perform drug safety tests.	(Kurt et al., 2017) (Hammer, Eckardt and Barton-Burke, 2016) (Jennings et al., 2015),	2
Relevance	Effort should be done to recruit the right number of participants for clinical trial tests		
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Ensure safety of participants		
	Build trustworthy relationships with participants		

35. Racial differences in participation in clinical trial		*Further reference*	
Meaning	A variety of ethnicity groups, races and both genders' response on the drugs needs to be tested	(Kurt, Semler, et al., 2017, Baylor College of Medicine, 2009)	2
Relevance	Given that drugs can be used by anyone, tests should be performed on various people to test for any difference in reactions or dosage requirements.		
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Build trustworthy relationships with participants		

42. Health data generation		*Further reference*	
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	2
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

10.5.7. Interpretation of Prize fund case study results

The incentive interventions solution set proposed for the Prize fund case study is presented based on the priority ratings of the decision criteria in Domains 1 to 4 of the decision-support framework, provided by the two SMEs. The aim is to provide stakeholders with an overview of the available, feasible options to encourage R&D for the specific case as well as to provide insight on the relative strengths and weaknesses of the feasible incentive interventions.

Even though the Prize fund case study is a retrospective case study with the pursued incentive intervention already selected, the solution set provided by the decision-support framework is formulated as it would have been in the case where an incentive intervention was not yet selected. However, during the interpretation and discussion of the solution set, the incentive intervention that was pursued in this retrospective case study, namely the 'prize fund', is identified in order to further enhance the ability to reflect on the value of utilizing the decision-support framework in this specific instance.

Through populating the decision-support framework results, it can be established whether the incentive intervention selected and implemented by the enabling organization is recommended as

a feasible incentive intervention to pursue by the framework. The retrospective case-study format also affords the opportunity to reflect on how other incentive interventions that are recommended for consideration by the framework would most likely have fared.

The interpretation of the incentive intervention solution set populated by the decision-support framework will be guided by investigating the following themes: (i) feasible and top performing incentives, (ii) infeasible and underperforming incentives; (iii) the variance in solutions suggested for respective enabler stakeholders; (iv) the impact of the end-consumer profile not completed fully; (v) the solution set by evaluating the 12 criteria clusters; and (vi) alterations suggested in stakeholder profiles with impact of changes anticipated.

10.5.7.1. Feasible and top performing incentive interventions

The most feasible incentive interventions are both PPP and hybrid PPPs, with an upper quartile criteria cluster score of 9 out of 12 (i.e. 75%). These two incentives correlate in their ability to address most of the criteria clusters, with varying abilities to address Criteria Clusters 6, 7, 9 and 10. More specifically, hybrid PPPs outperform PPPs in terms of addressing the barrier of enabler resource investment (Cluster 6); facilitating clinical trials (Cluster 9); and facilitating the R&D process / improving the R&D body of knowledge (Cluster 10). In contrast, PPPs perform more strongly in terms of encouraging competition in the innovation process (Cluster 7),

The third highest rated feasible incentive, i.e. the coordination mechanism, was not expected to be in the final solution set. The coordination mechanism refers to initiatives that coordinate R&D investments and activities. This incentive was not anticipated as a top feasible incentive intervention as it was assumed that the enabler stakeholders, in selecting the Prize fund as an incentive intervention, did not want to coordinate R&D activities but rather aimed to incentivize R&D by creating competition amongst innovators with a monetary reward as the outcome. The aforementioned assumption was proven wrong by the identification of the following enabler objectives as part of Domain 2: (i) wanting to play a role in improved access; (ii) facilitating collaboration between innovators; (iii) collaborate and build a partnership; and (iv) collaborate with innovator. Such objectives are typically achieved by an incentive that in some way or another aims to coordinate and facilitate collaboration between innovators, rather than creating competition.

The 'prize fund' incentive, which was the incentive pursued in reality, ranked 6th overall, performing in the upper quartile in terms of fulfilling 50% of the criteria clusters. This incentive outperforms the PPP and hybrid PPP incentives in three of the 12 criteria clusters, namely: (i) Cluster 3, the ability of incentive to accommodate different R&D initiatives; (ii) Cluster 7, to encourage competition in the innovation process; and (iii) Cluster 10 to facilitate/improve R&D process and R&D body of knowledge. This incentive also scored the highest for Cluster 3, fulfilling all the criteria set out by the stakeholders in terms of accommodating different R&D initiatives. The aforementioned score was expected, as the prize fund does not define any borders for research proposal applications, but rather considers all proposals that aim to innovate in the NTD R&D sphere.

10.5.7.2. Infeasible and underperforming incentive interventions

Of the 26 incentive interventions considered as solutions for this particular case study, 16 incentive interventions were deemed infeasible, based on the exclusion criteria provided by both enabler stakeholder profiles.

The infeasible incentive interventions of this case are excluded primarily as a result of the enabler stakeholders not having the capacity to fully fund the R&D process, or their ability to provide market exclusivity, market certainty or to adjust policies and facilitate with the regulatory process. As a result, though some of these incentive interventions perform well in terms of fulfilling a number of criteria clusters, it would not be feasible to implement them.

The underperforming feasible incentive interventions include: independent organizations; pooled fund; grants and patent buy-outs. Of these four incentives it was expected that the grant and pooled fund incentives would have fulfilled more of the criteria clusters, given its similarities to a prize fund. This underperformance can be attributed to its inability to facilitate collaboration (identified as a prominent objective by enabler stakeholders).

10.5.7.3. Different solution sets per enabler stakeholder

As discussed previously, the inputs of the two enabling stakeholders were provided separately and were subsequently merged to generate a consolidated solution set. In Figures 10.3 and 10.4, a separate feasible solution set is presented based on the inputs of only one enabling stakeholder at a time. This does not form part of the standardised output that is provided by the framework, but it is included here to facilitate thorough analysis of the framework as part of the case study application. As shown, the set of feasible incentive interventions is identical, though there is a slight difference in the number of upper-quartile scores achieved by each of the feasible interventions. This insight can be further interpreted to indicate that both enabler stakeholders have the same overall objectives and limitations, but that they prioritized them differently on the three-point scale provided.

Overall Heatmap: Fulfilment of clusters per incentive		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 8	Cluster 9	Cluster 10	Cluster 11	Cluster 12	Upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													9	Feasible
22	Hybrid PPP													9	Feasible
26	Coordination mechanism													8	Feasible
20	Joint venture													7	Feasible
24	Treaty													7	Feasible
21	Independent organization													6	Feasible
10	Prize fund													6	Feasible
9	Pooled fund													4	Feasible
1	Grant													3	Feasible
8	Patent buy-outs													3	Feasible
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	Infeasible

Figure 10.5: Solution set heatmap indicating the feasible incentive interventions, based on the perspective of the primary enabler stakeholder.

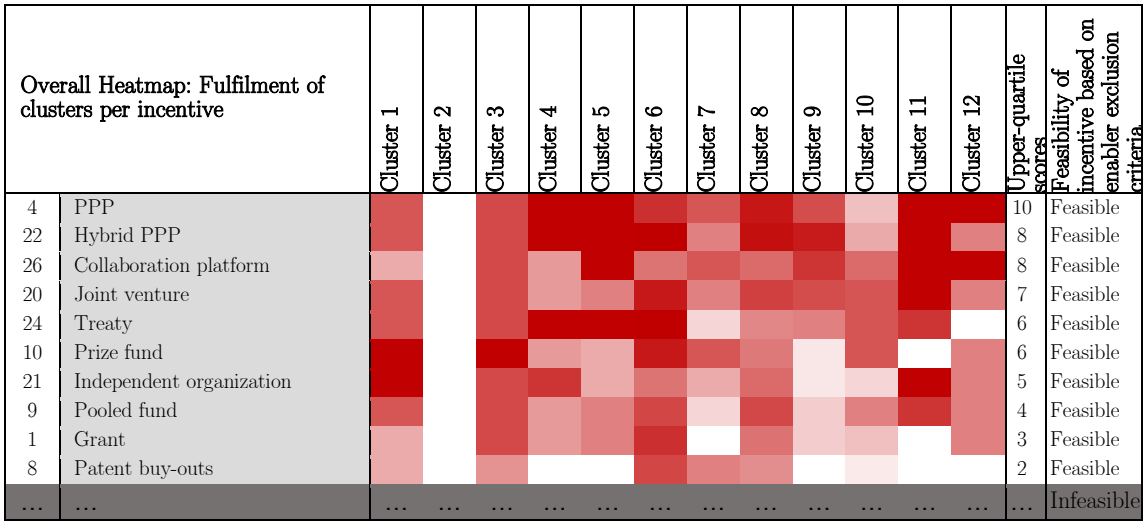


Figure 10.6: Solution set heatmap indicating the feasible incentive interventions, based on the perspective of the secondary enabler stakeholder.

10.5.7.4. End-consumer profile impact on solution set

Though the end-consumer profile was deemed a necessary component of the framework by most SMEs during the verification and validation of the decision-support framework (refer to Section 7.5), the SMEs that participated in this case study indicated that it was too far removed from the Prize fund to be relevant or hold value. This view could be attributed to the enabling stakeholders not having the intention to take part in the process of actually integrating and launching the product to the end-consumer stakeholders, with their desired involvement being limited to building the basic research body of knowledge. To test the effect of the consumer profile being completed entirely for this case, a simulation was run by prioritizing all consumer stakeholder decision criteria as a high priority. The results are depicted in Figure 10.7.

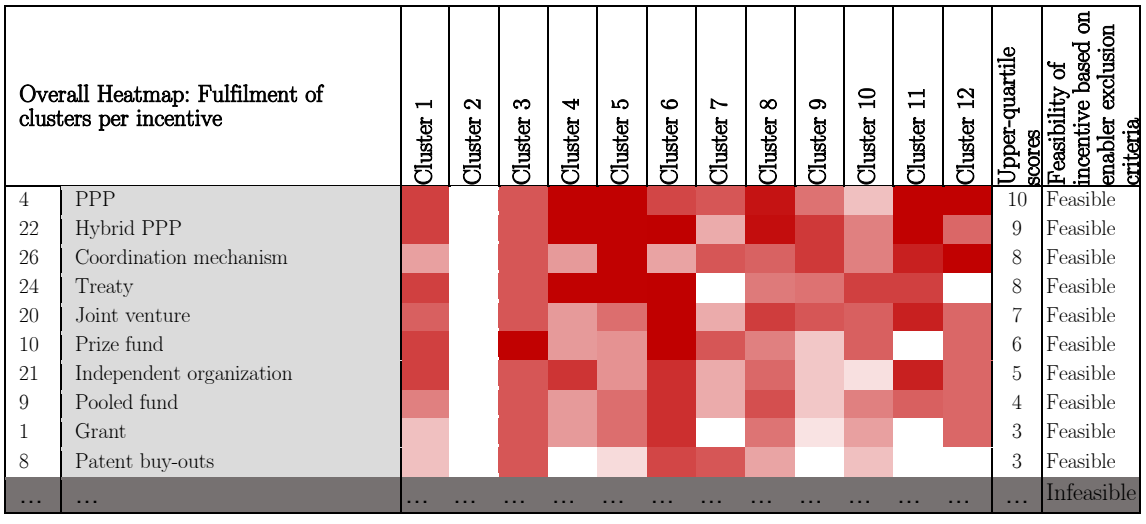


Figure 10.7: Solution set heatmap with end-consumer decision-criteria as high priority.

By comparing Figures 10.1 and Figure 10.7, it is evident that the set of feasible incentives remain unchanged (this is as expected, given that exclusion criteria are exclusively drawn from the enabler profile). The simulated results do, however differ in terms of the ranking of the feasible incentive interventions, and by implication, in terms of the abilities of each of the incentives to satisfy the 12 criteria clusters.

10.5.7.5. Evaluation of the 12 criteria clusters

When evaluating the incentives' abilities to address the 12 criteria clusters, it is important to note that the ability of the incentive intervention to address a specific criteria cluster is not measured based on the ability of the incentive to fulfil *all* the criteria that are encapsulated in a given criteria cluster. Instead, as per (1), defined in Section 8.4.10, only criterion that are assigned a priority rating of either 1 or 2 are considered when calculating the cluster score, and the ability to fulfil each of these applicable criterion is further weighted, based on the priority ratings provided by stakeholders. Thus, the criteria cluster scores that have been determined for this case study, and that are presented in the heatmaps and spider diagrams, do not give an absolute indication of each incentive intervention's ability to address each criteria cluster, in a holistic sense. Instead, these give an indication of the ability of each incentive intervention to address only those criteria in each cluster that have been deemed to be relevant, with additional weight attached to those criteria that have been deemed a high priority.

An evaluation of each of the criteria clusters, to understand and grasp the solution set output provided by the decision-support framework for this particular case study, is depicted in the following section. Refer to Table 8.6 in Section 8.4.10.2 for a description of each of the criteria clusters.

Criteria Cluster 1: Profitability and market forces

Of the 12 decision criteria categorized in the profitability and market forces criteria cluster, 7 are classified as having a priority rating of zero based on the information provided in the execution of this case study. This indicates that, in this case study, the primary aim of the stakeholders is not to maximize profits and overcome economic market forces by means of market exclusivity, market certainty, tax credits, and / or pricing policies. Decision criteria which were assigned a high priority include: (i) delinking revenue from sales volume; (ii) improving the NPV of stakeholders; and (iii) minimizing the barriers to implementation.

The incentive interventions that outperformed the rest of the incentive interventions in this criteria cluster include drug status designation, and differential pricing. Prize fund, treaty, independent organizations, PPP's as well as hybrid PPP's all address 75% of the applicable decision criteria within this criteria cluster. Grants, and patent buy-outs performed the poorest of all the feasible incentive interventions for this cluster. This might be attributed to the enabler stakeholders not prioritizing decision criteria such as 'allowing market exclusivity over an innovation', or because of the grant and patent buy-outs ability to overcome market forces and improve profitability for primarily the enabler and innovator stakeholders.

Criteria Cluster 2: Facilitate registration of drug/approval for use

This criteria cluster is the only cluster where all the incentive interventions scored null. A reason for this is that the decision criteria within this criteria cluster was not prioritized by the enablers and consumers, or by the system demarcation domain system elements (i.e. priority rating of 0). Another factor that contributed to the state of this criteria cluster is that more than 50% of the decision criteria within Criteria Cluster 2 are sourced from the consumer profile. The inability of the incentives to address this criteria cluster are resultingly from the consumer profile that is not completed in full, as well as the enabler stakeholder that do not prioritize and classify the potential incentive intervention to 'involve/require market authorization policies', or to 'involve/require national policies and legislation' to be altered.

Criteria Cluster 3: Ability of the incentive to accommodate different R&D initiatives

All, but one of the decision criteria within this criteria cluster are prioritized as either relevant or important (i.e. priority rating of 1 or 2). This indicates that the stakeholders aim to encourage and incentivize a variety of R&D initiatives, and not merely incentivize one specific type of R&D for one specific NTD. Decision criteria that have the highest assigned priorities include: (i) the incentive should encourage R&D of a drug/intervention; (ii) payoff to innovators should be based on (or influenced by) cost-effectiveness of the initiative developed; and (iii) contextual treatment criteria should be addressed by the innovation.

The prize fund incentive intervention was the only incentive that has the ability to fully address all the decision criteria that was prioritized by the stakeholders for this criteria cluster. The treaty incentive intervention performed the poorest of the feasible incentives addressing less than 50% of the decision criteria.

Criteria Cluster 4: Improved governance

Based on information provided in the system demarcation domain, the following two decision criteria in this cluster were rated as important: (i) promoting equitable health-focused governance; and (ii) promoting transparency and accountability in the NTD R&D sphere.

The incentive interventions that outperformed the rest include hybrid PPP's, PPP's, and treaties. The reason for the aforementioned incentive interventions outperforming the rest can be attributed to the involvement of governments and the public sector in these incentive interventions. Furthermore, the incentive intervention that performed the poorest (not addressing any of the decision criteria in this criteria cluster), is patent buy-outs. This is as expected as the patent buy-out incentive intervention does not aim to promote transparency, accountability or equitable governance through performing R&D for NTD, but rather focuses on acquiring an existing patent. The acquirer of the patent will, however, play a role in whether or not improved governance will be reached as a result of the patent being 'bought-out'. If the acquirer is a government, aiming to eliminate price distortions, then improved governance can be achieved.

Criteria Cluster 5: Population impact and access

Five of the seven decision criteria within the population impact and access criteria cluster are prioritized as either relevant or important by the stakeholders of the Prize fund case study. This indicates that the stakeholders do ultimately aim to improve population impact and access, even though the incentive that was in fact selected in the retrospective case study (i.e. the Prize fund)

does not directly aim to enable access. The decision criteria classified as high priority include: (i) improving access to consumers; (ii) minimizing the disruptive effects of the innovation to the population that will be receiving it; and (iii) aiming to eliminate all financial risk involved for the consumers of the innovation.

Incentive interventions that outperformed the rest of the incentives in terms of population impact and access are PPPs and hybrid PPPs, which both fully address the decision criteria prioritized by the stakeholders for this cluster. The patent buy-out and prize fund incentives performed the poorest of all the feasible incentives. Again, the patent buy-out influence on impact and access might vary with the type of stakeholder that buys the patent out. The prize fund most likely performs poorly as access and impact on the population is not necessarily included in the competition of performing innovative R&D.

Criteria Cluster 6: Enabler resource investment

Of the 12 decision criteria categorized in the enabler resource investment criteria cluster, five are prioritized as important (i.e. priority rating of 2). The inputs that were provided as part of the case study indicate that the enabler stakeholders do have the means to invest resources into the incentive and that the innovator stakeholders that are being targeted require financing to perform the R&D. The zero ratings of the following decision criteria support the aforementioned: (i) incentive does not require enabler funding; (ii) resources to develop incentives should be government financed; and (iii) the innovator does not require any funding from the enabler stakeholder.

The hybrid PPP, joint venture, treaty, and prize fund incentive interventions all fully address the decision criteria that are prioritized in this criteria cluster. As expected, the coordination mechanism incentive performed the poorest.

Criteria Cluster 7: Encourage competition in the innovation process

All but one of the decision criteria within this criteria cluster are prioritized as important. This indicates that the stakeholders in the case study do seek to encourage competition in the innovation process.

The feasible incentive interventions that outperformed the rest of the incentive interventions in addressing the decision criteria categorized in this criteria cluster include the PPP, coordination mechanism, prize fund and patent buy-out incentive interventions. Furthermore, treaties and grants were the incentives that addressed the least number of decision criteria categorized in this criteria cluster. The reason for the aforementioned can be directly attributed to treaties and grants not encouraging innovators to compete against one another.

Criteria Cluster 8: Overcome barriers to innovator participation in R&D process

Common barriers to innovator participation include decision criteria relating to the type of stakeholders that are encouraged to participate in the innovation process, the requirements that the innovators have regarding funding or resources offered by the enabling stakeholders, as well as the ability of the enabler stakeholders to accommodate and address the requirements of the innovator stakeholders.

The top performing feasible incentive interventions include the PPP and hybrid PPP. This can be attributed to the flexibility within these partnerships to accommodate the requirements and needs of the innovators, with most PPPs and hybrid PPPs being strategically aligned to accommodate synergy between the enabler, innovator and additional stakeholders that are involved. Most feasible incentive interventions adequately address this criteria cluster, with patent buyouts being the lowest performing feasible incentive, this might be attributed to the innovator needs that are not considered in patent buyouts, as the incentive places more focus on intellectual property rights.

Criteria Cluster 9: Facilitate clinical trials

Six of the eight decision criteria in this criteria cluster are classified as relevant or important (i.e. priority rating of 1 or 2). This indicates that the stakeholders involved in the case study prioritize facilitating clinical trials. With the two decision criteria with a priority rating of zero being to globalize clinical trials, and to address or influence clinical trial regulation policies.

The incentive interventions that outperformed the rest include the hybrid PPP, as well as the coordination mechanism. These incentive interventions provide insight or expertise to enable the clinical trial process. Grants and patent buy-outs are the worst performing feasible incentive interventions. This can be attributed to both the aforementioned incentive interventions being focused on only providing either a monetary amount, or intellectual property rights.

Criteria Cluster 10: Facilitate/ improve R&D process and R&D body of knowledge

Eight of the nine decision criteria categorized in this criteria cluster are prioritized as important by the stakeholders of the case study. The decision criteria that are not prioritized relates to an improvement in the R&D productivity. This indicates that the stakeholders prioritize the improvement of the R&D process and body of knowledge.

The feasible incentive interventions that outperformed the rest of the incentives in this criteria cluster include the treaty, joint venture, and prize fund incentives. These three incentive interventions provide the means to overcome frequently experienced R&D process obstacles and to improve the body knowledge. The incentive interventions that underperformed in this criteria cluster include independent organizations, as well as patent-buyouts. The average ability of incentive interventions to address the decision criteria in this criteria cluster is 43%, which is in the bottom quartile in terms of the overall ability of the incentives to address all the criteria clusters. A reason for the aforementioned might be that the incentives, though aiming to improve the R&D body of knowledge by encouraging R&D, do not always consider the limitations in the R&D process that needs to be addressed or overcome to successfully achieve an improvement in the state of the R&D pipeline.

Criteria Cluster 11: Facilitate collaboration during R&D

The stakeholders in the case study prioritized five of the six decision criteria that are categorized in this criteria cluster as relevant or important. This indicates that the enabling stakeholder's values collaboration and that the selected incentive intervention should have the ability to facilitate collaboration in the R&D process. This was not expected as the incentive intervention that was in fact selected in this retrospective case study involves the prize fund, which primarily aims to create some form of competition among innovators, rather than to facilitate collaboration.

The reasoning behind the prioritization of these decision criteria by the enabler stakeholders in this case study, was that even though they were ultimately awarding a prize, they still wanted the innovators that were applying to collaborate with competitors in order to learn from one another and to collectively improve the body of knowledge.

In this criteria cluster, an interesting occurrence is that the incentive interventions are either highly likely to facilitate collaboration, or not likely to do so at all. The ability of an incentive intervention to facilitate collaboration can be enforced by specific requirements that are defined for a specific incentive intervention. For instance, certain prize funds can have an additional condition of requiring collaboration between more than one organization, in order for the innovator stakeholders to apply. These cases are, however, viewed as exceptions rather than as the standard practice for the incentive interventions.

The incentive interventions that have full capacity to address the decision criteria prioritized in this criteria cluster include PPPs and hybrid PPPs. Feasible incentive interventions that underperformed in this criteria cluster, based on their ability to address the decision criteria that were prioritized, include the prize fund, grants, and patent buy-outs.

Criteria Cluster 12: Altruistic /political motivations

Four of the five decision criteria that are categorized in the altruistic/political motivation criteria cluster are prioritized as relevant or important, including: (i) that the incentive should convey an important message; (ii) that not for profit R&D is enabled; and (iii) that not for profit margins for drug procurers are accommodated. These decision criteria emphasize the altruistic motivation of the stakeholders involved in this case study. The only decision criteria that is not prioritized involves the requirement for the enabling stakeholder to fulfil political motivations.

The feasible incentive intervention that performed the best in this criteria cluster is the coordination mechanism, which addressed all of the decision criteria that are prioritized. Other incentives that performed well include the PPP, hybrid PPP, and independent organizations. The incentive interventions that under performed in this criteria cluster include the treaty and patent buy-out incentives. This is expected as the primary aims of the two underperforming feasible incentives are more politically and profit driven, with altruistic motivations not primarily addressed.

10.5.8. Case study limitations

Limitations of this Prize fund case study can be summarized as follows:

(i) The aim of the enabler stakeholders of this case study was broad with no definite boundary defined that limited innovators to innovate for a specified NTD, or a specific type of R&D innovations. This led to difficulty in the prioritization of decision-criteria that evaluates the state of the specified R&D environment and resulted in general assumptions that needed to be made, or prioritization to be generalized to accommodate the entire global NTD R&D sphere.

(ii) The incomplete consumer profile, although it provided additional insights into the priorities of enabler stakeholders, led to some abilities of the incentive interventions

not portrayed or considered in the solution set (e.g. to facilitate the registration of drug/approval for use).

(iii) The enabler stakeholders completed the innovator stakeholder profile, however, as mentioned in Section 10.5.4, it is intended to be completed by the innovator stakeholder/s themselves. The reason why this is a limitation is that the enabler stakeholders, though having a clear understanding of the innovator stakeholder, might not be aware of all the requirements and internal capabilities that the innovator stakeholders might have. As a result, the enabler stakeholder assumes certain attributes of the innovator stakeholder that is not necessarily the case.

10.6. Case study application 2: Hybrid PPP

Similar to the case study presented in Section 10.5, this section investigates and elaborates on a second retrospective case study, where a Hybrid PPP was initiated to improve R&D efforts and address primarily non-communicable diseases in Africa. The targeted diseases include any co-morbidities of NCDs, including NTDs. Similar to the presentation of the Prize fund case study in Section 10.5, the presentation of this Hybrid PPP case study also starts with a section that contextualises the problem and provides details regarding the stakeholders involved in the Hybrid PPP case. Second, the decision-support framework is applied to the case study and thirdly, the case study results are interpreted, and limitations highlighted.

10.6.1. Contextualization: Hybrid PPP

This hybrid PPP incentive is described as an open laboratory partnership incentive intervention and is defined as an integrated research and partnership environment, enabling various stakeholders to collaborate to achieve a common goal (Birx *et al.*, 2013). Furthermore, Birx *et al.* (2013) describe open laboratory partnerships as an intervention where a wide variety of stakeholders (including government, industry organizations, and/or academics) have access to multiple resources and work towards one common goal.

This retrospective case study involves one primary enabler stakeholder, as well as various secondary enabling stakeholders. The secondary enabler stakeholders differ per country and project that results from the Hybrid PPP, as each project (i.e. partnership that stems from the Hybrid PPP initiative) is unique and involves a specific set of stakeholders. Various innovator stakeholders are also targeted per project.

The primary enabler stakeholder, in the context of the case study, is a publicly listed international pharmaceutical organization. The fundamental aim of initiating the incentive intervention in this retrospective case study, was to create a new global R&D effort, with the primary enabler stakeholder partnering with other enabling stakeholders (i.e. major funding organizations, academic centres, and the governments through whom the incentive will be employed), to conduct high-quality research by sharing expertise and resources. The primary enabler stakeholder connects with innovator stakeholders (i.e. researchers who are at an early stage of their research career, associated with a university or research institution) through requesting research proposals on NCDs as well as NTDs that are co-morbidities of NCDs. The focus of the initiative is not on prominent neglected diseases that historically attracted significant research attention, but rather

on the neglected diseases for which there appear to still be significant research opportunities. The initiative's call for research proposals specified that the innovators that apply (i.e. academic institutions in target countries) are required to have an established collaboration with a UK-based academic institution. The innovator stakeholders were subsequently selected based on the research proposal that were submitted. Subsequently the enabling stakeholders involved in the specific project collectively provided the innovator stakeholder with funding, as well as R&D assistance, to advance and realize the R&D efforts proposed.

The geographic regions targeted by the incentive initiative include primarily sub-Saharan African countries. The most prominent participating countries include South Africa, Nigeria, Tanzania, Kenya, Uganda, and Malawi, and are selected based on their medical research capabilities.

As defined in Section 10.4.4, the data used to construct this case study is gathered from an interview held with SME 12, as well as from the initiative's website. Refer to Table 10.11 for further details regarding SME 12. This SME has been professionally involved in the incentive intervention that is the subject of this retrospective case study. Similar to the case study described in Section 10.5, SME 12 was asked to provide input from the perspective of the enabler-, innovator-, and consumer stakeholders for the purpose of completing the inputs required for the decision-support framework.

Table 10.11: Information concerning SME 12.

Person (*Date*) *Place*	Expertise of the SME	Perspective	Qualifications	Experience
SME: 12 (14 October 2019) *Skype meeting*	Medical doctor and regional medical affairs lead at international pharmaceutical organization. Subject areas of knowledge: Neglected disease R&D. Based in South Africa.	Enabler perspective	MBChB	5 years

10.6.2. Domain 1: System demarcation

This section establishes the general status quo of the pharmaceutical R&D system targeted by the incentive intervention.

10.6.2.1. Domain 1: Input and context

The pharmaceutical R&D problem targeted by the Hybrid PPP, differs from the Prize fund case study in Section 10.5, as it does not only target NTDs, but also NCDs, with the focus on NTDs being specifically in their capacity as co-morbidities of NCDs in sub-Saharan Africa. The system demarcation allows the enabling stakeholders of the Hybrid PPP to evaluate the unmet pharmaceutical R&D needs of a specified geographic region. The entire Domain 1, as completed by SME 12, is depicted in Appendix N, while key insights are discussed in the remainder of this section. Data gathered from the incentive intervention's website also informed the completion of Domain 1.

10.6.2.2. Domain 1: Assumptions and considerations

The aim of the Hybrid PPP is to target NCDs with a keen interest in the overlap between NCDs and NTDs. The Hybrid PPP case is considered applicable to this research as improving the state of the NTD pharmaceutical system is within its scope. The system demarcation of the Hybrid PPP case does not depict the status quo of NTDs in sub-Saharan Africa exclusively, but rather the status-quo of comorbidity between NTDs and NCDs in sub-Saharan Africa. Thus, the application of the decision-support framework to this case study enables an investigation into the transferability and generalizability of the decision-support framework to a wider scope of application.

10.6.2.3. Domain 1: Output

The following key insights with regard to the pharmaceutical R&D system and status-quo of NCDs and NTDs in sub-Saharan Africa are derived based on the input data to the case study:

(i) The countries targeted by the Hybrid PPP in sub-Saharan Africa, are LMICs with a disease burden and comorbidity disease burden that exceeds 35 000 DALYs per 100 000 population.

(ii) Mass drug administration efforts for NTDs that are co-morbidities of NCDs are low, consequently a priority rating of '2' is assigned to the mass drug administration evaluation criteria.

(iii) The scale of globalization, the level of cooperation among competitors, as well as the extent of data sharing and collaboration in the R&D system considered in this case study, is relatively high, with SME 12 classifying the two aforementioned system elements as being "*coordinated on various levels*", and "*data often shared with good collaboration between competitors*".

(iv) The current R&D system does not provide regulatory exclusivity for innovations, however domestic policy structures are evaluated in order to be fully operational in the sub-Saharan Africa sphere.

(v) The market potential for performing R&D on NTDs that are comorbidities of NCDs is evaluated as having "*no perceived potential*", however, it is classified to be a priority of the health agendas of the countries involved.

(vi) The R&D process of developing drugs for NCDs that overlap with NTDs, is considered to be low risk and clinical trial challenges such as commencement difficulty, and quality or registration concerns are not expected to be more difficult or expensive than is the case for clinical trials in general.

10.6.3. Domain 2: Enabler profile analysis

This domain investigates only the perspective of the primary enabler stakeholder as it is the only enabler stakeholder that is involved in all of the partnerships that exist as a result of the Hybrid PPP and it is the primary initiator of the Hybrid PPP incentive intervention.

10.6.3.1. Domain 2: Input and context

The 61 enabler decision criteria were prioritized by SME 12, who was asked to represent the perspective of the primary enabler in the case study, during an interview. The completed enabler inquiry form is provided in Appendix N, while key insights are discussed in the remainder of this section.

10.6.3.2. Domain 2: Assumptions and considerations

Similar to the Prize fund case study, a reasonable assumption to be made with regard to the enabler stakeholder, and the input provided by SME 12, is that the stakeholder has an understanding of the enabler stakeholder's objectives and limitations that is sufficiently accurate for the purpose of the case study.

The Hybrid PPP case involves other undefined enabler stakeholders, that differ for each project undertaken. Therefore, the information provided for the enabler profile for the Hybrid PPP case study does not include the objectives and limitations of all the enabler stakeholders that are involved in each of the projects that are launched as a result of the Hybrid PPP.

10.6.3.3. Domain 2: Output

One of the primary aims of the Hybrid PPP incentive, from the perspective of the primary enabler stakeholder, is to better understand the research networks in sub-Saharan Africa. This includes gaining an understanding of the research network profiles, the stakeholders involved, and who the prominent researchers in the field of NCDs and NTDs are. The unmet need around R&D for NCDs (including its comorbidity with NTDs) and how it affects sub-Saharan Africa specifically, was the impetus for the establishment of the incentive intervention.

The primary aim of the enabler profile is to provide a limited amount of funding, facilitate collaborations between different stakeholders, and to collaborate with the innovators that are performing R&D for the targeted diseases. The enabler stakeholder does not aim to gain market exclusivity over innovations, or to de-risk their own R&D pipelines and processes. Instead, the enabler is willing to contribute financial resources to selected academic institutions to: (i) advance the R&D field; (ii) increase bandwidth and networks (i.e. collaborations with other organizations); and to (iii) partially fulfil CSR.

The enabler stakeholders, including the primary stakeholder as well as secondary enabler stakeholders, are willing to provide: (i) access to key data; (ii) expertise and access to areas of research where the enabler is well-skilled (e.g. biomedical statistics); as well as (iii) some R&D expertise that the innovators request.

10.6.4. Domain 3: Innovator profile analysis

The typical perspective of the innovators targeted by the Hybrid PPP case are evaluated in the following section.

10.6.4.1. Domain 3: Input and context

The innovators targeted by the Hybrid PPP incentive case include researchers from sub-Saharan Africa that are affiliated with academic institutions. One of the pre-requisites for a researcher to

participate as an innovator stakeholder in this partnership, is that a collaboration between the researcher and any established research organisation that is based in the UK, must exist or be established. The innovator inquiry form was completed by SME 12, who was asked to provide insights on the objectives and limitations experienced by the innovators that typically apply or participate in the incentive intervention.

10.6.4.2. Domain 3: Assumptions and considerations

Similar to the Prize fund case study, it is assumed that ideally the innovator stakeholder profile should be completed by a participating Hybrid PPP innovator stakeholder. The completion of the innovator inquiry form by an SME that does not have personal experience in fulfilling the role of an innovator applying for funding does, however, provide deeper insights into the usage flexibility of the framework. In the case where an enabler stakeholder wishes to complete the innovator inquiry form on behalf of likely innovator stakeholders, the accuracy of the input data can be improved by performing research to accurately convey the innovator objectives and limitations, rather than merely providing generalized information that is based on assumptions.

10.6.4.3. Domain 3: Output

The key insights gained regarding the innovator stakeholders targeted by the Hybrid PPP incentive can be summarized as follow:

(i) The primary aim of the innovator stakeholders that participate or apply to be part of the Hybrid PPP, is to contribute to the research community and body of knowledge on NCDs and NTDs. This links with the fact that the innovators do not aim to make profit from performing R&D in this research field.

(ii) The innovators primarily require funding (not for R&D, but more specifically for research costs, i.e. basic research) and in addition the innovators want to collaborate with the enabler stakeholder of the incentive for partnership opportunities.

(iii) The capacity of the innovators to provide their own funding varies per project that results from the Hybrid PPP, however, most innovator stakeholders do not have any funding or have limited funding capacity.

(iv) The most frequent R&D limitations of the innovator stakeholders include having a shortage of finances and having inadequate equipment to perform the anticipated research.

(v) The innovator stakeholders targeted and involved in the Hybrid PPP always adhere to an accredited authorization organization.

(vi) The innovator stakeholders aim to do both preventative and treatment research for the targeted diseases.

10.6.5. Domain 4: Consumer profile analysis

The consumer inquiry form was deemed by SME 12 as out of the scope of the Hybrid PPP focus areas. The SME emphasised that the Hybrid PPP incentive is "*patient-focused*", but that the end-consumer stakeholder profile was not necessarily considered when the Hybrid PPP incentive type was selected. This included both the end-consumer and the procurer categories of Domain 4. The reason for the consumer profile not being deemed relevant to consider in the selection of an incentive for this case, could be attributed to the incentive intervention focusing more on basic

research rather than R&D of a market-ready product. The exclusion of the consumer profile in this case study is further elaborated on in the limitations of this case study (i.e. Section 10.6.8).

10.6.6. Domain 5: Solution set

The solution set of the decision-support framework provides a feasible set of incentive interventions for the case study, as well as information on the performance of these feasible interventions in terms of the requirements of the various stakeholders.

10.6.6.1. Domain 5: Input and context

The input used to generate the solution set, includes all the input provided by SME 12 to complete Domains 1 to 3[23], as well the hard-coded abilities of the 26 incentive interventions to address the decision criteria that are prioritized in this case study (in line with the description of the functioning of the framework provided in Section 8.4.10). The ability of the 26 incentive interventions to address all the decision criteria is consequently evaluated, and the priority of each decision criterion incorporated in constructing the final solution set.

10.6.6.2. Domain 5: Output

The output of the decision-support framework provides a feasible set of incentives to consider for encouraging R&D for NCDs and NTDs. The recommendations for this case study are divided into (i) incentive-based interventions, and (ii) non-incentive-based interventions. A detailed presentation of the results is provided in Appendix N, with the case study solution set interpretations included in Section 10.6.7.

(i) Incentive-based interventions

As shown in Figure 10.8, 16 of the 26 incentive interventions are classified as feasible based on the exclusion criteria of the enabler stakeholder. Nine of the 16 feasible incentive interventions perform in the top quartile in more than 50% of the criteria clusters, with five of the feasible incentives doing so in more than 75% of the criteria clusters. The top five performing incentive interventions are: (i) PPPs, (ii) hybrid PPP; (iii) joint venture; (iv) independent organization; and (v) collaboration network.

[23] As discussed in Section 10.6.5, Domain 4 was excluded from this case study.

Figure 10.8: Solution set heatmap indicating the extent to which the 26 incentive interventions address the 12 criteria clusters, based on the input provided b SME 12 for the open lab partnership.

Figure 10.9 depicts a detailed overview of the abilities of the top five performing incentive interventions to address the 12 criteria clusters.

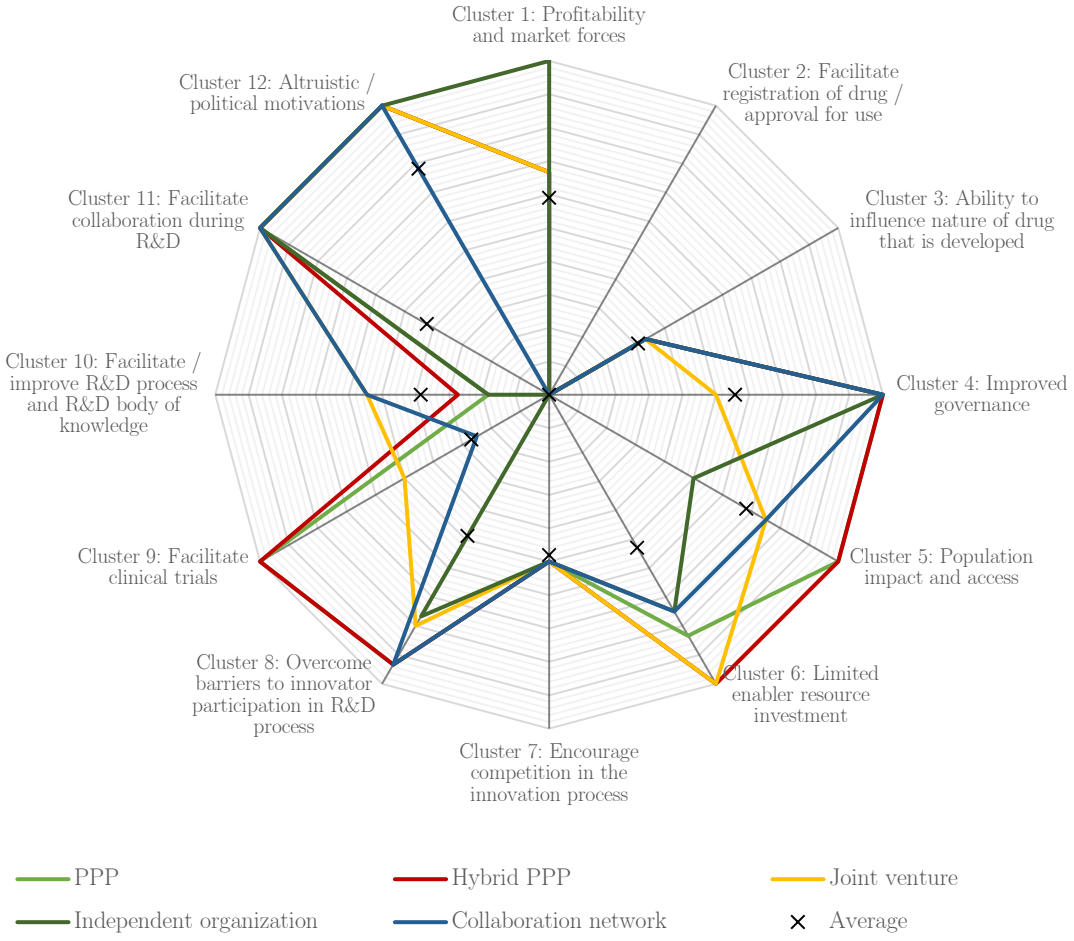


Figure 10.9: Top five performing incentive interventions' abilities to address criteria clusters.

(ii) Non-incentive-based interventions

As discussed previously, non-incentive-based interventions are derived from the system demarcation domain and suggest interventions that should be considered to improve the state of system elements (Domain 1) that cannot be addressed by incentive-based interventions. Non-incentive-based interventions that are recommended as being a high priority are indicated in Table 10.12 (priority rating indicated in the rightmost column), with the rest of the recommended non-incentive-based interventions listed in Appendix N.

Table 10.12: High prioritized non-incentive-based interventions.

1. Country economic status		*For further reference*	
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)	2
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

5. Availability of drugs for the desired population		*For further reference*	
Meaning	Drugs are available in the right quantities, on the right time to access.	(Jackson, 2018) ; (Niëns and Brouwer, 2013), (Holt, Gillam and Ngondi, 2012)	2
Relevance	If drugs are adequate but not available, then patients might not be effectively treated. Possible resistance to medicines.		
Intervention considerations	Supply chain management		
	Distribution networks		
	Inventory management at health facilities		
	Replenishment systems at health facilities		
	Burden characterization assists in inventory planning		

6. Affordability of current drugs to desired population		*For further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	2
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

17. Political will and contribution to improve R&D for disease		*For further reference*	
Meaning	The effort and contribution that the government of a country is willing to make towards R&D of diseases.	(Brinkerhoff, 2003; (Emmanuel and Emmanuel, 1996; World Health Organization, 2018)	2
Relevance	Governments should be obligated to make significant efforts to reduce disease burden within a country		
Intervention considerations	Enforce SDGs		
	Ministry of Health audit		
	Policy reform		
	Political accountability systems		

20. Adequate supply of the health service		*For further reference*	
Meaning	The health service should be sufficient, suitable for the target population.	(Jacobs et al., 2012; RAND Corporation, 2007; Manjit Kaur; Sarah Hall, 2002)	2
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

42. Health data generation		*For further reference*	
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	2
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

10.6.7. Interpretation of case study results

The results presented for the Hybrid PPP case study are based on the inputs provided by SME 12, with the end-consumer stakeholder profile having been omitted, as discussed previously.

Similar to the interpretation of the Prize fund case study, the discussion of the framework output is guided by the following themes: (i) feasible and top performing incentives; (ii) infeasible and underperforming incentives; and an (iii) evaluation of the 12 criteria clusters.

10.6.7.1. Feasible and top performing incentive interventions

16 of the 26 incentive interventions that are included in the decision-support framework, are deemed feasible for implementation as solutions for the particular case. The ability of these 16 incentives to address the criteria clusters range from performing in the upper quartile in three criteria clusters to doing so in ten criteria clusters. Nine of the 16 feasible incentives perform in the upper quartile in addressing at least 50% of the criteria clusters.

The top performing incentive interventions were similar to those identified in the Prize fund case study, namely: (i) PPP; and (ii) hybrid PPP, both with an upper quartile score of 10 out of 12. These are followed by: (iii) joint venture; (iv) independent organization; and (v) collaboration network. The top five performing incentives are remarkably similar in their abilities to address the criteria clusters, with Clusters 2, 3, 7, 11 and 12 being addressed to the same extent by the top five performing incentive interventions. This means that all five top performing incentive interventions have the exact same ability to address the five aforementioned criteria clusters and are interchangeable in the case where the five criteria clusters are the only criteria considered.

10.6.7.2. Infeasible and underperforming incentive interventions

Of the 26 incentive interventions considered by the decision-support framework, ten were classified as infeasible based on the exclusion criteria of the enabling stakeholder. This means that these incentives do not cater for the limitations that the enabler stakeholder identified. The feasible incentive interventions that performed most poorly include the: (i) colloquium and symposium; (ii) research laboratories; (iii) grant; (iv) intellectual property; and (v) patent buyout incentives.

10.6.7.3. Evaluation of the 12 criteria clusters

The abilities of the incentives to address each criteria cluster are investigated in the following section. The description of the criteria cluster scoring in Section 8.4.10 (also summarized in Section 20.5.7.5) provides important background information for enabling a deeper analysis of the results per criteria cluster.

Criteria Cluster 1: Profitability and market forces

A large number (eight out of 12) of the decision criteria categorized in the profitability and market forces criteria cluster are classified as not relevant (i.e. priority rating of 0) in this case study. This indicates that the enabler stakeholder does not necessarily classify the profitability and market forces as having high importance. Decision criteria classified as being important (i.e. priority rating 2) to be addressed by the selected incentive intervention include: (i) delinking revenue from sales volume; (ii) incentive should improve the NPV of stakeholders; and (iii) the incentive should minimize barriers to implementation of the incentive intervention.

Incentive interventions that outperformed the rest of the incentives in terms of this criteria cluster include the independent organization and differential pricing which both fully address the decision criteria that were prioritized by stakeholders. The collaboration network and colloquium and symposium incentives were the most poorly performing feasible incentive interventions. The aforementioned might be attributed to the incentives being focused more on collaboration and not necessarily on overcoming market forces to make a profit.

Criteria Cluster 2: Facilitate registration of drug/approval for use

The decision criteria in this criteria cluster are all prioritized as not relevant (i.e. priority rating of 0) to be addressed by the stakeholders of the Hybrid PPP case study. Similar to the Prize fund case study, the low prioritization of these decision criteria can potentially be attributed to the enabler stakeholders that are involved in the Hybrid PPP case study as the enabler stakeholders do not have the ability to influence, address or facilitate policy alterations relating to drug registration and / or approvals.

The low prioritization of the decision criteria in this criteria cluster, furthermore, resulted in no indication provided by the decision support framework with regards to the incentive intervention's ability to address this criteria cluster. It should therefore be noted that the low indicated ability of the incentives to address this criteria cluster does not necessarily indicate a lack of ability from the incentive interventions' side, but rather indicates that fulfilling the criteria in the cluster is not considered a priority in this case.

Criteria Cluster 3: Ability of the incentive to accommodate different R&D initiatives

Only two out of the six decision criteria that are classified in this criteria cluster are prioritized to be relevant (i.e. priority rating 1) to be considered for the case study. The decision criteria that are prioritized are that the incentive should encourage R&D of a drug or intervention (highlighted by the enabler stakeholder), as well as that the innovator stakeholders of the Hybrid PPP case study should receive payment tranches based on the cost effectiveness (prioritized by the innovator stakeholder).

The top performing feasible incentive intervention in this criteria cluster is the prize fund, with the ability to fully address the decision criteria that are prioritized. This might be attributed to the prize fund's core rationale being to encourage a specified R&D in exchange for a defined benefit. The least performing feasible incentive is the colloquium and symposium incentive intervention that does not address any of the prioritized decision criteria. This is expected as the primary aim of the colloquium and symposium incentive intervention is not to accommodate R&D, but rather to serve as communication or information platform.

Criteria Cluster 4: Improved governance

Of the decision criteria categorized in this criteria cluster, half are prioritized as important (i.e. priority rating 2), namely that the incentive should promote: (i) equitable health-focused governance; and (ii) transparency and accountability within the R&D process.

Of the feasible set of incentive interventions, five have the ability to fully address the decision criteria prioritized for this criteria cluster. The top performing incentive interventions are: (i) PPP; (ii) hybrid PPP; (iii) independent organization; (iv) collaboration networks; and (v) treaties.

The incentive interventions that underperformed include the: (i) working group; (ii) differential pricing; (iii) intellectual property; and (iv) patent buy-outs.

Criteria Cluster 5: Population impact and access

Four of the seven decision criteria in this cluster are prioritized as important to be addressed by the incentive intervention, namely: (i) improving consumer access; (ii) enabling mass drug administration; (iii) reducing the burden of disease in an area; and (iv) minimizing disruptive effects to the population. This indicates that the stakeholders involved in this case study prioritize the impact and access that the anticipated R&D will have on the population. It is, however, evident that this is not the primary priority, as decision criteria that involve: (i) eliminating all financial risk; and (ii) delivering affordable and accessible treatments to the receiving population, are not prioritized by the stakeholders involved in this case study.

A high number (10 out of 16) of the feasible incentive interventions, have the ability to address more than 75% of the decision criteria that are categorized in this criteria cluster. The incentive interventions that performed the poorest include: (i) colloquium and symposium, (ii) intellectual property; and (iii) patent buy-outs. The poor performance of these incentive interventions are expected as the primary aim of these incentives are not to beneficially impact the population.

Criteria Cluster 6: Enabler resource investment

Nearly 50% of the decision criteria that are categorized in this criteria cluster are prioritized as important. The highest rated decision criteria include that the incentive must: (i) be affordable to implement; (ii) enable the enabler stakeholder to partially fund R&D; and (iii) allow the payments to innovators to be limited to an amount and time frame. This indicates that even though the enabler stakeholder in this case study wants to contribute resources to the R&D of interventions against diseases, that the resources that the enabler stakeholder are able to provide is still limited.

The top performing incentive interventions that address all the prioritized decision criteria that are the: (i) hybrid PPP, (ii) joint venture; and (iii) pooled fund initiatives, with (iv) grants addressing more than 90% of the decision criteria prioritized. This indicates that these incentive interventions offer the enabler stakeholders the ability to contribute resources to R&D, but that the resources that are contributed can be limited. All the feasible incentive interventions had some ability to address the decision criteria prioritized in this criteria cluster, with research laboratories performing the poorest based on the decision criteria addressed.

Criteria Cluster 7: Encourage competition in the innovation process

Half of the decision criteria categorized in this criteria cluster are prioritized as important (i.e. priority rating 2) to be fulfilled by the incentive intervention, with the other half not prioritized at all (i.e. priority rating 0). The decision criteria that are prioritized indicate that the stakeholders involved in this case study prioritize the involvement of large firms and allow for some competition among parallel experiments. Based on the decision criteria that are prioritized, it can furthermore be derived that the stakeholders involved in this case study do not target all organizations to participate in the Hybrid PPP. This is expected, as the enabler stakeholder highlighted a list of requirements that need to be fulfilled by the innovator stakeholders if they wish to partake in this incentive intervention.

Of the feasible set of incentive interventions, intellectual property was the only incentive that has a full capacity to address the prioritized decision criteria. This is expected as intellectual property interventions mostly target large innovator firms and allow for competition among parallel experiments. The incentive interventions that did not perform well include treaties, working groups, research laboratories and grants.

Criteria Cluster 8: Overcome barriers to innovator participation in R&D process

More than 62% of the decision criteria classified in this criteria cluster are prioritized as being important. Some of the prioritized criteria include that the incentive intervention involves the enabler stakeholder providing some form of financing to the innovators, as well as that the incentive requires the enabler to offer their expertise and knowledge to the participating innovators. Furthermore, the stakeholders indicated that the incentive intervention should aim to reward innovation.

The feasible incentive interventions that outperformed the rest of the incentives in their ability to address the decision criteria categorized in this criteria cluster include: (i) PPP; (ii) hybrid PPP; (iii) collaboration networks; and (iv) working group. The four incentive interventions all relate to one another based on their provision of some form of a platform to provide assistance and some form of a platform to the innovator participants to overcome the barriers that are frequently experienced in performing R&D. The incentive interventions that underperformed in addressing this criteria cluster includes the differential pricing incentive intervention. This underperformance might be attributed to the aim of differential pricing incentive interventions not necessarily being to overcome barriers of R&D to the innovator stakeholders but rather being more aligned towards improving the access of the end-consumer stakeholders.

Criteria Cluster 9: Facilitate clinical trials

Only one of the eight decision criteria categorized in this criteria cluster is prioritized as important. The last-mentioned decision criteria that are prioritized is that the incentive intervention should provide some sort of a public subsidy to the innovator stakeholders to perform R&D. This indicates that the core function and aim of the incentive intervention are not to facilitate clinical trials but rather to facilitate in improving the body of knowledge and research performed in the defined NTD field.

The feasible incentive interventions that outperformed the rest in this criteria cluster include the (i) PPP; (ii) hybrid PPP; and (iii) treaty incentive interventions. This can be attributed to all three of these incentive interventions incorporating public enabler stakeholders in some way.

Criteria Cluster 10: Facilitate/ improve R&D process and R&D body of knowledge

All but two (seven of the nine) decision criteria categorized in this criteria cluster are prioritized as being either important (six) or relevant (one) to be addressed. This indicates that one of the core aims of the hybrid PPP is to facilitate and improve the R&D process and the body of knowledge. The decision criteria in this cluster that are not prioritized include (i) the ability of the innovator stakeholder to innovate easier, as well as (ii) the goal to improve the state of the R&D pipeline. However, both these decision criteria might be achieved due to the incentive intervention even though they are not classified as one of its primary aims.

The feasible incentive interventions that outperformed the rest of the incentives include research laboratories, collaboration networks, and treaties. Though, neither of the incentives have the ability to address more than 67% of the decision criteria prioritized in this criteria cluster. The top-performing incentive interventions might be attributed to all three incentives providing a platform to the innovator stakeholders to conduct research, whether alone (enabled by the research laboratory) or as part of a collaboration. None of the feasible incentive interventions failed to address any of the prioritized decision criteria in this criteria cluster.

Criteria Cluster 11: Facilitate collaboration during R&D

50% of the decision criteria are prioritized as important in this criteria cluster, with the rest not prioritized. Decision criteria that are prioritized indicate that some of the primary aims of the stakeholder of the Hybrid PPP case study are to facilitate cooperation and synergy, allow the coordination of innovator stakeholders, and enable the enabler stakeholder to collaborate with the innovator stakeholders. The aforementioned is expected as the Hybrid PPP incentive lists collaboration during R&D as a principal consideration throughout the rollout of the incentive. Decision criteria that are not prioritized include that the enabler stakeholder cannot play a role in facilitating the regulatory process or adjusting policies or regulations as per innovator requirements.

Eight feasible incentive interventions had the ability to fully address the decision criteria that are prioritized in this criteria cluster, including the top six feasible incentive interventions. This was anticipated as facilitating collaboration, and coordination is a core focus area of all of the top six feasible incentive interventions, namely: (i) PPP; (ii) hybrid PPP; (iii) joint venture; (iv) independent organization; (v) collaboration network; and (vi) coordination mechanism. Feasible incentives that did not perform well include: (i) prize funds; (ii) differential pricing; (iii) grants; (iv) intellectual property; and (v) patent buy-outs.

Criteria Cluster 12: Altruistic /political motivations

The only decision criterion prioritized as important to be addressed in this criteria cluster is that the incentive should accommodate innovator stakeholders to perform R&D for not-for-profit purposes. This was expected as the Hybrid PPP case study does not merely aim to perform R&D for profit but encourages R&D regardless of the profit it might hold for both the innovator and / or enabler stakeholders.

A large number (12 of the 16) feasible incentive interventions can fully address the prioritized decision criteria in this criteria cluster. This might be attributed to the small number of decision criteria that are prioritized in this criteria cluster. The feasible incentive interventions that do not have any ability to address the prioritized decision criteria include: (i) treaties; (ii) intellectual property; and (iii) patent buyouts.

10.6.1. Case study limitations

The limitations experienced in this case study correlate directly with the limitations in the Prize fund case study, namely:

(i) The aim of the primary enabler stakeholder was broad, targeting various projects in various LMIC settings. This led to difficulty in prioritizing decision criteria that

evaluated the state of the specified R&D environment and resulted in general assumptions that needed to be made or prioritization to be generalized to accommodate the entire global NTD R&D sphere.

(ii) The incomplete consumer profile led to some incentive interventions not being portrayed or considered in the solution set.

(iii) The Hybrid PPP incentive selected for this retrospective case study is a collaborative partnership involving more than one enabling stakeholder. This means that even though only inputs from the perspective of the primary enabling stakeholder were used as input data for this case study, various other enablers play a role in enabling the incentive and addressing resource limitations.

(iv) Resulting from the wide range and the large number of stakeholders involved per project within this case study, generalizations could not necessarily be made regarding the participating stakeholders' objectives, limitations, and abilities. However, reasonable derivations and insights could be gained from the primary enabler stakeholder, being the only constant in all the projects undertaken in this case study.

10.7. Case study application 3: PPP

This is the third and final retrospective case study that is applied to the decision-support framework. This case study, similar to the previous two case studies, investigates and elaborates on a retrospective case study, where a PPP was initiated to catalyze and foster collaborations for R&D of NTDS primarily. The PPP incentive is contextualized, followed by a description of the decision-support framework to the case study, and lastly, the decision-support framework results are depicted and interpreted, and limitations are highlighted.

10.7.1. Contextualization: PPP

A PPP involves collaboration between one or more private sector entities and one or more public sector entities, usually created to achieve a public health objective or develop a health-related product or service (Hussaarts *et al.*, 2017).

The primary aim of this PPP is to catalyze and foster innovative collaborations for encouraging R&D for NTDs, TB, and malaria through involving LMICs and higher-income countries and making IP available to scientists who need it. The incentive is a PPP that functions as a consortium with more than 100 member organizations (from across the globe). The member organizations include academic institutions, governments as well as pharmaceutical organizations from across the globe.

This PPP incentive intervention has two primary enabling organizations: two private, not-for-profit organizations, referred to in this case study as Enabler 1 and Enabler 2. Each enabler organization plays a unique role in ensuring the successful creation and sustainability of the created collaborations. Enabler 1 is proactively involved in managing and partnering consortium members in collaborations; this can also be described as being responsible for alliance management, whereas Enabler 1 acts as secretariat and host for the incentive intervention. All the members of the incentive intervention can be classified as innovator stakeholders. The

aforementioned is true, as the member entities of the incentive either perform the R&D work or are utilizing the representing organization's assets to innovate themselves.

A distinctive characteristic of this intervention is that some of the collaborations facilitated and created due to the incentive include public sector collaborations, with some of the consortium members also acting as an enabler to a certain extent. However, for the sake of simplicity, only the two primary enabler stakeholders are included as enabler stakeholders in the case study. Similarly, for the sake of simplicity, the innovator stakeholders in the case study are defined as all members of the consortium partnership that are encouraged to perform R&D for the defined set of neglected diseases.

The data used to construct this case study is sourced from an interview held with SME 5, who was asked to represent the perspective of the enabler-, innovator-, and consumer stakeholders. Further details relating to this stakeholder are defined in Table 9.2.

10.7.2. Domain 1: System demarcation

In this section, the pharmaceutical R&D system status quo targeted to be addressed by Enabler 1 in the PPP incentive intervention, is investigated.

10.7.2.1. Domain 1: Input and context

As mentioned in Section 10.7.1, the neglected diseases targeted include a list of 21 NTDs. More than 50 partnerships have resulted from the PPP incentive intervention initiated in this retrospective case study. The input provided for this domain needed to be generalized to apply to all targeted neglected diseases. The input is provided by SME 5. The complete set of evaluated system elements (i.e. Domain 1) is included in Appendix O, while key insights are discussed in the remainder of this section.

10.7.2.2. Domain 1: Assumptions and considerations

It is assumed that as a result of the large set of diseases targeted, the system elements in this domain are classified in a somewhat general manner. An expected result is that more incentives will perform similarly with similar rankings based on performance in the various criteria clusters.

10.7.2.3. Domain 1: Output

The key insights on the pharmaceutical R&D system that is targeted in this case study are:

(i) Only some neglected diseases require mass drug administration, with not all neglected diseases necessarily treatable through launching mass drug administration efforts.
(ii) According to SME 5, "*The lack of resources and finances is a huge barrier to new drug entrants*".
(iii) There is a limited body of knowledge that exists for the defined set of 21 NTDs.
(iv) The scale of globalization and cooperation in the neglected diseases sphere is relatively high, with the lack of resources and finances acting to a certain extent as a motive for the entities to work together in order to tackle it.
(v) Linking to the aforementioned, the extent of globalization and data sharing within the NTD sphere is better than when organizations keep information to themselves and aim to create a new blockbuster treatment, which is often the case in diseases for which there is strong purchasing power.
(vi) According to SME 5, the clinical trial risk for R&D of NTDs is not necessarily higher than for other diseases.

The key insights from Domain 1 allow the stakeholders to understand the pharmaceutical R&D system of the targeted 21 NTDs. The key insights highlight that the lack of resources and financing within the neglected disease sphere have direct and indirect consequences on the body of knowledge.

10.7.3. Domain 2: Enabler profile analysis

The enabler stakeholder profile depicts the objectives and requirements of the enabler stakeholders in the case of the PPP incentive.

10.7.3.1. Domain 2: Input and context

The enabler profile analysis performed for this case study focuses on Enabler 1. Thus SME 5 was asked to represent the perspective of this enabler specifically, rather than that of Enabler 2, as Enabler 1 is more directly involved in the management of the collaborations that result from the incentive intervention in this retrospective case study.

The completed enabler inquiry form is included in Appendix O, while noteworthy aspects are discussed in the remainder of this section.

10.7.3.2. Domain 2: Assumptions and considerations

Again, it is assumed that SME 5 has a sufficiently accurate perception of the enabler stakeholder to represent their perspective in the case study.

Another consideration that should be noted is that Enabler 2's objectives and internal limitations are not taken into account in the completion of this case study and that the case study focuses on only one enabler stakeholder. The latter is discussed in further detail in the limitations of this case study.

10.7.3.3. Domain 2: Output

Enabling stakeholder 1's primary objective for initiating and taking part in this incentive intervention is to improve the body of knowledge of 21 neglected diseases by creating innovative global collaborations. The enabler stakeholder (Enabler 2) wants to advance the R&D field and deliver affordable and accessible treatments to the sufferers of the defined set of diseases. The collaborations created as a result of the incentive intervention in this retrospective case study allow the innovators to: de-risk the process of performing R&D; fulfil corporate social responsibility by contributing to the R&D of the defined set of diseases; and increase their collaborative interaction with other pharmaceutical organizations. Lastly, the incentive conveys an important message globally relating to the importance of encouraging R&D for neglected diseases. Other objectives of this incentive intervention include sharing IP with the global research community and contributing to capacity-building in developing countries.

The intention for the consumers in launching this incentive intervention is to provide and deliver any form of treatment, diagnostic, or early-phase R&D to play a role in mitigating neglected diseases. There is a desire to build a long-term partnership and relationships with the members of the PPP consortium, with members partaking in more than one collaboration in line with their individual needs and abilities.

An important consideration for this incentive intervention is that the incentive does not aim to fund R&D. Neither Enablers 1 nor 2 have the capacity to provide funding to the innovator stakeholders. However, the incentive instead aims to 'team-up' different members of the PPP consortium to contribute what they can, leading to the innovator stakeholders adding what they can to enable R&D for the specified neglected diseases.

The last noteworthy insight with regards to the enabler profile is that the collaborations that are created are intended to enable access to (i) key data; (ii) compounds; (iii) IP; (iv) technology; as well as (v) R&D expertise.

10.7.4. Domain 3: Innovator profile analysis

The innovator profile establishes the requirements and limitations of the innovator stakeholders that are targeted.

10.7.4.1. Domain 3: Input and context

The innovator stakeholders targeted by this incentive intervention range from governmental institutions to large pharmaceutical organizations, with all the members of the PPP consortium viewed as innovator stakeholders encouraged to perform R&D for the defined set of NTDs.

SME 5 completed the innovator stakeholder profile by evaluating the 49 innovator criteria based on their knowledge of some of the member organizations of the PPP that was created in this retrospective case study.

10.7.4.2. Domain 3: Assumptions and considerations

Similar to the other domains, a limitation that should be considered is that the innovator profile is not completed by an SME with first-hand experience of playing the role of an innovator in this

retrospective case study. Furthermore, as the profile is being completed once, based on the most likely preferences of a large number of innovator stakeholders, some generalizations might occur.

10.7.4.3. Domain 3: Output

The completion of the innovator profile led to the following key insights:

(i) The intent of the innovator stakeholders that are partaking in this incentive intervention is not necessarily to maximize profit but rather for corporate social responsibility, political obligations, and profit improvement.

(ii) Even while the enabler stakeholders do not provide funding as part of the incentive intervention, most of the innovator stakeholders do require funding for the R&D that is initiated.

(iii) One of the primary objectives of the innovator stakeholders includes that they want to partake in the collaboration platform that is created, as well as collaborate with specific members of the PPP incentive.

(iv) The innovator stakeholders that partake in this incentive intervention include large pharmaceutical organizations, private and not-for-profit organizations, governmental institutions, and academic institutions.

(v) Some of the limitations experienced by most of the innovator stakeholders may include a: (i) lack of adequate equipment and research laboratories; (ii) lack of information and knowledge on the diseases; (iii) the cumbersome nature of clinical trials; and (iv) shortage of finances.

The aforementioned key insights gained into the innovator stakeholders again highlight that resources and finances are limited in the neglected disease sphere, with even large pharmaceutical organizations that are participating in this incentive intervention requiring funding to assist in covering the R&D costs of developing treatments for these diseases.

10.7.5. Domain 4: Consumer profile analysis

The consumer profile aims to sketch the consumer profile objectives, with the consumer including the end-product consumer as well as drug procurers.

10.7.5.1. Domain 4: Context and output

It was found that socioeconomic inequalities are evident for the targeted population group; thus, differential pricing is a requirement to a certain extent. Differential pricing of treatments will enable end-consumers who cannot afford the developed drugs to have improved access.

The fulfilment of contextual treatment criteria, as established for a specific population group, is also important in this case study. As discussed previously, contextual treatment criteria include aspects that the developed treatment needs to adhere to, such as: ethical considerations; drug safety; drug side-effects; advocacy; and WASH and sanitation initiatives.

Though the procurers of drugs are not necessarily a consideration in the PPP incentive intervention, SME 5 did mention that the incentive does play a role in allowing IP regulation to enable procurement to target areas. This might be attributed to one of the primary objectives of

the PPP incentive selected in this retrospective case study, namely to "*share IP with the global research community*".

10.7.6. Domain 5: Solution set

Domain 5 comprises the solution set as proposed by the decision-support framework.

10.7.6.1. Domain 5: Input and context

The inputs provided through the completion of Domains 1 to 4, as well as information that is hard-coded into the framework, are utilized to: evaluate the ability of each of the incentive interventions to address the decision criteria; and determine the feasibility of each incentive intervention based on the exclusion criteria.

10.7.6.2. Domain 5: Output

The recommendations and output of the decision-support framework for this case study can, again, be divided into incentive-based interventions and non-incentive-based interventions. A detailed depiction of the decision-support framework results is presented in Appendix O. The case study solution set is analysed in Section 10.7.7.

(i) Incentive-based interventions

A heatmap indicating each incentive intervention's ability to satisfy or address the 12 criteria clusters is depicted in Figure 10.10. From Figure 10.10, it can be derived that 9 of the 26 incentive interventions are classified as being feasible for the R&D system and stakeholder objectives and limitations as defined in Domains 1 to 4. Of the feasible incentive interventions, five perform in the upper-quartile range in terms of addressing more than 50% of the criteria clusters. The top five performing incentive interventions include: (i) PPPs; (ii) collaboration networks; (iii) coordination mechanisms; (iv) treaties; and (v) open-source initiatives.

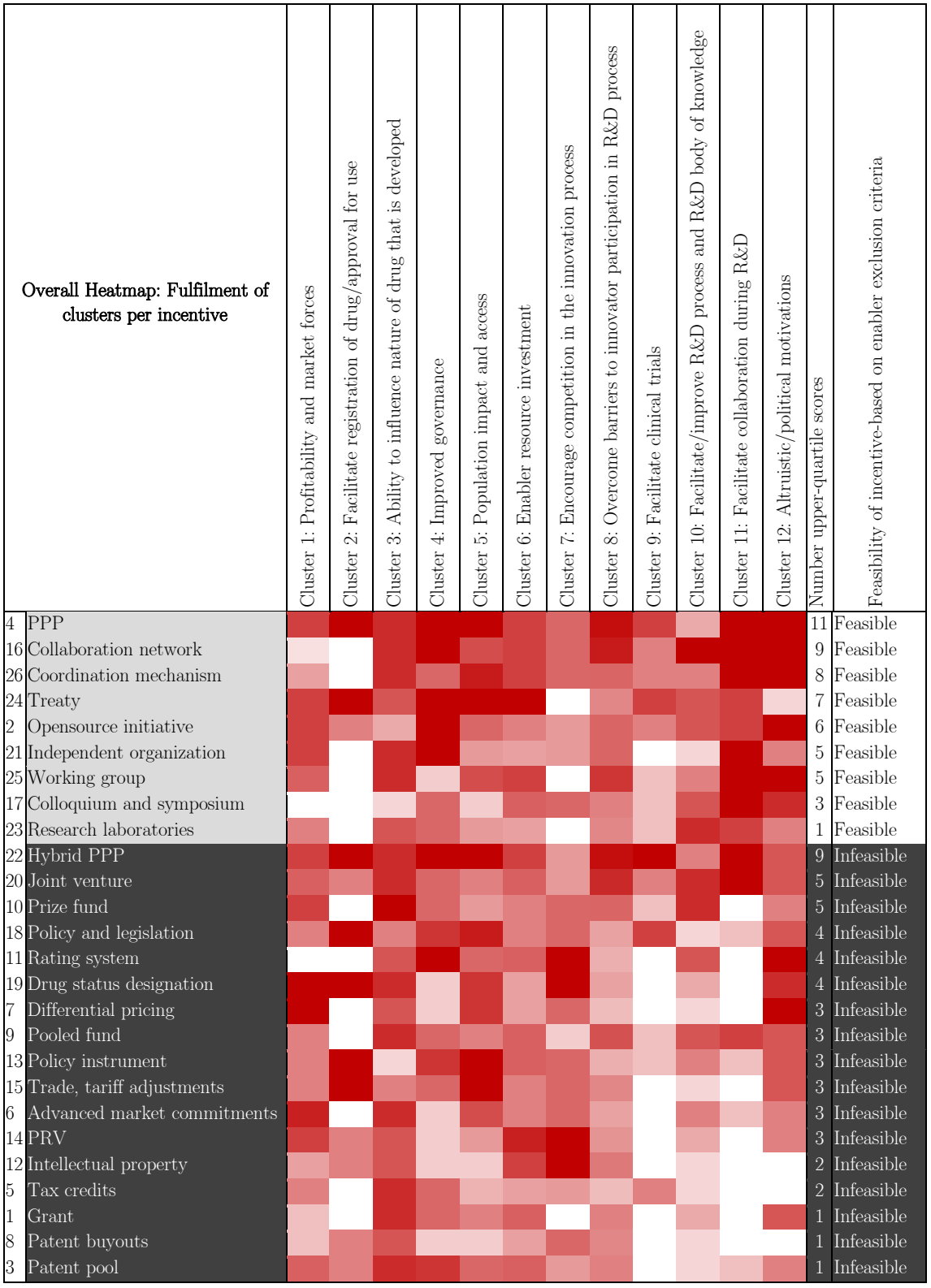


Figure 10.10: Solution set heatmap indicating the extent to which the 26 incentive interventions address the 12 criteria clusters, based on the input provided by SME 5 for the PPP.

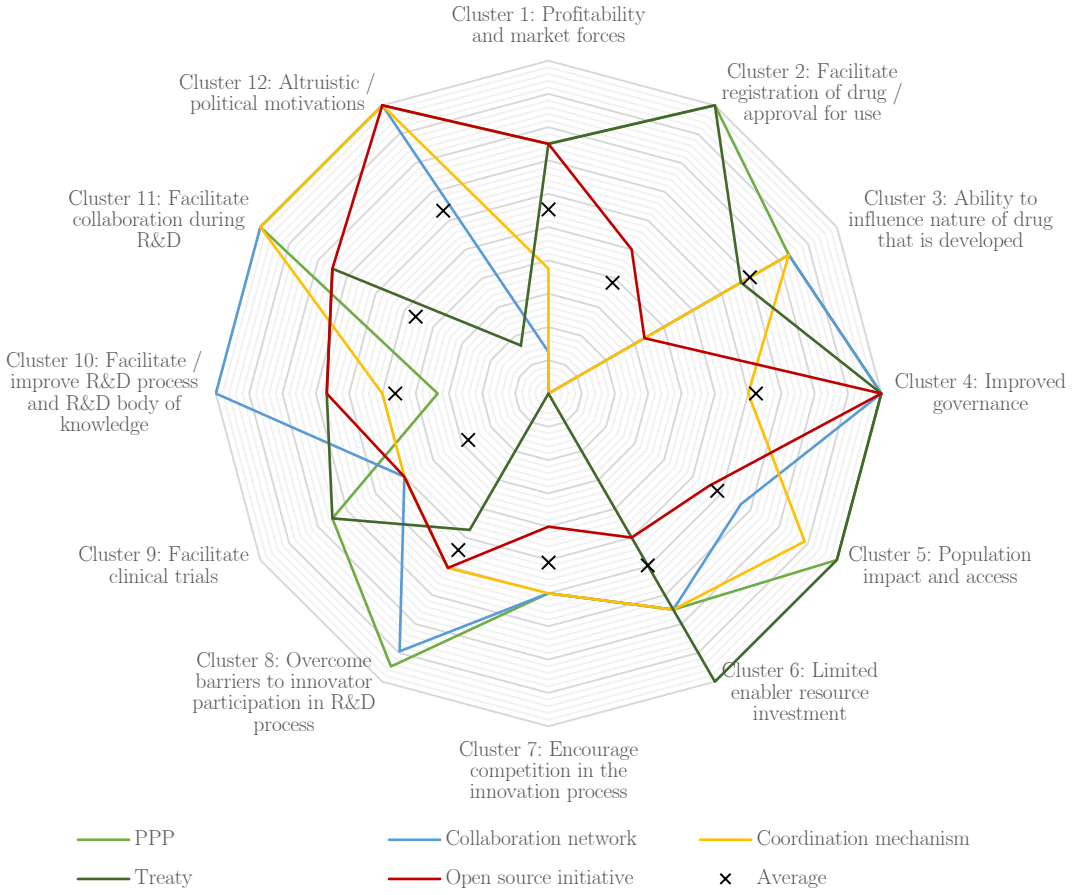


Figure 10.11: Top performing feasible incentive-based interventions' ability to address the 12 criteria clusters.

Figure 10.11 provides a visual presentation of the five top-performing incentives' abilities to address each criteria cluster, with the ability of the incentive to address the criteria cluster increasing as the distance of the series marker from the centre of the spider diagram increases.

(ii) Non-incentive-based interventions

Table 10.13 lists the highest prioritized non-incentive-based interventions, with the remaining non-incentive interventions depicted in Appendix O.

Table 10.13: High prioritized non-incentive-based interventions.

6. Affordability of current drugs to desired population		*For further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	2
Relevance	If the drugs are developed and available but not affordable, the disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include offering affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

12. Minimize waste of resources in service delivery		*For further reference*	
Meaning	Any resource that is not used or used in an effective or efficient manner, leads to waste and possible financial losses.	(Priya, Nandini and Selvamani, 2012)	2
Relevance	Given that most waste is preventable, resources could be used in a more effective manner.		
Intervention considerations	Monitor service delivery to identify and address waste.		
	Coordinate service delivery actions		
	Waste management		
	Inventory management		

20. Adequate supply of the health service		*For further reference*	
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Jacobs et al., 2012; RAND Corporation, 2007; Manjit Kaur; Sarah Hall, 2002)	2
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

22. Current investment capital and returns		*For further reference*	
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Vischer et al., 2017; Bates et al., 2015; Ho, Zarrinpar and Chow, 2016; Payne et al., 2015)	2
Relevance	This factor refers to the current ROI being profitable or not. If it is not profitable, then more investment in a similar research area is not likely.		
Intervention considerations	Financial analysis		
	Cost analysis of activities		
	Reduce indirect and operational costs		

10.7.7. Interpretation of case study results

The interpretation of the case study results is again described by discussing the following themes: (i) feasible and top-performing incentives; (ii) infeasible and underperforming incentives; and (iii) an evaluation of the 12 criteria clusters. The case study results focus on the incentive-based interventions, with non-incentive-based interventions not discussed in further detail, as these are viewed as complementary information but do not address the key focus of selecting an appropriate incentive intervention.

10.7.7.1. Feasible and top-performing incentive interventions

The PPP is the top-performing incentive intervention. It performed in the upper quartile range in terms of addressing 11 of the criteria clusters and scored the highest or shared the highest score

for all but two criteria clusters. The runner up incentives includes: (i) collaboration network; (ii) coordination mechanism; (iii) treaty; and (iv) open-source initiative, addressing 9, 8, 7, and 6 criteria clusters within the upper quartile range, respectively. The top three performing incentive interventions obtained the exact same score for Clusters 3, 6, 7, 11, and 12.

10.7.7.2. Infeasible and underperforming incentive interventions

Of the 26 incentive interventions, 15 incentives are classified as infeasible based on the enabler exclusion criteria in Domain 2. The primary reason why the incentive interventions are excluded from the feasible incentive list is because of the role and responsibility that the enabler stakeholders are willing and able to play. The inability to provide financing towards R&D for the neglected diseases is one of the primary reasons for the classification of the 15 infeasible incentives.

The four feasible incentive interventions that performed most poorly in terms of addressing the criteria clusters are: (i) independent organizations; (ii) working groups; (iii) colloquium and symposiums; and (iv) research laboratories.

10.7.7.3. Evaluation of the 12 criteria clusters

The following section provides an overview of each of the 12 criteria clusters. Refer to Section 8.4.10.2 for a description of each of the 12 criteria clusters as well as the cluster-scores.

Criteria Cluster 1: Profitability and market forces

A small number (3 of the 12) decision criteria in this cluster are prioritized as important to be addressed in the PPP case study. This indicates that the enabler stakeholder does not necessarily classify profitability and market forces as high priority and of high importance. The following decision criteria are as a high priority: (i) delink revenue from sales volume; (ii) improve the NPV of stakeholders; and (iii) minimize barriers to implementation of the incentive intervention.

None of the feasible incentive interventions can fully address the decision criteria that are prioritized in this criteria cluster. The PPP, treaty, open-source initiative and independent organizations each can address 75% of the decision criteria prioritized in this cluster. The colloquium and symposium incentive intervention performed the poorest, with no ability to address any of the prioritized decision criteria. The latter might be attributed to the incentive not aiming to overcome profitability and market force barriers but rather to focus on the R&D body of knowledge and encouraging collaboration between stakeholders.

Criteria Cluster 2: Facilitate registration of drug/approval for use

This criteria cluster scored the lowest with regard to the feasible incentive interventions' ability to address the decision criteria in this cluster. With 6 out of the nine infeasible incentive interventions not having any ability to address the prioritized decision criteria of this criteria cluster.

PPPs and treaties have full capacity to address the decision criteria prioritized in the cluster. The aforementioned might be attributed to the fact that PPPs and treaties are the only two feasible incentive interventions that include a strong involvement of governments, and governments, in turn, can influence national legislation and policies with regard to drug R&D.

Criteria Cluster 3: Ability of the incentive to accommodate different R&D initiatives
All of the decision criteria in this criteria cluster are prioritized to be addressed in the case study, indicating that the enabler stakeholder views it as important to accommodate different R&D initiatives instead of only promoting a specified R&D initiative.

The incentive interventions that outperformed the rest of the incentive interventions in addressing this criteria cluster include: PPP; collaboration network; coordination mechanism; independent organization; and working group. None of the aforementioned incentive interventions enforces stringent rules and regulations with regard to specific R&D initiatives to be developed, allowing the innovators the opportunity to perform R&D in their areas of expertise.

The feasible incentive interventions that underperformed in this criteria cluster include the open-source initiative and the colloquium and symposium incentive interventions. This underperformance could be attributed to the nature of the incentives that are not primarily aimed at accommodating R&D but rather to allow for better access and/or exposure to the body of knowledge of the targeted disease. The aforementioned will, however, also indirectly stimulate and encourage R&D initiatives to be initiated.

Criteria Cluster 4: Improved governance
75% of the decision criteria categorized in the improved governance criteria cluster are prioritized as important (i.e. priority rating of 2). This indicates that promoting equity, transparency and accountability of governance and functioning of domestic policies within the NTD R&D space is deemed as important by the enabler stakeholders in this case study.

The feasible incentive interventions that outperformed the rest in addressing this criteria cluster include the PPP, treaty, and open source initiatives. The working group incentive intervention underperformed compared to the other incentive interventions. This could be attributed to the working group not promoting equitable health-focused governance and not promoting transparency and accountability from the innovator's perspective. The working group does, however, play a role in advancing the priority of the targeted diseases on the health agenda.

Criteria Cluster 5: Population impact and access
Of the decision criteria prioritized in this criteria cluster, only one decision criteria (namely that the incentive eliminates all financial risk) was allocated a priority rating of zero (i.e. not relevant). This is expected as the enabler stakeholders in this case study do not eliminate all financial risk but rather facilitate collaboration between different stakeholders in order for risks (including financial risks) to be reduced and addressed. The enabler stakeholders consequently do not play a role in access provision in itself but rather prioritize the delivery of affordable and accessible interventions, such as sharing IP regulation of developed treatments with LMICs (having a direct impact on improved access and impact on the population groups). The prioritized decision criteria in this criteria cluster also highlight the aim of accommodating and improving the access of the population groups suffering from NTDs.

The feasible incentive interventions that outperformed the rest of the incentive interventions in this criteria cluster include the PPP; and the treaty. The incentive interventions that underperformed in this criteria cluster include the colloquium and symposium, independent

organizations and research laboratories. The reason for the three aforementioned incentive interventions underperforming could be attributed to the incentives not aiming to deliver any form of an intervention but rather promoting an improved body of knowledge and facilities for initiating R&D.

Criteria Cluster 6: Enabler resource investment

Only 2 of the 13 decision criteria categorized in this criteria cluster are prioritized as important. This was anticipated as the enabler stakeholders in this case study cannot provide any funding or resource investment to the innovator stakeholders. Consequently, it is understandable that PPP, collaboration network, coordination mechanism, treaty and the working group incentive interventions have the greatest ability to address this criteria cluster as these incentives do not necessarily require the enabler to invest resources. Instead, the aforementioned incentive interventions align with the objective to facilitate and manage collaborations, as expressed by the enabler stakeholders in this case study.

Criteria Cluster 7: Encourage competition in the innovation process

The motive of the PPP is not to encourage competition in the innovation process but rather to promote collaboration and allow innovators to work in alliance with one another to perform R&D for neglected diseases. The incentive interventions that scored the highest in this criteria cluster again include the top three performing feasible incentive interventions, as well as the colloquium and symposium incentive intervention, as these incentives align with the objective of the enablers to facilitate collaboration and incorporate a wide variety of innovator stakeholders as part of the R&D that is being encouraged.

Criteria Cluster 8: Overcome barriers to innovator participation in R&D process

The most evident barrier and limitation for innovator participation in the R&D process, as also highlighted by SME 5, is the lack of resources and funding. In addition, the body of knowledge for neglected diseases is not as advanced as for other diseases resulting in limitations with regard to data availability. These barriers are addressed by the PPP implemented in this retrospective case study by allowing different innovator stakeholders to collaborate and share resources.

The top-performing incentive interventions for this criteria cluster are again the PPP and collaboration network, with the working group having the third-highest ability to address this criteria cluster. This is expected as the actual incentive selected in the retrospective case study is a PPP with the primary aim to promote collaboration (as is the case for the collaboration network).

Criteria Cluster 9: Facilitate clinical trials

Only three of the eight decision criteria in the facilitation of clinical trials criteria cluster are prioritized, namely: (i) the incentive allows provision of public subsidies for clinical trials; (ii) the incentive assist in registration and monitor of trials; and (iii) the incentive enhances or prompt the quality of clinical trials.

The incentive interventions that outperformed the rest include the collaboration network and the coordination mechanism. These incentive interventions aid in facilitating clinical trials by

providing collaboration platforms where the innovator stakeholders can engage with other stakeholders that have relevant knowledge or experience in terms of clinical trials.

Criteria Cluster 10: Facilitate/ improve R&D process and R&D body of knowledge

All the decision criteria in this criteria cluster are prioritized, with the enabler stakeholders wanting to address the gap of R&D completed for the defined set of neglected diseases. The collaboration network has the highest ability to address the decision criteria that are prioritized in this criteria cluster.

The PPP performed within the bottom 50% of the feasible incentive interventions based on its ability to address this criteria cluster. This poor performance can be attributed to the PPP in itself not necessarily playing a role in improving the body of knowledge, meaning that the relationship between the two enabling stakeholders does not ensure the improvement of the body of knowledge. Instead, this is achieved indirectly as the act of creating collaborations among innovator stakeholders results in the improvement of the R&D body of knowledge for neglected diseases.

Criteria Cluster 11: Facilitate collaboration during R&D

The decision criteria that are prioritized in this criteria cluster include all but two decision criteria, namely the requirement of the enabler stakeholder to: (i) facilitate the regulatory process; and (ii) adjust policies and regulations.

This is the only criteria cluster where six of the nine feasible incentive interventions are able to completely fulfil the decision criteria that are prioritized in this case study. This could be attributed to most of the feasible incentive interventions aligning with the enabler exclusion criteria because they want to facilitate collaboration (as part of their primary objectives). Another reason might be that the feasible incentive interventions all allow for cooperation and synergy amongst the stakeholders. All of the feasible incentive interventions could address at least 25% of the decision criteria categorized in this criteria cluster, with the incentives that performed more poorly in addressing these decision criteria being classified as infeasible.

Criteria Cluster 12: Altruistic /political motivations

Only one of the five decision criteria categorized in this criteria cluster has a priority rating of zero (i.e. not relevant). This indicates that the enabler stakeholder of the case study has a strong altruistic motivation for performing and improving R&D for NTDs. The decision criteria in this criteria cluster that is highly prioritized include that the incentive must convey an important message and also that the incentive should allow the innovators and enabler stakeholders to collaborate, which are both some of the core motivations of the PPP applied in this retrospective case study.

Of the nine feasible incentive interventions, five have the complete ability to addresses the decision criteria categorized in this criteria cluster. Treaties underperformed, only addressing one of the six decision criteria categorized in this cluster.

10.7.8. Case study limitations

The limitations of this case study can be summarized as follow:

(i) The completion of only one of the enabler stakeholder profiles may result in a result that is biased towards the objectives and limitations of Enabling Stakeholder 1. However, the participant that was asked to provide input from the perspective of this stakeholder does have a thorough understanding of the case study.

(ii) Similar to the other case studies, the incentive targeting more than one neglected disease results in a somewhat generalized result for specifically Domain 1, with a number of the system elements in Domain 1 rated as 'somewhat relevant'.

10.8. SME case study validation

The following section aims to validate the outcomes of the three retrospective case studies. The purpose of validating the case study results is investigated, followed by a description of the validation questionnaires and an interpretation of the questionnaire feedback.

10.8.1. Purpose of the SME validation interviews

The purpose of the validation interviews is to confirm the decision-support framework's: (i) usability; (ii) practicability; (iii) applicability to the real-world; (iv) transferability; and (iv) value in solving the research problem.

10.8.2. Case study validation methodology

The validation of the case studies is completed by allowing the case study participants to evaluate the case study results and the value that the decision-support framework holds, using a questionnaire.

The methodology employed to validate the case study results is as follows:

(i) A document was created per retrospective case study, with a summary of the case study results presented in Sections 10.5 to 10.7. These documents are attached in Appendices M, N, and O.

(ii) The summary document was then emailed to the participant, with an online questionnaire attached.

(iii) The participant then had the freedom to answer the questions in their own time and the opportunity to ask the researcher to elaborate in the case where any uncertainty existed. Participants could also request documentation that depicts the decision-support framework results in more detail.

The questionnaire is reproduced in Table 10.14. The questions are divided into three categories. The first questionnaire category investigates the accuracy of the output produced by the framework. The questions assess accuracy in terms of each of the five domains of the framework, using a Likert scale. The results of this questionnaire section are described in Section 10.8.3.1.

The second category of questions aims to establish the decision-support framework's usability, applicability, and practicability. This is done by asking five closed-ended questions. The results of this questionnaire section are described in Section 10.8.3.2.

The final category of questions aims to establish and quantify the perceived ability of the decision-support framework to provide a feasible set of incentive interventions for the stakeholders to consider and pursue to encourage R&D in a specific NTD setting. Consequently, these questions relate to the ability of the decision-support framework to achieve the overall research aim, as depicted in Section 1.2.2. This set of questions consist of four open-ended questions, allowing the participants to elaborate and provide detailed insights into their views on the framework's value. The results of this questionnaire section are described in Section 10.8.3.3.

10.8.3. Case study validation data analysis and interpretation

The results of each category of the validation questionnaire are presented in the sections that follow.

10.8.3.1. Category 1: Evaluation of stakeholders involved

The first set of questions, presented in Table 10.14, aims to establish the decision-support frameworks' ability to investigate the stakeholders involved.

Table 10.14: Case study validation questionnaire and results, question category 1.

No	Validation questions	Case 1 SME 10	Case 1 SME 11	Case 2 SME 12	Case 3 SME 5	%
1.1	To what extent do you agree that the framework accurately provides stakeholders with the ability to gain insights into the pharmaceutical R&D system?	5	4	4	5	86.6
1.2	To what extent do you agree that the results accurately depict the pharmaceutical R&D system of the case considered?	5	3	3	4	75
2.1	To what extent do you agree that the framework captures the enabler stakeholder's objectives and limitations for wanting to incentivize R&D for NTDs?	4	4	4	5	85
2.2	To what extent do you agree that the results accurately depict the enabler stakeholder's objectives and limitations for the case considered?	4	4	3	4	75
3.1	To what extent do you agree that the framework captures the innovator stakeholder's objectives and limitations for a potential incentive intervention?	4	3	4	5	80
3.2	To what extent do you agree that the results accurately depict the innovator stakeholder's objectives and limitations for the case considered?	5	3	4	4	80
4.1	To what extent do you agree that the framework captures the consumer stakeholder's objectives and limitations for the potential treatment that will be developed?	5	4	4	5	90
4.2	To what extent do you agree that the results accurately depict the consumer stakeholder's characteristics and requirements for the case considered?	3	4	4	5	80
5.1	To what extent do you agree that the framework provides a feasible set of incentive interventions to consider for encouraging R&D for an/ a set of NTDs?	4	4	3	5	80
		86.7	73.3	73.3	93.3	81.2

It is evident from Table 10.14 that the results of validation question category 1 are positive. With an aggregated validation value of 75%, the performance was lowest in Questions 1.2, and 2.2 where the performance of the decision-support framework in terms of accurately depicting the R&D system and enabler stakeholder, respectively, was evaluated. The aforementioned may be attributed to these two questions drawing on the SMEs' understanding of the case (which they depicted) and how well the decision-support framework articulated the case study details. Some discrepancies between the actual case study and how the decision-support framework represents the details of the case studies are expected. This is due to the framework consisting of a set number of decision-criteria. Though this set of decision criteria is extensive, it is not exhaustive in the sense that it does not depict every detail within a pharmaceutical R&D system or every detail of a stakeholder. Furthermore, as discussed in Chapter 8, the use of a three-point scale to translate user inputs to quantitative data for use in the framework is, necessarily, somewhat crude, and it is therefore expected that some of the nuances of the real-world are lost in this translation.

The questions that scored the highest are Questions 1.1, 2.1, and 4.1. These three questions highlight that the framework can: (i) accurately provide the stakeholders with the ability to gain insights into the pharmaceutical R&D system; (ii) indicate the enabler stakeholder's objectives and limitations to incentivize R&D for NTDs; and (iii) capture the consumer stakeholder's objectives and limitations for the potential treatment that will be developed.

In summary, the results in Table 10.14 indicate that the decision-support framework can accurately evaluate the objectives and limitations of the stakeholders involved in incentivizing R&D for NTDs and that it can accurately take the characteristics of the specific R&D system into consideration.

10.8.3.2. Category 2: The applicability, practicability, and useability of the framework

The second set of questions aims to establish the usability of the decision-support framework by investigating its applicability, practicability, and useability. As mentioned, this set of questions are closed-ended, with results from the four participants summarized in Table 10.15.

Table 10.15: Case study validation questionnaire and results, question category 2.

No	Validation questions	Case 1 SME 10	Case 1 SME 11	Case 2 SME 12	Case 3 SME 5
6.1	Do you believe the decision-support framework contributes to the understanding of the pharmaceutical R&D system state?	YES	YES	UNDE-CIDED	YES
6.2	Do you believe the decision-support framework provides a means to establish the objectives and limitations of the enabler, innovator, and consumer stakeholders involved in an NTD incentive intervention?	YES	YES	UNDE-CIDED	YES
6.3	Do you believe the decision-support framework is a practical approach to evaluate the abilities of the existing incentive interventions to address the decision criteria?	YES	UNDE-CIDED	UNDE-CIDED	YES
6.4	Do you believe the decision-support framework provides guidance into the strengths and weaknesses of the feasible incentive interventions?	UNDE-CIDED	YES	UNDE-CIDED	YES
6.5	Do you believe the decision-support framework provides a means for enabler stakeholders to improve decision-making?	YES	UNDE-CIDED	UNDE-CIDED	YES

SME 12 provides inconclusive answers to the questions in this category, while SME 5 gives an entirely positive response. As SME 5 was involved in all the phases of verification and validation of the decision-support framework, this individual had the opportunity to provide input, critique, and suggestions in the initial design and development of the decision-support framework. This

individual most likely also has quite a thorough understanding of the framework, given the number of times that they have engaged with it. SMEs 10 and 11, which both provided inputs to the Prize fund case study, give differing feedback on Questions 6.3 to 6.5, highlighting the role of individual perspectives in evaluating an artefact such as the framework.

On balance, the responses provided to Questions 6.1 and 6.2 confirm that the framework can contribute to the understanding of the pharmaceutical R&D state and provide a means to establish the objectives and limitations of the enabler, innovator, and consumer stakeholders.

Conclusions based on the responses provided to Questions 6.3 to 6.5 are less clear cut. If these responses are viewed against the backdrop of the generally positive responses provided to the first and third sections of the validation questionnaires, however, it is deemed reasonable to conclude that the SMEs found these aspects of the framework to be adequate. The question of investigating alternative approaches to presenting the large amount of information contained in the framework outputs is considered as part of the discussion of future work in Chapter 11.

10.8.3.3. Category 3: Perceived ability to achieve research aim

The final set of questions are open-ended and requests deeper insights into the participants' views. The following section summarises the key insights gained per validation question.

Question 7.1: Based on the case study output, do you think that the framework provides a set of logical incentive interventions to consider for the enabling stakeholders of the respective case studies?

All SMEs answered that they believe the framework provides a set of logical incentive interventions for the enabling stakeholders of specific scenarios to consider. SME 10 stated that "*the framework is comprehensively designed to provide plausible incentive interventions for the stakeholders involved in the case studies*". SME 5 highlighted that the suggested incentives align well with the incentives currently in place. This SME also mentioned that it was an interesting finding that intellectual property, as an incentive, was not included in the results for the PPP case study. The SME suggested that this could be attributed to the definition of IP used in this research which differs from "*the positive message of IP as an incentive rather than any direct intellectual property policy changes*" that is employed in the retrospective case study.

Question 7.2: Based on case study output, do you think that the enabler organizations benefit from using the decision-support framework of this research to investigate the context-specific and context-non-specific requirements of an incentive intervention for a specific case?

In response to Question 7.2, all but SME 11 (answering with undecided) responded that they do believe that enabler stakeholders will benefit from using the decision-support framework to investigate requirements for an incentive intervention in a specific case. SME 10 highlighted that the framework "*best supports the context-specific requirements for an incentive intervention*". SME 12 emphasized that the framework does provide benefit but that ultimately the selection of an incentive intervention is still a "*go/no go decision*". SME 5 articulated that enabler organizations will benefit from using the decision-support framework and that the framework also provides a foundation for evaluating strategies employed to incentivize R&D.

Question 7.3: Based on the case study output, would you recommend the decision-support framework to enabling organizations and why?

In response to Question 7.3, all SMEs answered that they would recommend the decision-support framework to enabling organizations. SME 10, again, as in previous feedback, agrees that the framework does provide adequate solutions for decision-making while incentivizing innovative efforts to curb NTDs. SME 5 highlighted that the framework's output "*closely matches the incentives that are used in our scenario*" and that the "*predictability and accuracy of the model can be of help for new initiatives*". SME 5 lastly mentioned that the framework "*provides a significant amount of research and resources upfront that can be evaluated and further expanded upon, allowing staff to dedicate time to the refinement and structuring of the initiative instead of dedicating valuable time to collecting information*". With a final remark stating that the framework provides quantitative results, which provide a "*data-driven way to narrow down which incentives to be considered*".

Question 7.4: Do you have any additional comments or remarks regarding the decision-support framework, research performed, or the case studies conducted?

In response to Question 7.4, SMEs 10 and 5 provided additional remarks regarding the decision-support framework. SME 10 stated that the presented case study output and the decision-support framework are: "*excellent work*". SME 5 concluded by validating the framework's value, stating that the framework is a: "*very valuable tool that can provide direction to future endeavours seeking to incentivize R&D for neglected diseases*". SME 5 also mentioned that the framework should be included in the "*how to begin an R&D non-profit 101*" for groups aspiring to further innovate the neglected disease space.

10.9. Decision-support framework: Key insights and reflections

Resulting from the application of case study validation, as well as validation of the results of the case studies via SME interviews and validation questionnaire, key insights are gained concerning the decision-support framework's ease-of-use, practicability, applicability, transferability, and the value of the decision-support framework output in real-world settings. Furthermore, key learnings on the decision-support framework are derived from reflection on the aforementioned. These are subsequently discussed in the remainder of this chapter.

10.9.1. The usability of the decision-support framework

Usability of the decision-support framework is defined as whether it is easy to use and whether the framework provides stakeholders with the ability to use the framework as it was intended. Although the decision-support framework contains a high level of complexity, the systematic sequence in which the framework domains are presented and the effective use of background logic requires stakeholders to provide only the required information and provide a practical and structured approach for doing so. The input that the decision-support framework requires is limited to prioritizing a set of predefined decision criteria on a three-point scale.

The graphic design of the decision-support framework furthermore assist in providing users with the ability to understand easily, conceptualize and visually interpret the: (i) appropriate stakeholder required, evaluated and/ or involved per decision-support framework domain; (ii) feasible and infeasible incentive interventions; (iii) prioritized decision criteria; (iv) performance of the incentive interventions per criteria cluster; as well as the (v) performance of each incentive in comparison to the other incentive interventions. Finally, the users of the decision-support framework are logically navigated through the framework by the digital version of the decision-support framework that is operationalized in MS Excel.

10.9.2. The practicability of the decision support framework

The practicability of the decision-support framework measures whether the framework can be put into action. The primary aim of this research is to assist governance authorities, private or philanthropic institutions (i.e. enabler stakeholders) in selecting an appropriate means to increase the interest of pharmaceutical R&D stakeholders (innovators) to develop drugs for a specific disease. The decision-support framework practically assists the enabler stakeholders to achieve this aim through evaluating the relevant R&D system, interpreting the appropriate decision criteria and synthesizing the information to deliver an exhaustive set of feasible incentive interventions based on the score-based framework design. The feasibility of the decision-support framework was also highlighted in the SME questionnaires and interviews (see Sections 10.2.4.2 and 10.8.3.1).

10.9.3. The applicability of the decision-support framework

Applicability is defined as whether the decision-support framework is representative of real-world phenomena. The decision-support framework proceeds through five domains and five background logic functions, systematically investigating the demarcation of the applicable R&D system and the relevant decision criteria of the enabler, innovator and end-consumer stakeholders. The Prize fund, the Hybrid PPP, and the PPP case studies are three real-world cases where the interest of an innovator stakeholder or group of innovator stakeholders had to be increased to ultimately improve the R&D pipeline and / or body of knowledge for neglected diseases. The applicability of the decision support framework is logically analyzed by requesting the SMEs that provided the input data used in the case studies to provide feedback that relates to each of the five domains of the decision-support framework. The applicability of the decision-support framework in these three cases is evidenced by the feasible set of suggested incentives in the framework output. The ability of the decision-support framework to sufficiently evaluate the R&D system and appropriate stakeholder requirements is demonstrated as the incentive intervention that was selected (in the real-world) appeared within the top six feasible incentive interventions in all three case studies.

10.9.4. The transferability of the decision-support framework

Transferability of the decision-support framework is defined as the degree to which the decision-support framework can be transferred (used) in other contexts or settings with other stakeholders. The decision-support framework was applied to three distinct cases that are representative of, amongst other things, different: (i) R&D initiatives that were incentivized; (ii) sets of neglected

diseases that were targeted; (iii) types and numbers of enabler stakeholders involved; (iv) types and numbers of innovator stakeholders targeted; and (v) end-consumer focus areas considered.

In each of the case studies, the ability of the decision-support framework to effectively achieve the following objectives were evaluated:

(i) Accurately depict and provide insights into the case-specific pharmaceutical R&D system;
(ii) Capture the case-specific enabler stakeholder's objectives and limitations;
(iii) Capture the case-specific innovator stakeholder's objectives and limitations;
(iv) Capture the case-specific consumer stakeholder's characteristics and requirements;
(v) Provide a feasible set of incentive interventions based on the R&D system;

The SMEs involved in all three case studies rated the aforementioned objectives on a 5-point Likert scale, with the average ability of each objective rated between $75 - 90\%$ (refer to Section 10.8.3.1, Table 10.14). Furthermore, the feedback from SMEs 10, 11, 12 and 5 corroborated that the decision-support framework is recommended for use in each scenario (refer to Section 10.8.3.3).

10.9.5. The value of the decision-support framework in the real-world

The value that the decision-support framework provides is defined as the worth that it holds in the real-world. Based on the feedback received from SMEs 10, 11, 12 and 5 (case study participants), it can be concluded that the decision-support framework provides definite value to a real-world scenario, where R&D for a targeted disease needs to be encouraged. The value of the decision-support framework in the real-world can be summarized in the following key points (refer to Section 10.8.3):

(i) The framework allows enabler stakeholders to evaluate their objectives and limitations, as well as the objectives and limitations of the innovator and consumer stakeholders.
(ii) The framework accurately evaluates the pharmaceutical R&D system and portrays an overview of the relevant factors that influence the success of an incentive intervention.
(iii) The framework evaluates all feasible incentive interventions based on the input provided by the stakeholders.
(iv) The framework successfully proposes feasible interventions that should be considered to encourage R&D for a (set of) targeted neglected diseases.

10.9.6. Key decision-support framework take-outs and reflections

Table 10.16 summarizes and interprets final key reflections and findings per domain of the decision-support framework.

Table 10.16: Final decision-support framework key take-outs and reflections.

	Neglected disease R&D context findings	Overall decision-support framework findings
Domain 1: System demarcation	· The R&D body of knowledge for NTD's still experience a lack of priority, highlighting the need for an incentive intervention that allows expansion of the neglected disease R&D body of knowledge and intervention pipeline. · There is an increased global effort towards mitigating neglected diseases. This is facilitated by data sharing, as well as coordination of efforts. This is in contrast to diseases that have a high purchasing power, where blockbuster treatments are pursued in isolation. · The lack of resources and financing for neglected disease have direct and indirect consequences on the R&D body of knowledge and pipeline.	· The system elements that the system demarcation domain considers are a comprehensive list of factors that contribute to the holistic understanding of the neglected disease pharmaceutical R&D system. The system elements cover ten relevant themes that are grounded on theory-based evidence sourced from Chapters 3 to 7. · The three-point evaluation of each criterion facilitates easy decision-making for the framework user, simplifies the complex nature of each system element and reduces the complexity involved in articulating the state of an attribute in the real-world.
Domain 2: Enabler	· Each enabler stakeholder has unique requirements, capabilities, and objectives for wanting to incentivize R&D for neglected diseases. This supports the design of the decision-support framework to allow for variation in the motives for encouraging R&D. · All the objectives of the enabler stakeholders to encourage and improve the state of R&D for neglected diseases can often not be fulfilled due to a lack of resources and limitations in terms of the enabler stakeholders' internal capabilities.	· The enabler decision-criteria assist in clearly articulating the vision towards which the enabler stakeholder(s) work, as well as the means that the enabler(s) have to achieve their defined vision. · The decision-support framework provides visibility into the capabilities, as well as objectives into other enabler stakeholders, in the case where more than one enabler stakeholder is present. This assist in creating transparency between enablers, establishing mutual grounds, and facilitating conversations around what which enabler stakeholder can contribute.
Domain 3: Innovator	· The lack of funding and resources, the low purchasing power of the neglected disease patients, as well as the risk involved are the most evident reasons for innovator stakeholders to require an external incentive to perform R&D or research to improve the body of knowledge. · With the exception of large organizations, innovators rarely have the capacity to fund the entire R&D process of a drug going from discovery to launch into the market. This again highlights the intervention required from external enabling stakeholders.	· The innovator inquiry form assists in developing an understanding of the nature of the innovator stakeholder, whether the innovator has the means to achieve the intended R&D that the enabler stakeholder wants to encourage, and whether the innovator stakeholder characteristics can be met by the enabler stakeholder/s that are involved in the specific real-world pharmaceutical R&D system.

Table 10.16 continues on next page

Table 10.16 continued from previous page

Domain 4: End-consumer	· The end-consumer is often not considered when the research, discovery and development of an intervention against neglected diseases is launched. This might be attributed to the fact that the end-consumer will only need to be considered when the intervention is approved and when access to the consumers needs to realized. · Contextual treatment criteria is the attribute of the consumer stakeholder that was highlighted to be the most important consideration to take into account. This emphasizes that in order for a developed intervention to have the desired impact on the consumer stakeholder, contextual considerations need to be considered, adhered to, and incorporated in the intervention approach. · In general, socio-economic inequalities are evident in the neglected disease target population, which re-iterates one of the core reasons why the population has a low purchasing power.	· The consumer-profile guides the enabler stakeholder to develop insight into the contextual treatment criteria, as well as relevant social and economic considerations of the end-consumer population. Taking these three aspects into consideration allows the enabler and innovator stakeholders to obtain a holistic understanding of relevant requirements of the product that is developed for use by the end consumers. · The end-consumer stakeholder requirements are often omitted in the selection of an incentive intervention. This might be because the incentive in itself will not have a direct impact on the end-consumer; rather, it will lead to the development of an intervention that will ultimately reach the end-consumer population. The decision-support framework, therefore, considers the end-consumer requirements at a somewhat higher level (i.e. in less detail) in comparison to the approach applied to the enabler and innovator stakeholders. This reduced level of detail, however, still provides sufficient insight.
Domain 5: Solution set	· PPPs and Hybrid PPPs had the greatest ability to address the decision-criteria that were prioritized in all three case studies. This might be attributed to these incentive interventions incorporating more than one enabler stakeholder and having a broad range of functionalities. · The output of the decision-support framework closely matched the incentives that were used in the case study scenarios, providing evidence for the accuracy of the decision-support framework.	· The decision-support framework provides a score-based, logical, structured and graphic representation of the feasible incentives to consider as well as the respective abilities of the incentive interventions to perform in criteria clusters that represent the focus areas of the stakeholders and the R&D system under consideration. · The SME case study participants all agreed that they would recommend the decision-support framework to assist in understanding, evaluating and selecting a feasible set of incentive interventions to encourage pharmaceutical R&D for neglected diseases.

10.10. Conclusion: Validation

The objective of this chapter was to validate the framework to establish the extent to which the framework fulfils its intended purpose. The validation of the decision-support framework was completed in two ways, first SME validation, through semi-structured interviews with subject matter experts. Second, three retrospective case studies were applied to this research.

The SME validation corroborated that the developed framework is helpful, valuable and holistic to use for improving decision-making in selecting appropriate incentive interventions to ultimately

contribute to the state of the R&D pipeline for NDs. The feedback indicated that the most noteworthy strengths of the framework are that it is comprehensive in nature, employs a logical approach, and effectively portrays the elements of the pharmaceutical R&D environment, considerations that relate to the enabling stakeholder, and the respective incentive intervention types. All SMEs agreed that the framework is novel in its approach to solving the problem of selecting an appropriate incentive mechanism.

The case study validation resulted in establishing the practicality, practicability, applicability, and transferability of the decision-support framework in the real-world. All of the primary objectives of the validation phase were achieved as this section successfully established that: (i) the decision-support framework is applicable, useful and adds value to the real-world; (ii) the SMEs perceive the decision-support framework as a feasible solution to the problem at hand; and (iii) the outputs of the decision-support framework provide valid solutions to the problem that it aims to address.

CHAPTER 11

Research conclusion

This chapter considers the research conducted. An overview of the research performed is presented with an articulation of the research objectives achieved. The research contribution and limitations inhibiting the accomplishment of the research goals are discussed. Finally, existing opportunities for future work are explored.

11.1. Overview of research and achievement of research objectives

The overarching aim of this research is to improve the state of the neglected disease R&D pipeline. The outcome of this research is a decision-support framework to enable entities wanting to collaborate and partake in improving the state of the neglected pipeline, globally, in selecting an appropriate incentive to drive R&D for a specific instance. The framework integrates the ideal view of all health care systems, with factors that constrain the R&D processes, the neglected market and disease-specific inhibitors to conceptualize any neglected disease R&D landscape. The R&D landscape, together with stakeholder objectives and capabilities, acts as foundation to evaluate potential incentives to pursue for a specific instance.

Chapter 1 defines and provides background on the problem, including a description of the research aim, objectives and scope. The research strategy and methodology are described in Chapter 2. Chapter 2 also introduces the structure of the document, indicating that Chapters 3, 4, 5, 6 and 7 contain literature reviews that serve as foundation for Chapter 8, where the decision-support framework is developed. Verification, refinements and validation follow in Chapters 9 and 10.

Chapter 3 investigates the health care system to provide background on the complex pharmaceutical environment in which R&D for neglected drugs needs to be performed. A high-level overview of the taxonomy of care levels in the health system, as well as a breakdown of health system components are related to the neglected disease sphere to further develop understanding of the research question being considered. The desired outcomes of an improved pipeline of drugs for NDs are demarcated Thus, RO.1, as defined in Section 1.2.3, is achieved in this chapter.

The focus of Chapter 4 is on the pharmaceutical R&D process and pipeline. Systematic reviews identify the primary elements and trends influencing the advancement of R&D pipelines. A more specific breakdown is then performed to deepen the understanding of the state of the global R&D pipeline with a statistical analysis investigating the relationship between the global burden of disease and the number of drugs in the R&D pipeline. RO.2 is achieved in this chapter.

In Chapter 5 the concept of market attractiveness of diseases is investigated. The chapter leans on the argument that the willingness of pharmaceutical organizations to invest funding and resources in R&D depends on the perceived attractiveness of the market for which a product is to be developed. Characteristics that both improve and reduce market attractiveness are uncovered by performing: (i) a market analysis on the pharmaceutical R&D industry; as well as (ii) structured literature reviews on both diseases for which R&D is well-funded, and NDs, respectively. RO.3 is achieved in this chapter.

Chapter 6 is concerned with existing approaches to incentivizing pharmaceutical organisations to perform R&D for neglected drugs. A set of incentive intervention types are inductively derived from literature and these provide insight into different aspects of incentives, such as financing as well as policies governing the development and exclusivity of developed drugs. The advantages and disadvantages associated with the different incentive types are also articulated. RO.4.1 - 4.3 is achieved in this chapter.

In Chapter 7, the stakeholders that are involved in incentivizing and participating in performing R&D in the pharmaceutical industry are established by applying the locus of interest technique. The stakeholders identified to be involved in the selection of an incentive intervention for encouraging R&D for neglected diseases include the enabler, innovator and the consumer stakeholders. RO.4.4 is achieved in this chapter.

The decision-support framework is developed in Chapter 8. The design of the framework is based on the requirement specifications derived throughout the literature review in Chapters 3 - 7 (achievement of RO.5). A system demarcation (Domain 1), criteria matrix (Domain 2), enabler profile (Domain 3) and solution set (Domain 4), are developed and the operationalization thereof is explained. RO.6.1 is achieved in this chapter.

In Chapter 9, the accuracy and credibility of the framework is investigated by means of verification. The verification is completed in two stages, namely requirement specification verification (internal reflection) and SME interviews. Both stages of verification confirm that the design of the framework is accurate to perform its intended purpose and identified refinements that should be made to the framework. Refinements that are applicable, feasible and in-scope are incorporated into the framework, while other suggestions are categorized as future work. RO.6.2 and 6.3 is achieved in this chapter

In Chapter 10 validation of the framework is completed by means of SME interviews, as well as through the application of three case studies. The data gathered via the interviews confirms that the framework is a novel, feasible and accurate approach to solving the intended problem. RO.6.4 is achieved in this chapter. RO.6.5 is achieved in Chapter 11.

11.2. Final research insights and reflection

Retrospective reflection on the research process as well as the research outputs, specifically the decision-support framework, led to the following key insights.

The design research cycle approach was followed to guide this research and the development of the decision-support framework. The five phases of the approach provided appropriate guidance to develop a solution that is built on and substantiated by literature. This research falls in the theory and model building research design, where the research aims to find a solution to a real-world problem, being classified as applied research. The research objectives included to establish requirement specifications, through analysing the combination of mutually exclusive structured literature reviews that provided awareness of the problem context and suggestions of existing knowledge and theories. The consolidated requirement specifications were used to develop the decision-support framework, with the framework ultimately being operationalized in an MS Excel workbook.

The decision-support framework went through an evaluation process where SMEs confirmed the accuracy and comprehensiveness, as well as the thoroughness of the proposed solution. The evaluation process resulted in changes and refinements made to the initial version of the decision-support framework. The framework also underwent a parallel evaluation process where the validity and the perceived feasibility of the solution was confirmed by SMEs. The decision-support framework was applied to three real-world settings, by means of three retrospective case studies. This demonstrated how a real-life scenario progresses through the five domains of the decision-support framework, providing the expected outputs for each domain of the framework. The usability, applicability, and the practicability of the decision-support framework was demonstrated, with the outcome of the case studies providing substantial insight into:

(i) The current state of scenario specific R&D systems defined by means of context-specific as well as literature-based system elements;
(ii) A logical set of incentive-based and non-incentive-based interventions that are selected based on the input provided for each case study;
(iii) The objectives and requirements of the different stakeholders to participate and be involved in neglected disease R&D and incentive interventions;
(iv) An overview of the requirements, limitations as well as capabilities of the respective case study enabler, innovator and consumer stakeholders;
(v) The impact of specifically the enabler stakeholder's objectives and limitations on the feasibility of each incentive intervention for the specific case.

The decision-support framework provides an integrated, holistic approach for the selection of an incentive intervention to stimulate pharmaceutical R&D for neglected diseases. The scope of the study contributed to the complexity of the framework, as also perceived by some SMEs. The decision-support framework is comprehensively developed through integrating existing literature and quantifying its output by means of a score-based approach. This adds contextual value to the decision-support framework output and enhances the applicability of the decision-support framework on users. The framework furthermore mediates relevant context-specific, as well as context-non-specific decision criteria providing a combined holistic perspective.

This research adopted a pragmatic philosophical perspective, as defined in Chapter 2. This perspective allows the researcher to acknowledge that the problem being addressed in this research, can be interpreted and addressed in various ways. This implies that the solution which is developed to address the research problem in this study represents only one of many potential

solutions to the problem. In line with the pragmatic perspective, the intent was to develop a decision-support framework that (i) constituted a practical solution to the problem, and (ii) that informs future practice in terms of the selection of incentive interventions for R&D on neglected diseases. The extensive verification and validation activities, with a specific focus on gaining SME insights into the perceived value, usability and practicality of the decision-support framework, provided substantial evidence for the achievement of this goal.

11.3. Research contribution

The primary contribution of this research is the decision-support framework, presented in Chapter 8. As highlighted in Chapter 5, there is currently a lack of R&D market attractiveness resulting in an underperforming R&D pipeline for neglected diseases. Furthermore, there are various incentive interventions that aim to address this but not all incentive interventions are feasible in all R&D systems. The decision-support framework makes a contribution to overcoming poor market attractiveness of neglected diseases by providing sophisticated guidance on the selection of an incentive intervention that is: feasible; appropriate in the specific pharmaceutical R&D system; and aligned to the needs of relevant stakeholders.

The decision-support framework and its outputs represent a practical approach to significantly simplify the complex question of appropriately incentivizing pharmaceutical R&D. The contribution that this framework output is making, goes beyond theoretical evidence on criteria that determine the effectiveness of incentive approaches. Instead, the framework combines this theoretical perspective with a more holistic perspective that acknowledges that there are various stakeholders involved in the operationalization of an incentive mechanism, and that each of these stakeholders have preferences, objectives, and constraints that also play a role in how successful an incentive mechanism is likely to be. By design, the users of the decision-support framework therefore serve as the integrators of the real-world into the literature-based framework, also seen as co-creation of the decision-support framework. Finally, the various inputs are then synthesised and quantified based on hard-coded rules, formulas and decision-support logic that have all been developed as part of the framework design.

The final decision-support framework contributes to the understanding of feasible interventions to encourage R&D of drugs for neglected diseases in a specific scenario. The framework aids in the decision-making process, by guiding the enabling entity to conceptualize the status-quo of a specific pharmaceutical R&D landscape, through considering the enabling, innovating and consumer stakeholders. An in-depth and holistic understanding of the existing incentive interventions adds to the existing body of knowledge, where a comprehensive overview of interventions to improve neglected R&D does not currently exist. The complex interactions within the demarcated pharmaceutical environment, the enabler- innovator- and end-consumer-objectives and capabilities, and the functions of the existing incentive interventions are integrated, leading to an overview of the feasible incentive interventions. The ability of the incentives to satisfy 12 criteria clusters is further articulated, highlighting the strengths and weaknesses of each of the incentive interventions.

The final key contribution of this research stems from the uniqueness of this decision-support framework in the neglected disease R&D sphere. The novelty of this framework is corroborated

by seven international and two national SMEs, as well as by a structured literature review (discussed in Section 1.6). Eight of the nine SMEs are specialized in the neglected disease R&D and incentive spheres, with one SME specialized in the operations of innovating pharmaceutical organizations. The decision-support framework ultimately provide a novel approach that informs the future practice of decision-making in the neglected disease R&D sphere.

11.4. Research limitations

Limitations of the research are articulated with regard to the following: (i) the research scope; and (ii) the evaluation of the real-world feasibility.

11.4.1. Limitations regarding the research scope

Chapter 1 mentioned the broad scope applicable to this research, with a brief description of how the research developed as the understanding of relevant literature matured. The scope of this research may be perceived as a limitation. More specifically, as a large number of topics, each with an extensive scope, were relevant to the development of the framework, all topics could not be discussed in full detail in the dissertation document. An example of this is the 67 context-specific criteria elements included in Domain 1 of the decision-support framework. Ideally, all these criteria would have been discussed extensively to highlight the possible effects of the respective elements on all the applicable areas of the R&D pipeline and health care system being investigated. Instead, this information has been summarised in tabular format in Appendix G, with only high-level accompanying discussion.

The second limitation with regard to the scope of this research, is the scale used for evaluating the existing incentive interventions in Domains 2 to 4. The binary scale used in both cases indicates the ability of the incentive intervention to satisfy the respective sets of criteria. A binary scale eliminates much of the detail regarding the respective incentive intervention's abilities; however, it has the advantage of simplifying decision-making. The provision of a feasible set of solutions, rather than a single recommended solution, is intended to encourage the user to consider and explore in more detail a short list of incentive interventions with similar overall feasibilities, as well as their respective strong and weak points. The list of 105 incentive intervention instances also intends to fill the gap of possible details lost in the binary scale, by providing the user with the opportunity to refer to examples of implemented or suggested incentive interventions.

The third limitation is that the following key attributes are only somewhat incorporated into the decision-support framework, with further investigation being essential due to its potential effect on incentive intervention impact. These attributes include: (i) context, although the decision-support includes a broad scope of context, it should be noted that each case where incentive interventions are required differ from the other; (ii) risk, being the extensive number of risks involved with selecting and implementing an incentive intervention as well as risk sharing opportunities; and (iii) sustainability, referring to the long-term application of the incentive interventions in different contexts.

The fourth limitation is the exclusion of the role and impact of the observer stakeholder. Though, the observer stakeholder is not directly involved in the selection of the incentive intervention, or

the R&D of drugs for neglected diseases; the regulation and approval of this stakeholder is, however, necessary for the incentive to be selected and R&D to occur.

11.4.2. Real-world feasibility quantification

The evaluation of the real-world applicability and feasibility of the decision-support framework is demonstrated through the application of three case studies. The application of these case studies allows the reality regarding the implementation of a framework to be captured, which is not possible otherwise. Limitations in the application of these case studies can be highlighted as follow:

(i) The aims of the enabler stakeholders in the Prize fund and Hybrid PPP case studies are very broad, which caused difficulty in prioritizing the decision-criteria of specifically the system demarcation.

(ii) The enabler stakeholders in the Hybrid PPP, and PPP case studies completed the innovator stakeholder profile, even though the innovator profile is intended to be completed by the innovator stakeholder(s) themselves. The risk here is that the enabler stakeholder makes inaccurate assumptions about the innovator stakeholder.

(iii) The consumer profile of the Prize fund and Hybrid PPP case studies were not completed in full. This is seen as a limitation given that the abilities of the incentive interventions to address the requirements and needs of the consumer stakeholder were not portrayed.

11.5. Future work

It is recommended that the following four aspects are prioritised in future work on the framework: (i) the incorporation of feasible suggestions made by SMEs that are not included; (ii) alternative ways of presenting the large amounts of information (iii) establishing the feasibility of applying the framework to a broader set of diseases; and (iv) establishing the ability of the framework to be used for encouraging R&D for vaccine development.

11.5.1. Future iterations of the framework

The first major aspect that should be elaborated on in the future iterations of the decision-support framework, is that future work should incorporate all the significant and feasible aspects suggested by SMEs in the verification and validation interviews. Refer to Table 9.15 for all suggestions derived from the verification part of the interviews.

The second suggestion regarding future iterations is the consideration of investigating alternative approaches to presenting the large amount of information contained in the framework outputs. Presenting the output in different ways, will potentially result in additional insights gained, and information

11.5.2. Application of the framework to other diseases

The framework has been developed specifically for application to NDs. However, it is recommended that the possibility of applying the framework to a broader set of diseases should be investigated in future work. Although the theory of the framework development is based on

NDs, with all incentive interventions focused on neglected disease, it is possible that the framework may also be applicable and valuable outside of the ND scope. If the framework is deemed to hold value outside of this scope, consideration should be given to required changes to the framework in order to ensure that it is fit for purpose to this broader scope.

11.5.3. Feasibility of incentivizing vaccine R&D

The decision-support framework is developed to encourage the R&D of drugs for neglected diseases. As mentioned in Section 1.3, the potential application of the framework to encourage vaccine R&D is omitted from the scope of this research problem. The opportunity does, however, exist to investigate the feasibility of the framework to be applied to stimulate vaccine R&D. This will require in-depth analysis of the differences between the pharmaceutical R&D systems for drug versus vaccine development. An investigation of the different context-specific-, context-non-specific-, as well as stakeholder decision criteria that might influence the outcome of the current decision-support framework's ability to sufficiently encourage vaccine R&D, would also be required.

11.6. Conclusion: Research conclusion

This chapter provided an overview of the research completed. A summary of the research conducted per chapter, as well as an indication of where each of the research objectives were met. The contribution that this research makes to the body of neglected disease R&D knowledge is investigated, followed by research limitations encountered throughout the research. Lastly, future work is proposed.

BIBLIOGRAPHY

A.T. Kearney (2011) *Pharmaceutical: Getting back its luster*. Available at: https://www.atkearney.at/documents/10192/521705/EAXIV˙1˙Pharmaceutical˙Getting˙Back˙Its˙Luster.pdf/7b2fb14e-738a-4ff0-9ec2-dda7c23f5bbc (Accessed: 21 January 2019).

Aagaard-Hansen, J. and Chaignat, C. L. (2010) 'Neglected tropical diseases: equity and social determinants', *Equity, social determinants and public health programmes*, p. 77ff.

Aaker, D. A. (2013) *Strategic Market Management*. Tenth. Berkeley: John Wiley & Sons.

Access to medicine foundation (2018) *Access to Medicine Index 2018*. Amsterdam. Available at: www.accesstomedicineindex.org (Accessed: 18 May 2019).

Aerts, C. *et al.* (2017) 'Are public-private partnerships the solution to tackle neglected tropical diseases? A systematic review of the literature', *Health Policy*, 121(7), pp. 745–754.

African Health Observatory and WHO (2018) *Malawi: Factsheet of health statistics 2018*.

Al-Shamsi, M. (2017) 'Addressing the physicians' shortage in developing countries by accelerating and reforming the medical education: Is it possible?', *Journal of Advances in Medical Education & Professionalism*.

Allarakhia, M. and Ajuwon, L. (2012) 'Understanding and creating value from open source drug discovery for neglected tropical diseases', *Expert Opinion on Drug Discovery*, 7(8), pp. 643–657.

Alshammari, T. M. (2016) 'Drug safety: The concept, inception and its importance in patients' health', *Saudi Pharmaceutical Journal*. King Saud University, 24(4), pp. 405–412.

American Hospital Association (2019) *Fast Facts on US Hospitals*. Chicago. Available at: https://www.aha.org/system/files/2019-01/2019-aha-hospital-fast-facts.pdf (Accessed: 29 January 2019).

Arfwedson, J. (2004) *Re-importation (Parallel Trade) in Pharmaceuticals*, Policy Report 182.

AstraZeneca (2021) Available at: https://www.astrazeneca.com/ (Accessed: 7 February 2021).

ATLAS.ti (2019) *What is ATLAS.ti*. Available at: https://atlasti.com/product/what-is-atlas-ti/ (Accessed: 14 November 2019).

El Baghdady, A. S. and El Baghdady, Y. M. S. (2014) 'Unlocking the market potential of academic research', *Collaborative Innovation in Drug Discovery: Strategies for Public and Private Partnerships*.

Bai, J. *et al.* (2016) 'Bibliometric study of research and development for neglected diseases in the BRICS', *Infectious Diseases of Poverty*, 5(1).

Bailey, F. *et al.* (2019) 'Neglected Tropical Diseases and Mental Health: Progress, Partnerships, and Integration', *Trends in Parasitology*.

Bangert, M. *et al.* (2017) 'The cross-cutting contribution of the end of neglected tropical diseases to the sustainable development goals', *Infectious Diseases of Poverty*.

Bardosh, K. L. (2018) 'Towards a science of global health delivery: A socio-anthropological framework to improve the effectiveness of neglected tropical disease interventions', *PLoS Neglected Tropical Diseases*.

Bartlett, S. *et al.* (2019) 'Elimination through collaboration: Success factors in a global consortium', *International Health*.

Bastos, L. F. S. and Coelho, M. M. (2013) 'Drug repositioning: Playing dirty to kill pain', *Springer International Publishing Switzerland*, pp. 45–61.

Bates, S. E. *et al.* (2015) 'Advancing clinical trials to streamline drug development', *Clinical Cancer Research*, 21(20), pp. 4527–4535.

Bayazidi, Y. (2016) 'The impact of research and development and marketing costs on the profitability of pharmaceutical companies of Tehran Stock Exchange using panel data 2001–2013', 10(4), pp. 467–476.

Bayer (2021). Available at: https://www.bayer.com/en/ (Accessed: 7 February 2021).

Baylor College of Medicine (2009) 'Eliminating disparities in clinical trials'. Available at: http://www.bcm.edu/edict/home.html (Accessed: 13 July 2019).

Becker, B. *et al.* (2012) *Case studies*, Colorado State University.

Becker, B. (2015) 'Public R&D policies and private R&D investment: A survey of the empirical evidence', *Journal of Economic Surveys*, 29(5), pp. 917–942.

Benn, S., Abratt, R. and O'Leary, B. (2016) 'Defining and identifying stakeholders: Views from management and stakeholders', *South African Journal of Business Management*, 47(2), pp. 1–11.

Berchick, E., Hood, E. and Barnett, J. (2018) *Health Insurance Coverage in the United States: 2017*. Washington, DC.

Berdud, M., Towse, A. and Kettler, H. (2016) 'Fostering incentives for research, development, and delivery of interventions for neglected tropical diseases: Lessons from Malaria', *Oxford Review of Economic Policy*, 32(1), pp. 64–87.

Berman, S. and Giffin, R. B. (2004) 'Global perspectives on vaccine financing', *Expert Review of Vaccines*.

Beutels, P., Scuffham, P. A. and MacIntyre, C. R. (2008) 'Funding of drugs: Do vaccines warrant a different approach?', *The Lancet Infectious Diseases*.

Beyeler, N. *et al.* (2019) 'Improving resource mobilisation for global health R&D: A role for coordination platforms?', *BMJ Global Health*.

Bhaskar, R. (2013) *A Realist Theory of Science*, Available at: https://uberty.org/wp-content/uploads/2015/09/Roy˙Bhaskar˙A˙Realist˙Theory˙of˙Science.pdf

Birx, D. L., Ford, R. M. and Payne, C. A. (2013) 'The University as an Open Laboratory', *Journal of Research Administration*.

Błazejowski, M., Kwiatkowski, J. and Gazda, J. (2019) 'Sources of economic growth: A global perspective', *Sustainability (Switzerland)*, 11(2), pp. 1–14.

De Boeck, P., Dethlefs, S. and Villumsen, K. (2008) *Pharmaceutical and medical products practice perspectives and recommendations for European commercial pharmaceuticals*.

Bors, C. *et al.* (2015) 'Improving access to medicines in low-income countries: A review of mechanisms', *Journal of World Intellectual Property*, 18(1–2), pp. 1–28.

Bose, S. K., Sandhu, A. and Strommenger, S. (2017) 'Clinical trials: A data driven feasibility approach', *Pharmaceutical Outsourcing*.

Bradfielda, R. and El-Sayedb, H. (2009) 'Four scenarios for the future of the pharmaceutical industry', *Technology Analysis & Strategic Management*, 2(2), pp. 195–212.

Brenner, R. (2016) *What's a Model? What's a Tool?* Available at: https://chacocanyon.com/smm/readings/modelvstool.shtml (Accessed: 12 November 2019).

Brinkerhoff, D. (2003) 'Partners for Health Reformplus Accountability and Health Systems: Overview, Framework, and Strategies', *World Health Organization*. Available at: http://www.who.int/management/partnerships/accountability/AccountabilityHealthSystemsOverview.pdf (insert date accessed/date not available).

Brown, D. L. *et al.* (2015) 'Adolescent knowledge and attitudes related to clinical trials', *Clinical Trials*.

Browning, E. K. and Zupan, M. A. (2014) 'Monopolistic competition and Oligopoly', in

Microeconomics Theory and Applications.

Bujar, M., McAuslane, N. and Liberti, L. (2017) 'New drug approvals in six major authorities 2007–2016: Focus on the internationalisation of medicines R&D'.

Bunnage, M. E. (2011) 'Getting pharmaceutical R&D back on target', *Nature Publishing Group*. Nature Publishing Group, 7(6), pp. 335–339.

Burci, G. L. and Gostin, L. O. (2017) 'Privatized pharmaceutical innovation vs access to essential medicines: A global framework for equitable sharing of benefits', *Journal of the American Medical Association*.

Burn, S. C., Burn, A. S. and Burn, P. (2014) 'Delivering solutions and clinical benefits for diseases with small and intermediate-size patient populations', *The Value of BCG and TNF in Autoimmunity*.

Burnham, N. *et al.* (2015) 'Effective Drug Supply for Adaptive Clinical Trials: Recommendations by the DIA Adaptive Design Scientific Working Group Drug Supply Subteam', *Therapeutic Innovation and Regulatory Science*, 49(1), pp. 100–107.

Burrows, J. N. *et al.* (2014) 'The role of modern drug discovery in the fight against neglected and tropical diseases', *MedChemComm*, 5(6), p. 688.

Business Essentials (2017) *Automotive Manufacturing in SA*. Available at: https://www.businessessentials.co.za/2017/12/11/automotive-manufacturing-sa/ (Accessed: 5 November 2019).

Califf, R. M. and Sugarman, J. (2015) 'Exploring the ethical and regulatory issues in pragmatic clinical trials', *Clinical Trials*, 12(5), pp. 436–441.

Cambridge University Press (2020) *Cambridge International Dictionary of English*. Available at: https://dictionary.cambridge.org/dictionary/english/grant (Accessed: 3 August 2020).

Campa, M., Ryan, C. and Menter, A. (2016) 'Developing more open and equitable relationships with industry to improve advancements in clinical research in dermatology', *British Journal of Dermatology*, 174(6), pp. 1365–1369.

Cardot, J. M. *et al.* (2016) 'Implementing the Biopharmaceutics Classification System in Drug Development: Reconciling Similarities, Differences, and Shared Challenges in the EMA and US-FDA-Recommended Approaches', *The AAPS Journal*.

Chafulumira, A. F. (2009) 'Country data profile on the pharmaceutical situation in the SADC, Malawi'. Available at: http://www.who.int/medicines/areas/coordination/Malawiweb.pdf (Accessed: 2 November 2018).

Chaudhuri, S. (2010) 'R&D for development of new drugs for neglected diseases in India', *International Journal of Technology and Globalisation*, 5(1/2), p. 61.

Chen, B. A. *et al.* (2017) *Why has US Life Expectancy Fallen Below Other Countries?* Available at: https://crr.bc.edu/wp-content/uploads/2017/11/IB˙17-22.pdf.

Cheng, Z. and Xie, Z. (2017) 'Challenges in orphan drug development and regulatory policy in China', *Orphanet Journal of Rare Diseases*, 12(1), pp. 1–8.

Chu, S., Zhu, X. and Shi, Y. (2015) 'Influence of national cheap drug price reform on pharmaceutical industry', *Chinese Journal of New Drugs*.

Clarkson, M. E. (1994) 'A Risk-Based Model of Stakeholder Theory', in *Proceedings of the Second Toronto Conference on Stakeholders*. Toronto.

Clift, C. *et al.* (2015) *Towards a new global business model for antibiotics: Delinking revenues from sales*. Chatham House.

Clifton, G. T., Kohrt, H. E. and Peoples, G. E. (2015) 'Critical issues in cancer vaccine trial design', *Vaccine*, 33(51), pp. 7386–7392.

CMS (2018) *NHE Fact Sheet*. Available at: https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html (Accessed:

29 January 2019).

Cohen, J., Dibner, M. S. and Wilson, A. (2010) 'Development of and access to products for neglected diseases', *PLoS ONE*. Edited by J. S. Ross, 5(5), p. e10610.

Cohen, J. P. *et al.* (2016) 'Progress report on neglected tropical disease drug donation programs', *Clinical Therapeutics*, 38(5), pp. 1193–1204.

Compass (2015) *How to develop a logic model*. Available at: https://www.thecompassforsbc.org/how-to-guides/how-develop-logic-model-0 (Accessed: 7 November 2019).

Condon, D. L. *et al.* (2017) 'A cross-cutting approach to enhancing clinical trial site success: The Department of Veterans Affairs' Network of Dedicated Enrollment Sites (NODES) model', *Contemporary Clinical Trials Communications*.

Congress Budget Office (2006) *Research and development in the pharmaceutical industry*. Available at: https://www.cbo.gov/sites/default/files/109th-congress-2005-2006/reports/10-02-drugr-d.pdf (Accessed: 5 November 2019).

Cortright, J., Observatory, C. and Mayer, H. (2014) 'Signs of Life: The Growth of Biotechnology in Centers in the U.S.', (Accessed: 10 May 2019).

Country Economy (2018) *United States (USA) GDP – Gross Domestic Product*. Available at: https://countryeconomy.com/gdp/usa (Accessed: 29 January 2019).

Courtay-Cahen, C. (2018) 'Bringing new treatments to people suffering from neglected diseases – The DNDi initiative', *Regulatory Rapporteur*, 15(6), pp. 22–25.

Creswell, J. (2014) *Research design: Qualitative methods*. Available at: https://researchskillsgmm.files.wordpress.com/2014/10/research-design-creswell-chapter-9.pdf (Accessed: 14 October 2019).

Dandona, L. *et al.* (2017) 'Mapping of health research funding in India', *National Medical Journal of India*.

Darmon, R. Y., Duclos, L. G. and Rigaux, B. B. (2013) 'A measure of dynamic market performance', *American Journal of Industrial and Business Management*, 2013(April), pp. 164–177.

Davey, L. (1991) 'The application of case study evaluations', *Practical Assessment, Research and Evaluation*, 2(9).

Defense Aquisition University Press (2001) *US Department of Defense Systems Management College*. Available at: http://ocw.mit.edu/courses/aeronautics-and-astronautics/16-885j-aircraft-systems-engineering-fall-2005/readings/sefguide˙01˙01.pdf (Accessed: 10 October 2019).

DHHS (2016) 'Clinical trials registration and results information submission', *Federal Register*.

Dickson, A., Adu-Agyem, J. and Emad Kamil, H. (2018) 'Theoretical and conceptual framework: Mandatory ingredients of a quality research', *International Journal of Scientific Research*, 7(1), pp. 438–441.

Dimitri, N. (2012) 'R&D Incentives for Neglected Diseases', *PLoS ONE*. Edited by A. R. Hernandez Montoya, 7(12), p. e50835.

Donnelly, G. (2018) *Here's Why Life Expectancy in the U.S. Dropped Again This Year*. Available at: http://fortune.com/2018/02/09/us-life-expectancy-dropped-again/ (Accessed: 29 January 2019).

Dorlo, T. P. C. *et al.* (2012) 'Commentary: Substandard medicines are the priority for neglected tropical diseases', *BMJ (Online)*, 345(7884), pp. 1–2.

Droppert, H. and Bennett, S. (2015) 'Corporate social responsibility in global health: An exploratory study of multinational pharmaceutical firms', (April).

Dudovskiy, J. (2018) 'The ultimate guide to writing a dissertation in business studies: A step-by-step assistance', *Research Methodology*.

Dudovskiy, J. (2019) *Research methodology: Fundamental research*. Available at: https://research-methodology.net/research-methodology/research-types/fundamental-research/ (Accessed: 16 November 2019).

Eichler, H. G. *et al.* (2008) 'Balancing early market access to new drugs with the need for benefit/risk data: A mounting dilemma', *Nature Reviews Drug Discovery*.

Eisenhardt, K. M. (1989) 'Building Theories from Case Study Research', *Academy of Management Review*.

Elwin, P. and Hirst, R. (2007) *Guide to key performance indicators*. PricewaterhouseCoopers.

Emmanuel, E. J. and Emmanuel, L. L. (1996) 'What is accountability in health care?', *Annals of Internal Medicine*, 124(2), pp. 229–239.

Fatt, Q. K. and Ramadas, A. (2018) 'The usefulness and challenges of big data in healthcare', *Journal of Healthcare Communications*, 03(02), pp. 1–4.

FDA (2021) *Development & approval process*. Available at: https://www.fda.gov/drugs/development-approval-process-drugs (Accessed: 7 February 2021).

Fehr, A., Thürmann, P. and Razum, O. (2011) 'Expert Delphi survey on research and development into drugs for neglected diseases', *BMC Health Services Research*. BioMed Central Ltd, 11(1), p. 312.

Fenwick, A. (2012) 'The global burden of neglected tropical diseases', *Public Health*, 126(3), pp. 233–236.

Ferpozzi, H. (2018) 'Public participation and the co-production of open scientific knowledge: What is at stake?', in *Information Services and Use*.

Fitchetta, J. R., Lib, J. F. and Atuna, R. (2016) 'Innovative financing for late-stage global health research and development: The Global Health Investment Fund', *International Health*.

Gallini, N. (2017) 'Do patents work? Thickets, trolls and antibiotic resistance', *Canadian Journal of Economics*.

Geraghty, J. A. (2009) 'Expanding the biopharmaceutical industry's involvement in fighting neglected diseases', *Health Affairs*, 28(6), pp. 1774–1777.

Global Forum for Health Research (2004) *The 10/90 report on health research 2003–2004*. Edited by S. Davey. Global Forum for Health Research.

Gokhale, S. G. and Gokhale, S. (2016) 'Shuffling adaptive clinical trials', *American Journal of Therapeutics*, 23(3), pp. e663–e669.

Grabowski, H. G., DiMasi, J. A. and Long, G. (2015) 'The roles of patents and research and development incentives in biopharmaceutical innovation', *Health Affairs*, 34(2), pp. 302–310.

Granville, B. and Trushin, E. (2010) *The hope for neglected diseases: R&D incentives*.

Griffiths, S. (2008) 'Pharmaceutical branding: To brand or not to brand', *Journal of Medical Marketing*.

Gul, R. B. and Ali, P. A. (2010) 'Clinical trials: The challenge of recruitment and retention of participants', *Journal of Clinical Nursing*.

Gupta, K. K. *et al.* (2016) 'Basic concepts for sample size calculation: Critical step for any clinical trials', *Saudi Journal of Anaesthesia*, 10(3), pp. 328–331.

Hammer, M. and Champy, J. (1993) 'Re-engineering the corporation: A manifesto for business revolution', *Business Horizons*, 36(5), pp. 90–91.

Hammer, M. J., Eckardt, P. and Barton-Burke, M. (2016) 'Informed consent: A clinical trials perspective', *Oncology Nursing Forum*, 43(6), pp. 694–696.

Harrington, J. A., Hernandez-Guerrero, T. C. and Basu, B. (2017) 'Early Phase Clinical Trial Designs – State of Play and Adapting for the Future', *Clinical Oncology*.

Hassoun, N. (2012) 'Global health impact: A basis for labeling and licensing campaigns?', *Developing World Bioethics*, 12(3), pp. 121–134.

Hay, M. *et al.* (2014) 'Clinical development success rates for investigational drugs', 32(1).

Hayes, R., Kyer, B. and Weber, E. (2015) 'The Case Study Cookbook', pp. 1–27. Available at: https://web.wpi.edu/Pubs/E-project/Available/E-project-121615-164731/unrestricted/USPTO˙CookbookFinal.pdf (Accessed: 15 February 2020).

Henry, D. and Searles, A. (2012) 'Pharmaceutical pricing policy', in *Managing access to medicines and health technologies*. Arlington: Management Sciences for Health. Available at: http://apps.who.int/medicinedocs/documents/s19577en/s19577en.pdf (Accessed: 20 July 2019).

Herrling, P. (2009) 'Financing R&D for neglected diseases', *Nature Reviews*, 8(February), p. 91.

Hill, A. M. (2013) 'Ambigious regulation and questuinable patentability: A toxic future for in vitro companion diagnostic device and personalized medicine'. Available at: http://wisconsinlawreview.org/wp-content/uploads/2014/01/5-Hill-Final.pdf (Accessed: 7 May 2020).

Ho, D., Zarrinpar, A. and Chow, E. K. H. (2016) 'Diamonds, Digital Health, and Drug Development: Optimizing Combinatorial Nanomedicine', *ACS Nano*, 10(10), pp. 9087–9092.

Hoebel, J. *et al.* (2017) 'Socioeconomic inequalities in health and perceived unmet needs for healthcare among the elderly in Germany', *International Journal of Environmental Research and Public Health*, 14(10).

Hoen, E. F. (2009) *The global politics of pharmaceutical monopoly power*. AMB. Available at: www.msfaccess.org (Accessed: 5 November 2019).

Hoen, E. F. (2016) *Private Patents and Public Health, Changing Intellectual Property Rules for Access to Medicines*. Amsterdam: Health Action International. Available at: www.accesstomedicines.org (Accessed: April 2020).

Hoffman, S. J. *et al.* (2014) 'Assessing 15 proposals for promoting innovation and access to medicines globally', *Annals of Global Health*.

Holland, S. and Bátiz-Lazo, B. (2005) *The Global Pharmaceutical Industry*, Instructor's Manual. Available at: https://www.researchgate.net/profile/Sarah˙Holland4/publication/265114484˙The˙Global˙Pharmaceutical˙Industry/links/547489970cf2778985abe60a.pdf (Accessed: 14 January 2019).

Holt, F., Gillam, S. J. and Ngondi, J. M. (2012) 'Improving access to medicines for neglected tropical diseases in developing countries: Lessons from three emerging economies', *PLoS Neglected Tropical Diseases*. Edited by R. Correa-Oliveira, 6(2), p. e1390.

Hotez, P. J. (2008) 'Stigma: The stealth weapon of the NTD', *PLoS Neglected Tropical Diseases*, 2(4), pp. 1–2.

Hotez, P. J. (2013) 'NTDs V.2.0: "Blue Marble Health" – Neglected Tropical Disease Control and Elimination in a Shifting Health Policy Landscape', *PLoS Neglected Tropical Diseases*, 7(11).

Hotez, P. J. (2017) 'Developing and financing neglected disease vaccines in our new era of "blue marble health" and the anthropocene epoch', *Vaccine*.

Hunter, J. (2011) 'Challenges for pharmaceutical industry: new partnerships for sustainable human health', in *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*.

Hussaarts, L. *et al.* (2017) 'Product development programs for neglected tropical diseases: A crucial role for expert meetings', *PLoS Neglected Tropical Diseases*, 11(2), pp. 1–7.

IFPMA (2017) *The pharmaceutical industry and global health: Facts and figures 2017*. Geneva.

IGI Global (2018) *What is market performance*. Available at: https://www.igi-global.com/dictionary/market-performance/48121 (Accessed: 17 October 2018).

IHME (2019) *GBD results tool*. Available at: http://ghdx.healthdata.org/gbd-results-tool

(Accessed: 3 February 2019).

Influenza (2016) 'More than just numbers: Exploring the concept of "burden of disease" '. National Collaborating Centre for Infectious Diseases. Available at: https://nccid.ca/wp-content/uploads/sites/2/2016/07/ExploringBoD˙E.pdf (Accessed: 20 October 2020).

Institute of Medicine (2009) *Breakthrough business models: Drug development for rare and neglected diseases and individualized therapies: Workshop summary*. Washington, DC: The National Academic Press.

Institute of Medicine & Committee on Quality of Health Care in America (2001) *Crossing the quality chasm: A new health system for the 21st century*, *British Medical Journal*.

International Federation of Pharmaceutical Manufacturers & Associations (2015) 'Pharmacovigilance good pharmacovigilance principles and considerations for biotherapeutic medicines'. Available at: https://www.ifpma.org/wp-content/uploads/2016/02/IFPMA-PV-Brochure.pdf (Accessed: 19 September 2019).

International Labour Office (2010) *A skilled workforce for strong, sustainable and balanced growth: A G20 training strategy*, *International Labour Office*.

Ioset, J. R. and Chang, S. (2011) 'Drugs for neglected diseases initiative model of drug development for neglected diseases: Current status and future challenges', *Future Medicinal Chemistry,* 3(11), pp. 1361–1371.

Jabareen, Y. (2009) 'Building a conceptual framework: Philosophy, definitions, and procedure', *International Journal of Qualitative Methods*, 8(4), pp. 49–62.

Jackson, V. H. (2010) *Healthy children and families: Reducing behavioral health disparities in rural and frontier areas*. Georgetown University: Washington.

Jackson, V. H. (2018) 'A look at disparities by availability, accessibility, affordability, appropriateness, acceptability', *Data not available*.

Jacobs, B. *et al.* (2012) 'Addressing access barriers to health services: An analytical framework for selecting appropriate interventions in low-income Asian countries', *Health Policy and Planning*, 27(4), pp. 288–300.

Jaczynska, E., Outterson, K. and Mestre-ferrandiz, J. (2015) 'Business model options for antibiotics learning from other industries', *Chatham House, The Royal Institute of International Affairs (London) and the Big Innovation Centre (London)*, 24(February), pp. 1–42.

Jakobsen, P. H., Wang, M. W. and Nwaka, S. (2011) 'Innovative partnerships for drug discovery against neglected diseases', *PLoS Neglected Tropical Diseases*. Edited by T. G. Geary, 5(9), p. e1221.

Jalava, J. and Pohjola, M. (2002) 'Economic growth in the new economy: Evidence from advanced economies', *Information Economics and Policy*, 14(2), pp. 189–210.

Jamasoft (2014) *Pharmaceutical distribution (and wholesaling)*. Available at: https://www.fpharm.uniba.sk/fileadmin/faf/Pracoviska-subory/KORF/Texty˙ENG/Propedeutics/12˙Pharmaceutical˙distribution˙and˙wholesaling.pdf (Accessed: 25 November 2018).

Jennings, C. G. *et al.* (2015) 'Does offering an incentive payment improve recruitment to clinical trials and increase the proportion of socially deprived and elderly participants?', *Trials,* pp.2-9.

Johnson, T. and Kar, S. (2014) 'Open source drug discovery for neglected diseases', in *Collaborative Innovation in Drug Discovery: Strategies for Public and Private Partnerships*.

Jones, C. W. *et al.* (2015) 'Comparison of registered and published outcomes in randomized controlled trials: A systematic review', *BMC Medicine*, 13(1).

Kagan, J. *et al.* (2016) 'Assessing clinical research capacity in Vietnam: A framework for strengthening capability for clinical trials in developing countries', *Public Health Reports*.

Kameda, K. (2014) 'Needs-driven versus market-driven pharmaceutical innovation: The consortium

for the development of a new medicine against malaria in Brazil', *Developing World Bioethics,* 14(2), pp. 101–108.

Kataria, M. K. *et al.* (2011) 'An insight on regulations governing orphan diseases and drugs', *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 2(3), pp. 373–384.

Keating, C. (2014) 'Ken Warren and the Rockefeller foundation's great neglected diseases network, 1978–1988: The transformation of tropical and global medicine', *Molecular Medicine*.

Kellar, E. *et al.* (2017) 'Optimizing the use of electronic data sources in clinical trials: The technology landscape', *Therapeutic Innovation and Regulatory Science*.

Kent, D. M. *et al.* (2010) 'Assessing and reporting heterogeneity in treatment effects in clinical trials: A proposal', *Trials*.

Kenton, W. (2018) *Investopedia: Market Power*. Available at: https://www.investopedia.com/terms/m/market-power.asp (Accessed: 20 August 2018).

Kim, H. R. (2014) 'Formulation of a success model in pharmaceutical R&D: Efficient innovation model', *SAGE Open*.

Kirigia, J. *et al.* (2015) 'Counting the cost of child mortality in the World Health Organization African region', *BMC Public Health*, 15(1103).

Kirigia, J. M. and Mburugu, G. N. (2017) 'The monetary value of human lives lost due to neglected tropical diseases in Africa', *Infectious Diseases of Poverty*, 6(1).

Koeberle, M. and Schiemenz, W. (2017) 'QbD: Improving pharmaceutical development and manufacturing workflows to deliver better patient outcomes', *Pharmaceutical Technology*, (4), pp. S20–S23.

Koh Jun, O. (2012) 'Optimal use of donor funding to incentivize vaccine research & development for neglected diseases: An analysis of different R&D incentive mechanisms', *Journal of Public and International Affairs*, (80), pp. 80-103.

Kola, I. and Landis, J. (2004) 'Can the pharmaceutical industry reduce attrition rates?', *Nature Reviews Drug Discovery*, (August).

Kondal, A., Krishna, G. V. M. and Bansal, D. (2016) 'Clinical Trial Regulations in India: Progress and Challenges Arising from Recent Amendments to Schedule Y of the Drugs and Cosmetics (D&C) Act 1940 (D&C Rules 1945)', *Pharmaceutical Medicine*.

Kuada, J. (2016) 'A framework for market opportunity analysis', in *Marketing Decisions and Strategies – An International Perspective*. Adonis and Abbey Publishers: London.

Kurt, A. *et al.* (2017) 'Racial differences among factors associated with participation in clinical research trials', *Journal of Racial and Ethnic Health Disparities*, 4(5), pp. 827–836.

Larsen, J. (2016) 'Economic incentives for antibiotic development: An overview', *BARDA*.

Le, J. (2014) 'Financing sustainable drug development for neglected diseases: A case of push-pull mechanisms and global public goods', *Economic and Social Review*, 45(2), pp. 245–259.

Lee, B. Y., Bartsch, S. M. and Gorham, K. M. (2015) 'Economic and financial evaluation of neglected tropical diseases', *Advances in Parasitology*, 87, pp. 329–417.

Lee, Howard *et al.* (2017) 'Failure mode and effects analysis drastically reduced potential risks in clinical trial conduct', *Drug Design, Development and Therapy*.

Lehman, B. (2003) *The pharmaceutical industry and the patent system*. Available at: https://users.wfu.edu/mcfallta/DIR0/pharma˙patents.pdf (Accessed: 30 March 2019)insert date accessed/date not available).

Leisinger, K. M., Garabedian, L. F. and Wagner, A. K. (2012) 'Improving access to medicines in low and middle income countries: corporate responsibilities in context', *Southern Med Review*.

Lendrem, D. *et al.* (2015) 'R&D productivity rides again?', *Pharmaceutical Statistics*, 14(1), pp. 1–

3.

Levaggi, R., Moretto, M. and Pertile, P. (2017) 'The dynamics of pharmaceutical regulation and R&D investments', *Journal of Public Economic Theory*, 19(1), pp. 121–141.

Li, J. F. and Garnsey, E. (2014) 'Policy-driven ecosystems for new vaccine development', *Technovation*.

Li, R. H. *et al.* (2016) 'Incorporating ethical principles into clinical research protocols: A tool for protocol writers and ethics committees', *Journal of Medical Ethics*, 42(4), pp. 229–234.

Lichtenberg, F. R. (2005) 'Pharmaceutical innovation and the burden of disease in developing and developed countries', *Journal of Medicine and Philosophy*, 30(6), pp. 663–690.

Liese, B. H. and Schubert, L. (2009) 'Official development assistance for health – how neglected are neglected tropical diseases? An analysis of health financing', *International Health*, 1(2), pp. 141–147.

Light, D. W. (2009) 'Advanced market commitments, current realities and alternate approaches', *Health Action International (HAI) Europe*, (June), pp. 1–38.

Logan, J. K. *et al.* (2017) 'Analysis of factors affecting successful clinical trial enrollment in the context of three prospective, randomized, controlled trials', *International Journal of Radiation Oncology, Biology, Physics*.

Løkke, A. and Sørensen, P. D. (2014) 'Theory Testing Using Case Studies Interdisciplinary Centre for Organizational Architecture (ICOA), School of Business and Social', *The Electronic Journal of Business Research Methods*, 12(1), pp. 66–74.

Lopez, A. D. *et al.* (2014) 'Remembering the forgotten non-communicable diseases', *BMC Medicine*, 12(1).

Luchetti, M. (2014) 'Global health and the 10/90 gap', *British Journal of Medical Practitioners*, 7(December). Available at: https://www.researchgate.net/publication/270048142 (Accessed: 18 March 2019).

Maarouf, H. (2019) 'Pragmatism as a supportive paradigm for the mixed research approach: Conceptualizing the ontological, epistemological, and axiological stances of pragmatism', *International Business Research*, 12(9), p. 1.

Mackey, T. K. and Liang, B. A. (2012) 'Global health policy coordination to address neglected tropical diseases', *Tropical Medicine & International Health*, 17(9), pp. 1053–1056.

Mahmoodabad, S. S. M. *et al.* (2017) 'Investigating the factors related to substance use in the Iranian high school students using the positive youth development model', *Iranian Journal of Psychiatry and Behavioral Sciences*.

Mahmoud, A. and Zerhounl, E. (2009) 'Neglected tropical diseases: Moving beyond mass drug treatment to understanding the science', *Health Affairs*, 28(6), pp. 1726–1733.

Manjit Kaur; Sarah Hall (2002) 'Medical supplies and equipment for primary health care – A practical resource for procurement and management', *Transactions of the Royal Society of Tropical Medicine and Hygiene*.

Manu, T. (2014) 'Exploring a regional pharmaceutical innovation network as a possible solution to the market failure in the innovation of essential medicines for tropical diseases in sub-Saharan Africa', *African Journal of Science, Technology, Innovation and Development*.

Marshall, C. (1984) 'The case study evaluation', *Evaluation and Program Planning*, 7(3), pp. 253–266.

Martin, A. B. *et al.* (2019) 'National health care spending in 2017: Growth slows to post-great recession rates', *Health Affairs*, 38(1).

Martin, B. R. (2016) 'R&D policy instruments – a critical review of what we do and don't know', *Industry and Innovation*.

Martinez, D. A. *et al.* (2016) 'Activating clinical trials: A process improvement approach', *Trials*.

Mathur, S. *et al.* (2015) 'Rising to the Challenges of Clinical Trial Improvement in Parkinson's Disease', *Journal of Parkinson's Disease*.

Maurer, S. M., Rai, A. and Sali, A. (2004) 'Finding cures for tropical diseases: is open source an answer?', *PLoS Medicine*.

Maxmen, A. (2016) 'Busting the billion-dollar myth: how to slash the cost of drug development', *Nature*, 536(7617), pp. 388–390.

Maxwell, J. A. (2005) 'A model for qualitative research design', in *Qualitative Research Design: An Interactive Approach*.

Mayo, C. S. *et al.* (2017) 'Big data in designing clinical trials: Opportunities and challenges', *Frontiers in Oncology*, 7(August).

Mccabe, C., Claxton, K. and Hagan, A. O. (2008) 'Why licensing authorities need to consider the net value of new drugs in assigning review priorities : Addressing the tension between licensing and reimbursement', *International Journal of Technology Assessment in Health Care*, 24(2), pp. 140–145.

McGrath, S. K. and Whitty, S. J. (2017) 'Stakeholder defined', *International Journal of Managing Projects in Business*, 10(4), pp. 721–748.

McKinsey & Company (2017) 'Digital R&D: The Next Frontier for Biopharmaceuticals'. Available at: https://www.mckinsey.com/~/media/McKinsey/Industries/Pharmaceuticals and Medical Products/Our Insights/Digital RD The Next Frontier for Biopharmaceuticals/DigitalRDthenextfrontierforbiopharma.ashx (Accessed: 2 September 2019).

Mesut, B., Özsoy, Y. and Aksu, B. (2015) 'The place of drug product critical quality parameters in quality by design (QBD)', *Turkish Journal of Pharmaceutical Sciences*.

Milton, I. (1993) 'National Health Systems Throughout the World: Lessons for Health System Reform in the United States'. *American Behavioral Scientist*. 1993;36(6):694-708.

MindTools (2019) *Porter's Five Forces: Understanding Competitive Forces to Maximize Profitability*. Available at: https://www.mindtools.com/pages/article/newTMC˙08.htm (Accessed: 14 January 2019).

Mirsaidi, C. K. (2016) 'Integrating drug discovery and development to improve efficiency & candidate success', *American Pharmaceutical Review*.

Mitchell, A. (2018) 'A review of mixed methods, pragmatism and abduction techniques', *Electronic Journal of Business Research Methods*, 16(3), pp. 103–116.

Moatti, M. *et al.* (2016) 'A Bayesian hybrid adaptive randomisation design for clinical trials with survival outcomes', *Methods of Information in Medicine*, 55(1), pp. 4–13.

Molyneux, D. H. (2017) 'The London Declaration on Neglected Tropical Diseases: 5 years on', *Transactions of The Royal Society of Tropical Medicine and Hygiene*.

Molyneux, D. H., Savioli, L. and Engels, D. (2017) 'Neglected tropical diseases: progress towards addressing the chronic pandemic', *The Lancet*, 389(10066), pp. 312–325.

Moon, S., Bermudez, J. and Hoen, E. (2012) 'Innovation and access to medicines for neglected populations: Could a treaty address a broken pharmaceutical R&D system?', *PLoS Medicine*.

Moran, M. (2005) 'A breakthrough in R&D for neglected diseases: New ways to get the drugs we need', *PLoS Medicine*, 2(9), pp. 0828–0832.

Moran, M. (2014) 'History and overview of pooled funding mechanisms', in *Global Health Technologies Coaltition*.

Morland, J. K. *et al.* (1992) 'A Case for the Case Study', *Social Forces*.

Mossialos, E. *et al.* (2010) 'Policies and incentives for promoting innovation in antibiotic research',

World Health Organization. Regional Office for Europe, pp. 1–197. Available at: http://www.euro.who.int/en/home/projects/observatory/publications (Accessed: 26 September 2019

Mouton, J. (2001) *How to succeed in your Master's and Doctoral Studies: A South African Guide and Research Book*. Pretoria: Van Schaik Publishers.

MSF (2001) 'Fatal imbalance: The crisis in research and development for drugs for neglected diseases', *Geneva Campaign for Access to Essential Medicines/MSF*.

MSF (2014) 'Drugs for the poor, drugs for the rich: Why the current R&D model doesn't deliver', pp. 1–7. Available at: https://blogs.plos.org/speakingofmedicine/2014/02/14/drugs-poor-drugs-rich-current-rd-model-doesnt-deliver-2/ (Accessed: 20 March 2019).

Mueller-Langer, F. (2013a) 'Neglected infectious diseases: Are push and pull incentive mechanisms suitable for promoting drug development research?', *Health Economics, Policy and Law*, 8(2), pp. 185–208.

Mueller-Langer, F. (2013b) 'Neglected infectious diseases: Are push and pull incentive mechanisms suitable for promoting drug development research?', *Health Economics, Policy and Law*, 8(2), pp. 185–208.

Munos, B. (2006) 'Can open-source R&D reinvigorate drug research?', *Nature Reviews Drug Discovery*, 5, pp. 723–729.

Munos, B. (2009) 'Lessons from 60 years of pharmaceutical innovation', *Nature Reviews Drug Discovery*. Nature Publishing Group, 8(12), pp. 959–968.

Musgrove, P. *et al.* (2000) *The World Health Report*. Geneva. Available at: https://www.who.int/whr/2000/en/whr00˙en.pdf?ua=1 (Accessed: 27 January 2019).

Musgrove, P. and Hotez, P. J. (2009) 'Turning neglected tropical diseases into forgotten maladies', *Health Affairs*, 28(6), pp. 1691–1706.

Naci, H., Carter, A. W. and Mossialos, E. (2015) 'Why the drug development pipeline is not delivering better medicines'.

Nagpal, S., Sinclair, D. and Garner, P. (2013) 'Has the NTD community neglected evidence-based policy?', *PLoS Neglected Tropical Diseases*, 7(7), pp. 2–4.

Nelson, V. and Martin, A. (2013) 'The strategic use of case studies', pp. 1–59.

Nemat, R. (2011) 'Taking a look at different types of e-commerce', *World Applied Programming*, 1(June), pp. 100–104.

Newman, A. B. *et al.* (2016) 'Embedding clinical interventions into observational studies', *Contemporary Clinical Trials*, 46, pp. 100–105.

Nicholson, S. (2012) *Financing research and development*, The Oxford Handbook of the Economics of the Biopharmaceutical Industry. United Kingdom: Oxford University Press.

Niëns, L. M. and Brouwer, W. B. F. (2013) 'Measuring the affordability of medicines: Importance and challenges', *Health Policy* , 112(1–2), pp. 45–52.

NIH (2017) 'FAQs About Rare Diseases'. *Genetic and Rare Diseases Information Centre*. Available at: https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases (Accessed: 29 October 2019).

Novak, M. T. *et al.* (2013) 'Diagnostic tools and technologies for infectious and non-communicable diseases in low-and-middle-income countries', *Health and Technology*, 3(4), pp. 271–281.

Novasecta (2018) *Top 100 pharma companies shaping the future of healthcare*. Available at: https://pharmaboardroom.com/facts/top-100-pharma-companies-globally/ (Accessed: 16 November 2019).

Nuffield Council on Bioethics (2016) *Genome editing: An ethical review*. Available at: https://www.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf (Accessed: 5 November 2019).

Nugent, T., Upton, D. and Cimpoesu, M. (2016) 'Improving data transparency in clinical trials using blockchain smart contracts', *F1000Research*.

O'Keefe, J. and Wintermantel, T. (2013) 'Unleashing pharma from the R&D value chain'. A.T. Kearney, pp. 1–15.

OECD (2009) 'Unmet health care needs', *Health at a Glance 2009: OECD Indicators*. Paris: OECD Publishing, pp. 142–143.

de Oliveira, E. A. M. and Lang, K. L. (2018) 'Drug repositioning: Concept, classification, methodology, and importance in rare/orphans and neglected diseases', *Journal of Applied Pharmaceutical Science*, 8(8), pp. 157–165.

van Olmen, J. *et al.* (2010) 'Analysing health systems to make them stronger', *Studies in Health Services Organisation & Policy*.

Olmsted, S. S. *et al.* (2006) 'Developing and interpreting models to improve diagnostics in developing countries', *Nature*, pp. 3–8.

Outterson, K. (2004) *Pharmaceutical Arbitrage: Balancing access and innovation in international prescription drug markets*. Available at: http://whqlibdoc.who.int/hq/2001/a73725.pdf (Accessed: 5 November 2019).

Oxford University Press (2019) *Oxford Learner's Dictionary*. Available at: https://www.oxfordlearnersdictionaries.com/definition/english/verification.

Pacheco, L. M. *et al.* (2016) *The SWITCH-ON market analysis framework: Support to European innovators on commercialising water information products*.

Panchal, S. K., Khan, B. M. and Ramesh, S. (2012) 'Importance of "brand loyalty, brand awareness and perceived quality parameters" in building brand equity in the Indian pharmaceutical industry', *Journal of Medical Marketing*.

Parker, C. *et al.* (2017) 'A randomized controlled trial of an additional funding intervention to improve clinical trial enrollment', *JNCCN Journal of the National Comprehensive Cancer Network*.

Payne, D. J. *et al.* (2015) 'Time for a change: Addressing R&D and commercialization challenges for antibacterials', *Philosophical Transactions of the Royal Society B: Biological Sciences*.

Pefindo (2018) 'Pharmaceutical industry: Key success factors'. Available at: http://www.pefindo.com (Accessed: 25 November 2018).

Phadnis, M. A., Wetmore, J. B. and Mayo, M. S. (2017) 'A clinical trial design using the concept of proportional time using the generalized gamma ratio distribution', *Statistics in Medicine*.

PhRMA (2007) 'Drug discovery and development: Understanding the R&D process'. Washington, DC.

PhRMA (2015) 'Biopharmaceutical Research and Development: The Process Behind New Medicines.' Washington, DC. Available at: http://phrma-docs.phrma.org/sites/default/files/pdf/rd˙brochure˙022307.pdf

Pierce, R. J. *et al.* (2017) 'The future of drug development for neglected tropical diseases: How the European Commission can continue to make a difference', *Trends in Parasitology*.

Pogge, T. and Hollis, A. (2011) 'Epilogue: New drugs for neglected diseases', *Cambridge Quarterly of Healthcare Ethics: CQ: the International Journal of Healthcare Ethics Committees*, 20(2), pp. 329–334.

Pollastri, M. P. and Campbell, R. K. (2011) 'Target repurposing for neglected diseases', *Future Medicinal Chemistry*, 3(10), pp. 1307–1315.

Porter, M. E. (1991) 'Towards a dynamic theory of strategy', *Strategic Management Journal*, 12, pp. 95–117.

Porter, M. E. (2014) 'The five competitive forces that shape strategy'. Available at:

https://www.youtube.com/watch?v=WS0TfJGfKGk.

Porter, M. E. (2015) 'Michael Porter explains his famous five forces and how they can be used in business strategy'. Harvard Business Publishing. Available at: https://www.youtube.com/watch?v=WS0TfJGfKGk (Accessed: 20 November 2019).

ProductPlan (2019) *Roadmap Basics: What is a Roadmap?* Available at: https://www.productplan.com/roadmap-basics/ (Accessed: 8 November 2019).

PubMed (2019) *National Library of Medicine, National Institutes of Health*. Available at: https://www.ncbi.nlm.nih.gov/pubmed/ (Accessed: 16 November 2019).

Pugatch, M. P. (2011) 'Patent pools and collaborative initiatives : Assessing the efficacy of alternatives to IP in the development of new pharmaceutical drugs, especially for neglected diseases - an empirical analysis', *EJRR*, 4, pp. 566–571.

Pund, S. and Joshi, A. (2017) 'Nanoarchitectures for neglected tropical Protozoal diseases: Challenges and state of the art', *Nano- and Microscale Drug Delivery Systems: Design and Fabrication*, pp. 439–480.

PWC (2009) *Pharma 2020: Marketing the future - Which path will you take?*

Radulescu, V. (2012) 'Healthcare marketing contribution to the sustainable development of society', 2(11), pp. 351–358.

Raheja, K., Dubey, A. and Chawda, R. (2017) 'Data analysis and its importance in health care', *International Journal of Computer Trends and Technology*, 48(4), pp. 176–180.

Ramaraj, R. and Alpert, J. S. (2008) 'Indian poverty and cardiovascular disease'.

Ranade, K. *et al.* (2013) *Application of translational science to clinical development*, *Genomic Biomarkers for Pharmaceutical Development: Advancing Personalized Health Carevancing Personalized Health Care*.

RAND Corporation (2007) 'Estimating the global health impact of improved diagnostic tools for the developing world', p. 4. Available at: https://www.rand.org/pubs/research˙briefs/RB9293/index1.html (Accessed: 12 January 2019).

von Ranke, N. L., Fierro, I. M. and Antunes, A. M. S. (2016) 'Trends in biotechnological drugs for cancer treatment', *Recent Patents on Anti-Cancer Drug Discovery*, 11(1), pp. 112–120.

Rardin, R. L. (2007) 'Research agenda for heath care systems engineering'.

Ratain, M. J. and Sargent, D. J. (2009) 'Optimising the design of phase II oncology trials: The importance of randomisation', *European Journal of Cancer*.

Rauscher, M., Walkowiak, H. and Djara, M. B. (2018) 'Leadership, management, and governance evidence compendium: Medical products, vaccines, and technologies'.

Régnier, S. A. and Huels, J. (2013) 'Drug versus vaccine investment: A modelled comparison of economic incentives', *Cost Effectiveness and Resource Allocation*.

Reinstein, A. and Churyk, N. T. (2004) 'An overview of investor sentiment in stock market', (Thorp), pp. 1–7.

Renwick, M. J., Brogan, D. M. and Mossialos, E. (2016) 'A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics', *The Journal of Antibiotics*. Nature Publishing Group, 69(2), pp. 73–88.

Ricotti, V., Muntoni, F. and Voit, T. (2015) 'Challenges of clinical trial design for DMD', *Neuromuscular Disorders*.

Ridley, D. B. and Sánchez, A. C. (2010) 'Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases', *The Lancet*.

Riley, J. (2015) 'Porter's five forces model of industry competiton'. Available at: https://www.youtube.com/watch?v=cm9SsMa56r4 (Accessed: 18 November 2018).

Riley, S. (2015) 'Market Structure (Types of Competition)'. Available at:

https://slideplayer.com/slide/4453216/ (Accessed: 13 November 2018).

Røttingen, J. A. *et al.* (2013) 'Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?', *The Lancet*, 382(9900), pp. 1286–1307.

Rouse, W. B. (2008) 'Health care as a complex adaptive system: Implications for design and management', *Organization Science*, 38(1), p. 17.

Ruminski, P. G. (2011) 'From bench to clinic: bridging the translational gap in neglected disease drug development', *Future Medicinal Chemistry*, 3(10), pp. 1253–1257.

Russo, G. and Banda, G. (2015) 'Re-Thinking Pharmaceutical Production in Africa; Insights from the Analysis of the Local Manufacturing Dynamics in Mozambique and Zimbabwe', *Springer Science and Business Media*, pp. 258–281.

Sachs-Barrable, K. *et al.* (2014) 'The use of the United States FDA programs as a strategy to advance the development of drug products for neglected tropical diseases', *Drug Development and Industrial Pharmacy*, 40(11), pp. 1429–1434.

Salas, S. P. (2017) 'Ethical challenges posed by clinical trials in preterm labor: A case study', *Reproductive Health*, 14.

Saldana, J. (2009) *The Coding Manual for Qualitative Researchers*. Thousand Oaks, CA: SAGE Publications. Available at: https://stevescollection.weebly.com/uploads/1/3/8/6/13866629/saldana˙2009˙the-coding-manual-for-qualitative-researchers.pdf (Accessed: 14 October 2019).

Sanchez, A. C. (2014) 'The "priority review vouchers" for neglected pharmaceutical innovation and their impact on pharmaceutical patents', *Pharmaceuticals Policy and Law*.

Santana, R. S., Lupatini, E. O. and Leite, S. N. (2017) 'The regulation and adoption of health technologies under Brazil's unified health system: Barriers to access to medicines for diseases of poverty?', *Ciencia e Saude Coletiva*, 22(5), pp. 1417–1428.

Santo, do Espírito, R. D. *et al.* (2014) 'Use of Guanidine Compounds in the Treatment of Neglected Tropical Diseases', *Current Organic Chemistry,* 18(20), pp. 2572–2602.

Sarkar, A. N. (2013) 'Promoting eco-innovations to leverage sustainable development of eco-industry and green growth', *International Journal of Ecology and Development*, 25(2), pp. 71–104.

Saunders, M., Lewis, P. and Thornhill, A. (2009) 'Chapter 4: Understanding research philosophy and approaches to theory development', in *Research Methods for Business Students*.

Sauter, V. (2002) 'Decision support systems (DSS)'. Available at: http://www.umsl.edu/˜sauterv/analysis/488˙f02˙papers/dss.html (Accessed: 16 November 2019).

Saviano, M. *et al.* (2019) 'From Rare to Neglected Diseases: A Sustainable and Inclusive Healthcare Perspective for Reframing the Orphan Drugs Issue', *Sustainability*, 11(5), pp. 1–21.

Scannell, J. W. *et al.* (2012) 'Diagnosing the decline in pharmaceutical R&D efficiency', 11(March).

Scarchuk, M. (2013) 'Market Structures: Examples in the Real World'. Available at: https://prezi.com/htq7pljqr-it/market-structures-examples-in-the-real-world/ (Accessed: 8 August 2020)

Schneeweiss, S. *et al.* (2011) 'Assessing the comparative effectiveness of newly marketed medications: Methodological challenges and implications for drug development', *Clinical Pharmacology and Therapeutics*.

Schroeder, D. and Singer, P. (2011) 'Access to Life-Saving Medicines and Intellectual Property Rights: An Ethical Assessment', *Cambridge Quarterly of Healthcare Ethics*, 20(02), pp. 279–289.

Schuh, K. and Barab, S. (2007) '7 Philosophical Perspectives', *Philosophical Perspectives*, pp. 67–82.

Schulze, U. *et al.* (2014) 'R&D productivity: on the comeback trial', *Nature Reviews Drug Discovery*, 13, pp. 331–332.

Segen's Medical Dictionary (2012) Philadelphia: Farlex, Inc.

Sertkaya, A. *et al.* (2016) 'Key cost drivers of pharmaceutical clinical trials in the United States', *Clinical Trials*, 13(2), pp. 117–126.

Sewell, F. *et al.* (2016) 'Opportunities to apply the 3Rs in safety assessment programs', *ILAR Journal*.

Shapiro, B. S. *et al.* (2015) 'Freeze-all at the blastocyst or bipronuclear stage: A randomized clinical trial', *Fertility and Sterility*.

Shapley, S., O'Shaughnessy, J. and Woodcock, J. (2017) 'Center for drug evaluation and research perspective on quality in clinical trials', *Therapeutic Innovation and Regulatory Science*.

Shaw, D. L. and Ross, J. S. (2015) 'US Federal Government efforts to improve clinical trial transparency with expanded trial registries and open data sharing', *AMA Journal of Ethics*, 17(12), pp. 1152–1159.

Sheldon, T. (1998) 'Promoting health care quality: What role performance indicators?', *Quality in Health Care*, 7, pp. S45–S50.

Singh, S. and Loke, Y. K. (2012) 'Drug safety assessment in clinical trials: methodological challenges and opportunities', *Trials*, 13(1), p. 1.

Slovak, J. (2018) *The average profit margin of pharmaceuticals*. Available at: https://yourbusiness.azcentral.com/average-profit-margin-pharmaceuticals-20671.html (Accessed: 22 November 2018).

Smartsheet Inc. (2018) *What is the definition of strategic marketing?* Available at: https://www.smartsheet.com/strategic-marketing-processes-and-planning (Accessed: 20 August 2010).

Snapinn, S. (2017) 'Some remaining challenges regarding multiple endpoints in clinical trials', *Statistics in Medicine*.

So, A. D. and Ruiz-Esparza, Q. (2012) 'Technology innovation for infectious diseases in the developing world', *Infectious Diseases of Poverty*, 1(1), pp. 1–9.

Šolić, I. *et al.* (2017) 'Transparency and public accessibility of clinical trial information in Croatia: How it affects patient participation in clinical trials', *Biochemia Medica*, 27(2), pp. 259–269.

Souder, W. E. and Nassar, S. (1990) 'Choosing an R&D Consortium', *Research-Technology Management*.

Sowa, P. M., Butler, J. R. G. and Connelly, L. B. (2014) 'Unmet medical needs and health care accessibility in seven countries of Eastern Europe', *MPRA*. Available at: https://mpra.ub.uni-muenchen.de/75619/ (Accessed: 11 November 2019).

Spohn, D. (2004) *Evaluating Market Attractiveness – A New Venture Perspective*. Available at: https://www1.unisg.ch/www/edis.nsf/SysLkpByIdentifier/2917/$FILE/dis2917.pdf (Accessed: 13 September 2019).

Squire, S. B. (2015) 'CAHRD Consultation 2014: The 10-20 year Horizon Introduction and Overview – As Circulated to Consultation Participants', in *BMC Proceedings*.

Starr, A., Graef, K. M. and Dent, J. (2016) 'Fostering innovative product development for neglected tropical diseases through partnerships', *Pharmaceutical Patent Analyst*.

Statista (2019) *Community hospital beds per population U.S. 2000–2015*. Available at: https://www.statista.com/statistics/184546/community-hospital-beds-per-1000-population-in-the-us/ (Accessed: 29 January 2019).

Stevens, P. (2004) 'Diseases of poverty and the 90/10 gap', *International Policy Network*, p. 16.

Stolk, W. A. *et al.* (2016) 'Between-Country Inequalities in the Neglected Tropical Disease Burden

in 1990 and 2010, with Projections for 2020', *PLoS Neglected Tropical Diseases*.

Surowiecki, J. (2004) 'The pipeline problem', *The New Yorker*. Available at: https://www.newyorker.com/magazine/2004/02/16/the-pipeline-problem (Accessed: 20 August 2018).

Takeda, H. *et al.* (1990) 'Modeling design processes', *AI Magazine*, pp. 37–48.

Thacker, B. H. *et al.* (2004) 'Concepts of model verification and validation', Southwest Research Institute.

Thacker, T., Wegele, A. R. and Richardson, S. P. (2016) 'Utility of electronic medical record for recruitment in clinical research: From rare to common disease', *Movement Disorders Clinical Practice*, pp. 507–509.

Thakor, R. T. *et al.* (2017) 'Just how good an investment is the biopharmaceutical sector?', *Nature Biotechnology*, 35(12), pp. 1149–1157.

Thakor, R. T. and Lo, A. W. (2018) 'Competition and R&D Financing: Evidence from the Biopharmaceutical Industry', *MIT Sloan Research Paper*.

The World Bank (2019) *Malawi*. Available at: https://data.worldbank.org/country/malawi (Accessed: 27 January 2019).

The World Bank (2018) *Classifying countries by income*. Available at: http://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html (Accessed: 17 May 2019).

Tóth, P. and Zemčík, P. (2006) *What Makes Firms in Emerging Markets Attractive to Foreign Investors? Micro-Evidence from the Czech Republic*. Prague. Available at: https://www.cerge-ei.cz/pdf/wp/Wp294.pdf

Towse, A. *et al.* (2012) *Drugs and vaccines for developing countries*, The Oxford Handbook of the Economics of the Biopharmaceutical Industry. United Kingdom: Oxford University Press.

Tripathi, K. P. (2011) 'Decision support system is a tool for making better decisions in the organization', *Indian Journal of Computer Science and Engineering*, 2(1), pp. 112–117. Available at: http://www.ijcse.com/docs/IJCSE11-02-01-054.pdf (Accessed: 18 October 2019).

Trouiller, P. *et al.* (2002) 'Drug development for neglected diseases: a deficient market and a public health policy failure', *The Lancet*, 359(9324), pp. 2188–2194.

Tsourounis, M. *et al.* (2015) 'Challenges in the Development of Drug/Device and Biologic/Device Combination Products in the United States and European Union: A Summary from the 2013 DIA Meeting on Combination Products', *Therapeutic Innovation & Regulatory Science*.

Tsukamoto, K. *et al.* (2016) 'Improvement of pediatric drug sevelopment: Regulatory and practical frameworks', *Clinical Therapeutics*, 38(3), pp. 574–581.

Umemura, M. (2011) 'A second-tier performance: reflections on Japan's pharmaceutical industry, 1945–2005', *Japan Forum*, 23(2), pp. 207–233.

UNAIDS (2013) 'TRIPS transition period extensions for least-developed countries'. Geneva.

UNDP and UNAIDS (2012) *The potential impact of free trade agreements on public health*. Geneva.

UNICEF (2017) *Health Budget Brief: Malawi*.

UNITAID (2016) 'An Economic Perspective on Delinking the cost of R&D from the price of medicines'. Perspective on the Notion of "Human Capital". Is dit nie veronderstel om presies ooreen te stem nie?

United States Health (2017) 'Sources of payment for health care, by selected population characteristics: United States, selected years 1987–2013'. Available at: https://www.cdc.gov/nchs/data/hus/2016/098.pdf (Accessed: 21 August 2019).

Universal Health Coverage Partnership *et al.* (2016) 'Strategizing national health in the 21st century: a handbook', *World Health Organization*.

Urbšienė, L., Monkevičiūtė, R. and Navikaitė, U. (2014) 'Analysis of the attractiveness and competitiveness of the securities market', 93(3).

USAID (2013) 'Technical note: Evaluative case studies', (November), pp. 1–11. Available at: https://usaidlearninglab.org/ (Accessed: 17 February 2020).

Vaccine Alliance (2017) *Advance market commitment for pneumococcal vaccines*.

Van Aaken, J. E., Berends, H. and van der Bij, H. (2007) *Problem-solving in organizations*. Cambridge: Cambridge University Press.

Verbrugge, B. (2017) *Best Practice, Model, Framework, Method, Guidance, Standard: Towards a Consistent Use of Terminology*. Available at: https://www.vanharen.net/blog/best-practice-model-framework-method-guidance-standard-towards-consistent-use-terminology/ (Accessed: 8 November 2019).

Viergever, R. F. (2013) 'The mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken: an overview of the problem, the causes, and solutions', *Global Health Action*.

Viergever, R. F. and Li, K. (2015) 'Trends in global clinical trial registration: An analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013', *BMJ Open*, 5(9).

Villa, S., Compagni, A. and Reich, M. R. (2009) 'Orphan drug legislation: Lessons for neglected tropical diseases', *International Journal of Health Planning and Management*, 24(1), pp. 27–42.

Vischer, N. *et al.* (2017) ' "You can save time if ..." – A qualititative study on internal factors slowing down clinical trials in Sub-Saharan Africa', *Plos One*, 12(3).

Waters, H. (2011) 'Patent-sharing scheme for neglected diseases might have a catch', *Nature Medicine*, 17(12), p. 1529.

Web of Science Group (2019) *Web of Science*. Available at: https://clarivate.com/webofsciencegroup/solutions/web-of-science/ (Accessed: 16 November 2019).

Webber, D. and Kremer, M. (2001) 'Perspectives on stimulating industrial research and development for neglected infectious diseases', *Bulletin of the World Health Organization*, 79(8), pp. 735–741.

Wechsler, J. (2015) 'Breakthrough Drugs Raise Development and Production Challenges, *Pharmaceutical Technology*, 39(7), pp. 14–15.

Wechsler, Jill (2015) 'Manufacturers face key policy and regulatory challenges: Legislation to streamline drug development may get tangled up in user fee negotiations and drug pricing battles', *BioPharm International*.

Weilbaecher, A. (2009) 'Diseases Endemic in Developing Countries: How to Incentive Innovation', *Annals of Health Law*. Available at: https://lawecommons.luc.edu/cgi/viewcontent.cgi?article=1115&context=annals (voeg datum in wat bron geraadpleeg is)

Weng, H. B., Chen, H. X. and Wang, M. W. (2018) 'Innovation in neglected tropical disease drug discovery and development', *Infectious Diseases of Poverty*.

Whiteside, E. (2016) *The industry handbook: Pharma industry*. Available at: https://www.investopedia.com/articles/markets/051316/industry-handbook-pharma-industry.asp (Accessed: 21 November 2018).

WHO (2000) *WHO medicines strategy: Framework for action essential drugs and medicines policy 2000–2003*. Geneva. Available at: http://apps.who.int/medicinedocs/pdf/whozip16e/whozip16e.pdf (Accessed: 8 April 2019).

WHO (2002) 'The Global Burden of Disease concept', Available at https://www.who.int/quantifying˙ehimpacts/publications/en/9241546204chap3.pdf, pp. 27–40.

WHO (2003) *Poverty and Health*. Available at: www.SourceOECD.org (Accessed: 11 July 2021).

WHO (2010a) 'Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies', *WHO*, pp. 1–92.

WHO (2010b) 'The world health report: The path to universal coverage', *The World Health Report*, pp. 1–128.

WHO (2011a) *Local Production and Access to Medicines in Low- and Middle-Income Countries*.

WHO (2011b) *Pharmaceutical Production and Related Technology Transfer*. Available at: http://www.who.int/phi/en/%0Ahttp://%0Awww.who.int/about/licensing/copyright˙form/en/index.html (Accessed: 18 January 2021)

WHO (2012) *Why are Some Tropical Diseases Called Neglected?* Available at: http://www.who.int/features/qa/58/en/ (Accessed: 14 September 2018)

WHO (2015a) *Investing to Overcome the Global Impact of Neglected Tropical Diseases*. Available at: www.who.int (Accessed: 5 November 2019).

WHO (2015b) 'Malawi: Statistical Profile', *Country statistics and global health estimates*. Available at: http://who.int/gho/mortality˙burden˙disease/en/ (Accessed: 3 October 2018)

WHO (2015c) 'United States of America: WHO statistical profile'. Available at: http://www.who.int/gho/countries/usa.pdf (Accessed: 3 October 2018)

WHO (2016) 'The world medicines situation', *WHO*.

WHO (2017) *Global Tuberculosis Report (2017)* . Geneva. Available at: http://www.who.int/tb/publications/global˙report/gtbr2017˙main˙text.pdf

WHO (2018a) *Cancer: Factsheet*. Available at: http://www.who.int/news-room/fact-sheets/detail/cancer (Accessed: 20 August 2011).

WHO (2018b) 'Country Cooperation Strategy: Malawi', pp. 1–2.

WHO (2018c) *Essential Medicines*. Available at: http://www.who.int/topics/essential˙medicines/en/ (Accessed: 15 August 2018).

WHO (2018d) *The Global Tuberculosis Report 2018*. Geneva.

WHO (2018e) *World health statistics 2018: monitoring health for the SDGs, sustainable development goals*.

WHO (2020a) *Ending the neglect to attain the Sustainable Development Goals: A Road map for neglected tropical diseases 2021-2030*.

WHO (2020b) *Landscape of funding and financing opportunities for access and delivery of health technologies for neglected diseases*.

WHO (2020c) *Neglected tropical diseases: World Health Assembly endorses bold new road map targets for 2030*. Available at: https://www.who.int/news/item/12-11-2020-neglected-tropical-diseases-world-health-assembly-endorses-bold-new-road-map-targets-for-2030 (Accessed: 7 February 2021).

Wierzchowiecka, K. (2014) *Engineering Services in Poland: The Mining and Energy Industries*. Finland: Tampere University of Technology.

Willyard, C. (2013) 'Neglected diseases see few new drugs despite upped investment', *Nature Medicine*, 19(1), p. 2.

Wilson, C. (2013) 'Policies and research funding', in *Orphan drugs: Understanding the rare disease market and its dynamics*.

Wilson, C. (2016) *New technologies are accelerating drug development, bringing hope to patients*. Available at: https://www.elsevier.com/connect/new-technologies-are-accelerating-drug-development-bringing-hope-to-patients (Accessed: 5 November 2019).

Witty, A. (2011) 'New strategies for innovation in global health: A pharmaceutical industry perspective', *Health Affairs*.

Worldometers (2018) *Malawi population: Worldometers*. Available at: http://www.worldometers.info/world-population/malawi-population/ (Accessed: 19 November 2018).

Worrell, C. and Mathieu, E. (2012) 'Drug coverage surveys for neglected tropical diseases: 10 years

of field experience', *American Journal of Tropical Medicine and Hygiene*, 87(2), pp. 216–222.

Yin, R. K. (2014) *Case Study Research: Design and Methods* (5th ed.). Thousand Oaks, CA: SAGE Publications.

Young, A. *et al.* (2017) 'A census of actively licensed physicians in the United States', *Journal of Medical Regulation*, 103(2), pp. 7–21. Available at: https://www.fsmb.org/siteassets/advocacy/publications/2016census.pdf (Accessed: 23 September 2019).

Yousefi, N. *et al.* (2017) 'New product development in the pharmaceutical industry: Evidence from a generic market', *Iranian Journal of Pharmaceutical Research*.

Zhou, Y. *et al.* (2015) 'Choosing appropriate metrics to evaluate adverse events in safety evaluation', *Therapeutic Innovation and Regulatory Science*, 49(3), pp. 398–404.

APPENDICES

Appendix A: Pharmaceutical R&D influencing factors

A structured systematic literature review, completed in Section 3.1.2, resulted in 37 factors that influences the pharmaceutical R&D pipeline. The 37 influencing factors, as well as its occurrence, are depicted in this appendix.

No.	Disease setting and properties	Occurrence
1	Policy & Regulatory Issues including regulatory policy for orphan drug development	13
2	Setup of clinical trial phases and methodology; randomization in trials; and trial methodology	13
3	Participant recruitment and retention; enrolment & minority representation; and little clinical trial awareness	11
4	Complexity of trials; deal with multiple endpoints; better operational framework; clinical trial activation difficulty	10
5	Clinical trial risk	7
6	Lack of transparency; accountability; and accessibility of clinical trial information	7
7	Quality of clinical trial; improved use of innovative clinical trial tools; quality of pre-clinical trials	7
8	Physician participation; relationships between stakeholders; collaboration	6
9	Lack of capacity and funding; lack of return on investment	5
10	Ethical obstacles and issues	5
11	Complexity of the disease	4
12	Clinical trial registration and monitoring	4
13	Technological innovation and electronic medical record-based screening	4
14	Lack of health authority guidance; clinical trial result submission; and guidance & monitoring committees	4
15	Lack of interest of pharmaceutical organizations	3
16	Ineffective testing & manufacturing systems	2
17	Manufacturers & FDA can't meet demand and manufacturing strategies	2
18	Struggling to prove efficacy	2
19	Easier to show non-inferiority than superiority	2
20	Marketing related and low market potential (rare diseases)	2
21	Effective budget allocation; increased pharmaceutical cost; key direct cost drivers	2
22	Insufficient data on the disease	1
23	Lack of breakthrough drugs	1
24	Matrix of new targets, new agents & companion diagnostics	1
25	Adaptive clinical trials	1
26	Racial differences in participation in clinical trial	1
27	Difficult drug approval	1

No.	Disease setting and properties	Occurrence
28	Clinical trial globalization	1
29	In vitro alternative testing	1
30	Safety assessment	1
31	Statistical principles & methodologies	1
32	Data integrity	1
33	Structure based drug design	1
34	Block chain	1
35	Social media	1
36	Stakeholder demand	1
37	Lack of resources	1

Appendix B: Relationship between drugs in R&D and disease burden

The analysis completed to establish the relationship between drugs in R&D and disease burden, is described as in the section below.

1. Design of experiment

The null hypothesis of the test is as follow:

> H_0: There is no statistically significant correlation between GBD and the number of medicines currently in R&D.

To complete the analysis, data on (i) the burden of disease for all countries (2016) reported by (IHME, 2019); as well as data on (ii) the number of medicines in R&D (2018) as reported by the Access to Medicine Foundation (2018) was utilized. A descriptive statistical analysis included reconciling the disease categories for the two sets of data. A simple linear regression was carried out to test the significance of the relationship between burden of disease (independent variable) and medicines in R&D (dependent variable). The following assumptions were made for the regression analysis to be applied:

(i) The relationship between burden of disease and the number of medicines in R&D is linear;
(ii) The residuals are approximately normally distributed; and
(iii) Homoscedasticity[24] applies.

It could not be assumed that no observations have a large overall influence, as it was observed that the data set contains one outlier value. Consequently, the regression analysis was completed with and without the outlier value to observe differences in the results.

2. Findings

A linear regression scatterplot, as well as regression coefficients was derived from the reconciled set of data. Figure 3.1 (Section 3.4) indicates the linear regression analysis between the number of drugs in R&D (2018) and the GBD (2016).

The scatterplot indicates that the two measures are directly proportionate to one another. The aforementioned is supported by the statistical analysis outputs. The correlation coefficient ($r = 0.5831$) indicates that a strong positive relationship exists between the number of drugs in R&D and the GBD. In support, the linear regression indicated that at a 5% confidence level, a significant relationship exists between the number of drugs in R&D, and the GBD ($p = 0.0009$). The null hypothesis can therefore be rejected, as a significant relationship between the two variables is evident. However, the R^2 value of the analysis ($R^2 = 0.3399$) indicates that only 34% of the variation in number of medicines allocated can be explained by the G

[24] When all the random variables in a set of data have the same finite variance.

Appendix C: Market analysis methods

The following sections describe seven market analysis methods and a brief description of each.

1. Framework for market opportunity analysis

Market opportunity analysis, according to Wierzchowiecka (2014) is the process of evaluating the market opportunities in a market. According to Kuada (2017) the primary determinants of market opportunity includes, the size of the market, marketing requirements to satisfy market expectation, and competitors' marketing strategies. Kuada also states that the determinants can be established by completing the following five analyses.

(i) Demand analysis;
(ii) segmentation analysis;
(iii) industry analysis;
(iv) competitor analysis; and
(v) channel analysis.

The concept behind this market analysis method is that each of the five analyses identifies essential information that will explain, provide information of, and give insight into the three primary determinants that influences market opportunity.

2. Aaker's strategic market analysis

Aaker (2013) focuses his research on the strategic management of markets. Aaker states that strategic market management is a system that enables management to investigate current, create new, and alter existing business strategies. In order to complete this strategic management, three principle elements are required, namely: (i) strategic analysis; (ii) strategic analysis outputs; and (iii) creating, adapting and implementing strategy. For this research, focus will be placed on the first two analyses of this management structure.

A market opportunity analysis contains two independent aspects, namely an internal and external analyses (Aaker, 2013). The external analysis includes analyzing customer, competitor, market and environmental analysis. The internal analysis includes evaluating the company itself and defining its performance and strategic goals. Figure B.1 shows the strategic market analysis suggested in (Aaker, 2013). The strategic analysis outputs, second step of the Aaker's strategic management analysis, comprises of the findings in the strategic analysis, and structures the output.

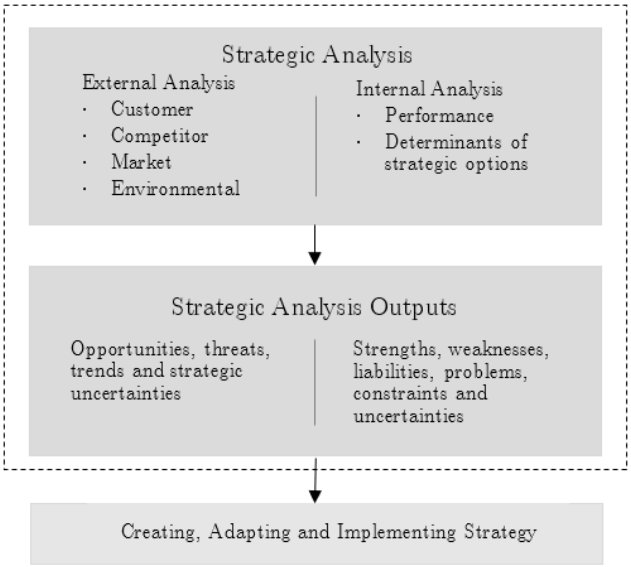


Figure B. 1 Woodruff and Gurdial's market analysis method, (adapted from Wierzchowiecka (2014)).

3. Woodruff and Gardial's market analysis method

This market analysis method involves five distinct phases, as seen in Figure B.2. This is a framework to complete a market opportunity analysis, thus evaluating the opportunities within the market. Wierzchowiecka (2014) suggests that the five phases of Woodruff and Gardial, can be applied to the strategic market analysis concept of Aaker (2013). The five phases can be divided to fall into both external and internal analyses. The first four phases of the above mentioned market analysis method, depicts an external analysis, whereas phase 5, and the supplier analysis of phase 3, investigates the internal capabilities of the given market.

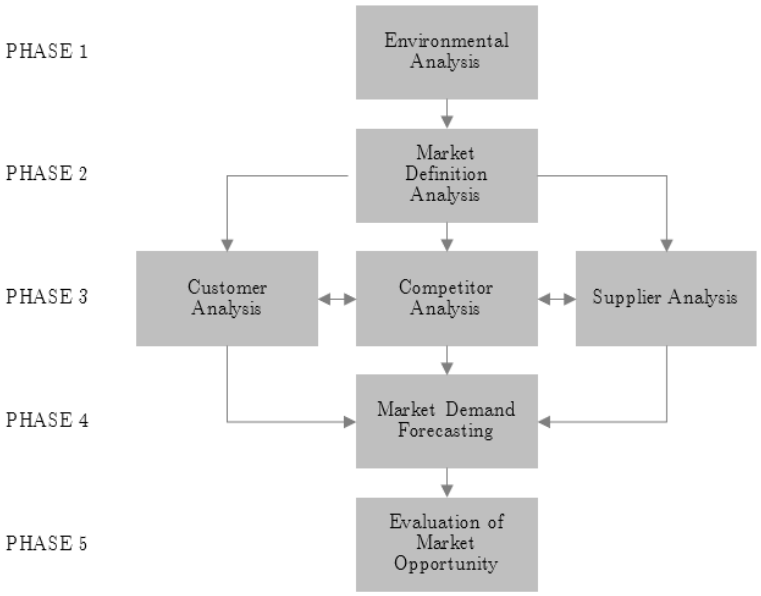


Figure B. 2 Market Analysis Phases, (adapted from Woodruff and Gardial 1996).

4. SWITCH-ON's market analysis framework

This framework is structured into two parts, Part I, identifies and analysis external influencers that affects markets, where as Part II, analysis the market by taking a product specific approach (Pacheco *et al.*, 2016). The primary objectives of each step of the market analysis framework, as well as the tools suggested to complete for each step is defined in Table B.1.

Table B. 1 SWITCH-ON Market analysis framework (adapted from Pacheco et al., (2016)).

MAF activities	*Main goal*	*Tools suggested*
Market Definition	Specify market boundaries and the need(s) to be satisfied by the product or service	· Approach selection (top-down or bottom-up)
Market Intelligence	Assess macro-environmental factors that influence a product or service's market using a strategic analysis tool	· PESTLE analysis
Market Segmentation	Understand the needs and behaviour of potential end users and select the most attractive markets to target	· Market segment definition · Target group selection
Market Analysis	Exercises and tools used to determine the attractiveness of the selected market segment and understand its dynamics.	· Secondary research · Market size estimation · Market growth rate estimation · SWOT analysis · Competitor identification framework · Competitive strength map · Porter's five forces · Cost-Volume - profit analysis · Ansoff matrix · Risk matrix

5. The 5C analysis

This model aims to describe the external environment by examining the external environmental factors as well as the internal organizational capabilities and the potential impact thereof on the organization or market (Smartsheet Inc., 2018). Figure B.3 gives an overview of the 5C analysis.

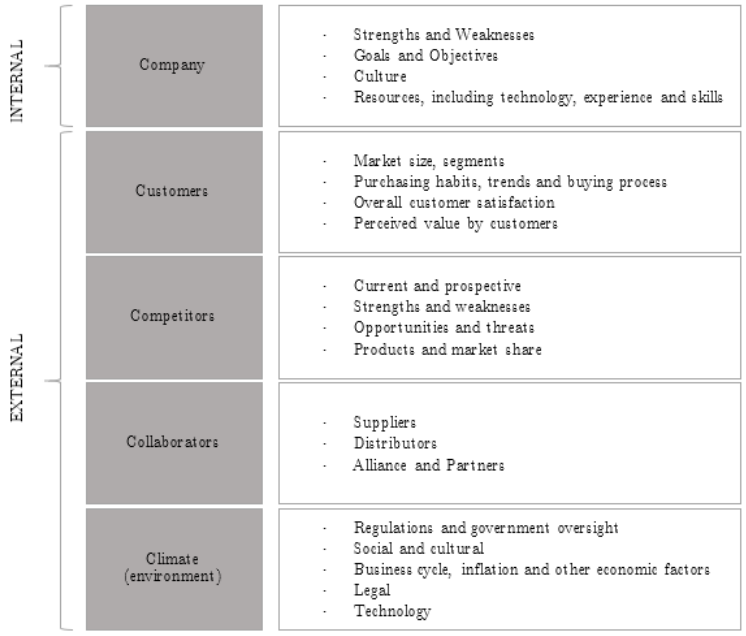


Figure B. 3 The 5C Analysis Framework (adapted from (Smartsheet Inc., 2018)).

6. Michael Porter's five forces model

The five forces model of Michael Porter provides a holistic way to look at any industry and to determine the underlying structural drivers of profitability, it is important to note that every industry have different sets of economic fundamentals (Porter, 2015). According to Porter (2015) the model should be used to assess both the market attractiveness of a given market as well as the nature of the competition within the sector. The model aims to describe the reason behind high or low industry profits in a specific market.

Porter also states that the nature of the competition within an industry should be determined by completing an industry analysis. The industry analysis will identify differences in industries with regards to the following factors:

- Size — sales revenue, volumes and numbers of customers;
- Organizational structure — number of brands and competitors;
- Distribution channels;
- Customer expectations;
- Growth —rate of growth of the organization, as well as its competitors;
- Product life cycle —stage at which the organization is situated; and
- Alternative products for consumers.

The five forces model, analysis the industry and its competitors to identify, with the use of the information established in the industry analysis, why certain industries or markets generate higher profits than its competitors. The nature of the competition within the industry is determined, according to the Porter model, to be the result of five factors that act together (J. Riley, 2015). The five forces of the Porter's five forces model, according to (MindTools, 2019) are:

- Threat of new entrants: High when it takes little effort and money to enter the market, or when there is little protection for key IP; low when there are strong and durable barriers to entry.
- Bargaining power of buyers: High when there are few customers; low when there are many customers.
- Bargaining power of suppliers: High when there are a lot of suppliers to choose from; low when there are a few suppliers.
- Threat of substitute products: High when a substitution is easy and cheap to make; low when it is difficult for customers to switch to a different product.
- Rivalry among existing competitors: High when there are a lot of rivals in your industry; low when there are no organizations offering the same product or service that you are providing.

Each of the forces should be analyzed in detail to grasp the industry attractiveness in total. With regards to the state and influence of each of the five forces, Porter identified characteristics that are associated with high and low industry profits respectively, as depicted in Figure B.4.

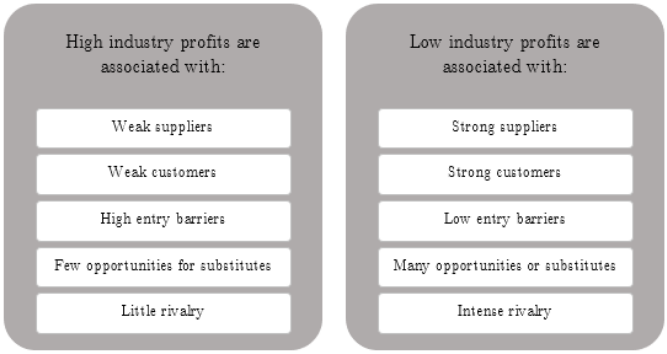


Figure B. 4 Characteristics associated with high and low industry profits (adapted from J. Riley (2015)).

7. Michael Porter's value chain model

Porter (1991) assumes that a firm's success in manifested when it attains a competitive advantage or has an advantage over its competitors that leads to a superior and sustainable financial performance. Porter also assumes that the motive behind why some organizations use the competitive performance position 'fruits' on meeting social objectives is addressed as a separate question. From a broad perspective, success of a firm is a function of two attributes namely: (i) the attractiveness of the industry in which the firm competes, and (ii) the relative position of the firm in the industry.

Porter (1991) links environmental circumstances and firm behavior to market outcomes in order to explain the competitive success of firms. Porter argues that when an industry structure is held constant, then a successful firm is one with an attractive relative position. This attractive position is an outcome and not a cause which, according to Porter, arises when a firm has a sustainable competitive advantage over its rivals. Where competitive advantage is said to exist as a result from one or both of two factors: (i) the firm has lower costs than its rivals, or (ii) the firm can obtain a higher price that exceeds its costs to produce what it is offering to the market (Porter, 1991). The importance of considering competitive advantage taking the scope of the organization into account. The scope of the organization refers to anything from the customer segments served, the geographic locations of the organizations, and the level of vertical integration to mention a few. In order to create this competitive advantage, a firm needs to perform certain activities.

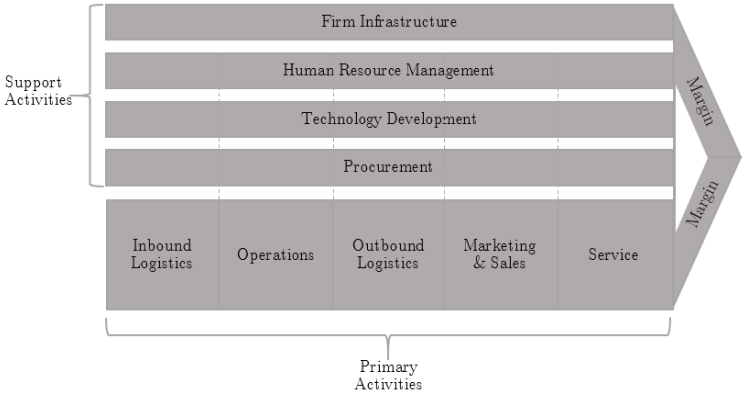


Figure B. 5 Michael Porter's value chain (adapted from Porter (1991)).

Appendix D: Customer segmentation

This appendix depicts the customer segmentation of both Malawi and the United States. Table B.2 depicts the customer analysis of Malawi. Table B. 3 depicts the customer segmentation of the United states.

Table B. 2 Customer segmentation low-income country: Malawi.

	Measure of analysis	State of measure for Malawi	Reference
Geographic	Country	Malawi	
	Population size	18.14 million (2018)	Worldometers.info (2018)
	Population growth	2.68% (2018)	Chafulumira (2009)
	Population Density	192 p/km^2 (2018)	Worldometers.info (2018)
	Ratio of population urban	17.9% (2018)	Worldometers.info (2018)
Role	The healthcare delivery system stakeholders	Mainly consists of government facilities (63%), Christian Health Associations (26%), and other private (for-profit) providers.	WHO (2018)
	Health system challenges	Inadequate human resources and lack of resource distribution in rural areas.	WHO (2018)
	Finance	Inadequate financing, infrastructure, and equipment	WHO (2018)
	Contribution of donors to total health expenditure	73.8% (2016)	(UNICEF, 2017)
Behavioural	Health system rank	Number 185 out of 190 (2000)	(Musgrove *et al.*, 2000)
	Public health sector	Provides healthcare to all citizens. Only 46% live within a 5km radius from any kind of health facility	WHO (2018)
Firmographic	Industry sector	Public health sector	
	Birth registration coverage	2% (children below age 5) (2015)	WHO (2015)
	Life expectancy at birth	64.2 years (2016)	(African Health observatory and WHO, 2018)
	Hospital beds per 10 000 population	52 (2011)	(African Health observatory and WHO, 2018)
	GDP	$ 6.3 billion (2017)	(The world bank, 2019)
	Total expenditure on health per capita	$93	WHO (2016)
	Total expenditure on health as % of GDP	11.1% (2016)	(UNICEF, 2017)
	Out-of-pocket as % of total current health expenditure	11% (2015)	(African Health observatory and WHO, 2018)
	Physicians per 1000 population	0.019 (2016)	(UNICEF, 2017)
	Source of health financing as % of total health expenditure	28.6 % (Government); 17.5 % (Domestic private); and 53.5 % (External sources)	(African Health observatory and WHO, 2018)
	NAICS Code	923120	

The customer segmentation of the United States is depicted in Table B. 3.

Table B. 3 Customer segmentation high-income country: United States.

	Measure of analysis	*State of measure for United States*	*Reference*
Geographic	Country	United States of America	
	Population size	327.7 million (2018)	Worldometers.info (2018)
	Population growth	0.7% annually (2018)	Worldometers.info (2018)
	Population Density	36 p/km^2 (2018)	Worldometers.info (2018)
	% of population urban	83.7% (2018)	Worldometers.info (2018)
Role	State of health system	US health care system rated highest in cost, first in responsiveness.	(WHO, 2015c)
	Health facilities	Total US Hospitals 6210, of which 5262 are community hospitals (not for profit, investor owned, and local government); 208 Federal government hospitals; and other.	(American Hospital Association, 2019)
Behavioural	Health system rank	Number 37 of 190 (2000)	(Musgrove *et al.*, 2000)
	Universal healthcare	No universal healthcare (2017)	(CMS, 2018)
	Health financing	91.2 % of people have health insurance coverage, of which 67.2% is private and 37.7% government coverage (2017).	(Berchick *et al.*, 2018)
Firmographic	Industry sector	Public health sector	
	Birth registration coverage	100% (children below age 5) (2009)	(WHO, 2015c)
	Life expectancy at birth	78.7 years (2018)	(Donnelly, 2018)
	Hospital beds per 10 000 population	24 (2015)	(Statista, 2019)
	GDP	$19.49 trillion (2017)	(Country Economy, 2018)
	Total expenditure on health per capita	$9 523 (2014)	WHO (2016)
	Total expenditure on health as % of GDP	17.9% (2017)	(Martin *et al.*, 2019)
	Out-of-pocket as % of total current health expenditure	12.4 % (2014)	(United States Health, 2017)
	Physicians per 1000 population	29.5	(Young *et al.*, 2017)
	The source of health financing	75% health Insurance (of which 34% private) (2017)	(CMS, 2018)
	NAICS Code	923120	

Appendix E: Incentive-based interventions

A complete list of the 96 incentive-based interventions, as well as the 26 incentive categories are depicted below. The definition of each intervention category is provided as a merged definition, aimed to provide a holistic meaning of the incentive interventions categorized underneath it.

Push strategies	
Grant Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project and require a certain level of compliance and reporting.	
USA Small Business Innovation and Research award programme: Provide grants to small businesses engaged in the R&D of NTD.	(Mackey and Liang, 2012)
The Global Health Investment Fund (GHIF): Finance primarily late-stage R&D innovations for poverty related diseases.	(Fitchetta *et al.*, 2016; Starr *et al.*, 2016; Hotez, 2017)
Office of Orphan Product Development (OOPD): Aim to advance the evaluation and development of products that demonstrate potential for diagnostics or treatment of rare diseases and conditions by providing grants.	(Sachs-Barrable *et al.*, 2014)
Open-source initiative Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets could benefit all participants.	
PLOS open access journal: Open access journal devoted to NTDs of the world.	(Allarakhia and Ajuwon, 2012)
ChEMBL Neglected tropical disease database: Open access repository of data for the development of NTD medicinal chemistry.	(Allarakhia and Ajuwon, 2012)
Tropical Disease Initiative (TDI): A decentralized, internet-based, community-wide effort for tropical diseases, including NTDs.	(Allarakhia and Ajuwon, 2012)
MalariaGEN (Malaria Genomic Epidemiology Network): Researchers from 20 countries collaborate to R&D technology and control efforts for Malaria.	(Allarakhia and Ajuwon, 2012)
GNTD database: A database of 12 000 survey locations aimed at NTDs.	(Allarakhia and Ajuwon, 2012)
D3 (Distributed Drug Discovery): A strategy to accelerate the discovery of drugs to treat neglected diseases where multiple stakeholders engage to improve R&D capacity and capital development.	(Allarakhia and Ajuwon, 2012)
Leishmaniasis Research Network (redeLeish Network): The network operates through a Web Forum, and promote the exchange of information, enhances the consensus of clinical trial designs, encourage debates on the disease and enables collaborative research projects.	(Allarakhia and Ajuwon, 2012)
G-Finder survey: Tracks public, private and philanthropic funding of basic research and product development (R&D) for global health priorities.	(Beyeler *et al.*, 2019)
InfoNTD: An online platform and repository for cross-cutting research, tools and other information on NTDs (centralized information platform).	(Bailey *et al.*, 2019)
Wide in Silico Docking on Malaria (WISDOM): Links known chemical compounds with structural data from the Malaria parasite by the means of a network.	(Allarakhia and Ajuwon, 2012)
Patent pool Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.	
Pool for Open Innovation Against Tropical neglected diseases: Donation of essential patents and know-hows to drive R&D on NTDs.	(So and Ruiz-Esparza, 2012)

Medicine's Patent Pool (MPP): Negotiating voluntary license to enable the manufacturing of primarily HIV, Hepatitis C, and TB medicines for LMICs.	SME 3, SME 2
GSKs Patent Pool for NTD: The pharmaceutical company GSK will share its patented knowledge used to develop medicines for NTDs.	(Weilbaecher, 2009; Johnson and Kar, 2014)
PPP Public-private partnerships is any arrangement between one or more public and private entities respectively. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.	
Anti-Parasitic Drug Discovery in Epigenetics (A-ParaDDisE): Target-based strategy for the R&D of novel drug leads against certain NTDs.	(Pierce *et al.*, 2017)
Anti-Wolbachia Consortium (A-Wol): Develop drugs for specific NTD by developing products that targets the intracellular bacterium. The consortium comprises of both industry and academic partners.	(Starr *et al.*, 2016)
Coalition for Epidemic Preparedness Innovations (CEPI): The fund would support emerging pandemic threats as well as NTD pathogens, while ensuring a market for product sales. Thus, focus on gaps in product R&D which results from market failures.	(Hotez, 2017)
Council on Health Research and Development (COHRED): Global NGO with goal to maximize the research of diseases primarily occurring in LMICs.	(Manu, 2014)
Critical Path to TB Drug regimens (CPTR): Brings leading pharmaceutical and other drug developers in partnership to support the necessary infrastructure to facilitate the successful R&D of TB drug treatments.	(Burci and Gostin, 2017)
DNDi partnered with GSK: Partnership to develop drugs for NTD.	(Johnson and Kar, 2014)
Drugs for Neglected Diseases Initiative (DNDi): NGO R&D organization that is committed to the R&D of improved or novel treatments for NTD.	(Ioset and Chang, 2011; Moon *et al.*, 2012; Mueller-Langer, 2013b)
Fixed-Dose Artesunate Combination Therapy (FACT) project consortium: Various entities are brought together for enhancing the development of anti-malarial treatments.	(Geraghty, 2009)
Foundation for Innovative New Diagnostics (FIND): International NGO that enable the R&D of much-needed diagnostic tests for poverty-related diseases.	(Mueller-Langer, 2013b)
Genzyme's Humanitarian Assistance for Neglected Diseases program (HAND): Work with partnerships or developing world institutions to R&D products from early stage of pipeline through clinical trial phases.	(Geraghty, 2009)
Global Alliance for TB drug development (TB Alliance): NGO dedicated to R&D for improved TB medicines.	(Mueller-Langer, 2013b)
Global Health Innovative Technology Fund (GHIT): Provides funding to support neglected infectious disease R&D collaborations between Japanese and global pharmaceutical organizations.	(Starr *et al.*, 2016)
Infectious Disease Research Institute (IDRI): NGO that conducts global health research on infectious diseases, with partners.	(Towse *et al.*, 2012; Mueller-Langer, 2013b)
Innovative Vector consortium (IVCC): Not for profit, aim to develop and deliver new vector control tools.	(Mackey and Liang, 2012)
Institute for One World Health (IOWH): NGO develops safe, effective, affordable medicines to people with diseases of the developing world.	(Starr *et al.*, 2016)
KINDReD: Promote R&D of novel drug molecules against NTDs.	(Starr *et al.*, 2016)
Macrofilaricide Drug Accelerator (MacDA): Bring entities together to advance R&D for drugs that are capable of killing the adult forms of the onchocerciasis and lymphatic filariasis parasites.	(Starr *et al.*, 2016)
Medicines for Malaria Venture (MMV): The basic mission of the organization was to discover, develop and deliver safe and effective anti-malarial agents.	(Hunter, 2011; Mueller-Langer, 2013b; Hotez, 2017)
Novartis and Institute of Microbiology and Epidemiology in Beijing: R&D and distribution of antimalarial drug.	(Johnson and Kar, 2014)
NTD NGDO Network: A global forum for non-governmental development organizations. Facilitate partnerships among group members.	(Bangert *et al.*, 2017)
PDP+ Fund: Raise funding by product development and the coordination of funding to many PDPs.	(Burci and Gostin, 2017)

Roll Back Malaria (RBM): Mobilises action against Malaria (funding, scale up control and conduct resource mobilization).	(Berdud *et al.*, 2016)
Sanofi-Aventis and DNDi: Develop and manufacture drugs against and treat African trypanosomiasis and Malaria.	(Johnson and Kar, 2014)
Therapeutics for Rare and Neglected Diseases (TRND) Program: Supports pre-clinical R&D of drug compounds that are intended to treat rare or neglected diseases.	(Wilson, 2013)
UK Department for International Development (DFID): Funds R&D by PDPs. Includes both product development and operational research.	(Pugatch, 2011)
United States Agency for International Development Neglected Tropical Diseases (USAID NTD) Program: The NTD Program invests in priority research needs for NTD control and elimination to guide improved mapping, stop treatment decision-making and create sustainable disease surveillance.	(Hotez, 2017)
Uniting to Combat NTDs: Dedicated partners to perform R&D to combat NTDs.	(Bangert *et al.*, 2017)
WHO Alliance for the Global Elimination of Trachoma by 2020 (GET2020): Partnership that supports and carries out essential activities to eliminate Trachoma.	(Bartlett *et al.*, 2019)
WHO Special Program for Research and Training in Tropical Diseases (WHO/TDR): Support for R&D in Chagas and similar diseases. Assists in establishing PDPs for R&D of drugs for NTDs.	(Towse *et al.*, 2012; Manu, 2014; Ferpozzi, 2018; Weng *et al.*, 2018)
Tax credits Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.	
Pull strategies	
Outcome-based pull strategies	
Advanced market commitments (AMC) AMCs are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.	
Differential pricing Differential pricing is when people with different backgrounds or that are from different regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental, or economic reasons.	
Value-based differential pricing: Increase returns on R&D and expand overall access to medicines in LMIC.	(Towse *et al.*, 2012)
Patent buyouts IP rights can be purchased by donors. Thus, the patent holding organization is financially compensated in exchange for the IP laws of the R&D of the drug or vaccine.	
Patent buyouts suggested by (Granslandt et. al. (2001)): Donors purchase IP rights to deliver products to developing countries.	(Røttingen *et al.*, 2013)
Pooled fund When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.	
Fund for Research into Neglected Diseases (FRIND): Allocate stepwise funding to only the most promising compound, will also focus on funding late stage product development.	(Hassoun, 2012)
Prize fund Prizes are large monetary rewards, provided mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded for incremental milestones met by the pharmaceutical organizations.	
Health Impact Fund (HIF): Pay-for-performance scheme for new medicines. Pharmaceutical companies would be free to abandon monopoly pricing, and register products with HIF, which would reward them for the health impact.	(Mueller-Langer, 2013b)
Priority Medicines and Vaccines Prize Fund (PMV/pf): Lumpsum prize money. 90% of the prize money will go to the winning entrant; whereas the other 10% will go to the other entrants who did not win.	(Weilbaecher, 2009)
Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis: The total prize will be awarded to the entrant once the entrant provides a satisfactory diagnostic test.	(Weilbaecher, 2009)

Prize Fund to Support Innovation and Access for Donor Supported Markets: Prizes to reward participation in a qualified, voluntary patent pool.	(Weilbaecher, 2009)
Drugs for Neglected Diseases Working Group (DND-WG): Aim to launch or fund drug development pilot projects.	(Kameda, 2014)
Licensed Products Prize Fund (LP/pf) for Donors: Developers will be rewarder with cash prizes, if they voluntarily license their innovations for TB, Malaria and HIV/AIDS to a patent pool.	(Weilbaecher, 2009)
Rating system Pharmaceutical companies are rated according to a certain set of criteria; some of which can relate to the resourcing of R&D for NDs. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.	
Access to Medicine Index: An international NGO that ranks pharmaceutical organizations based on making medicines, vaccines and diagnostics more accessible to LMICs.	(Hassoun, 2012)
Global Health Impact Rating system: Objective and output-based rating system will rate companies on their R&D results and charitable contributions.	(Hassoun, 2012)
Lego-regulatory pull strategies	
Intellectual property and market exclusivity Intellectual property refers to the right that the innovator receives, when an innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.	
Transferable IP Rights (TIPRs): Companies are awarded an IP extension for a product of their choice, should they successfully being a neglected disease product into the market and ensure product delivery in target population.	(Koh Jun, 2012; Hoffman *et al.*, 2014)
TRIPS agreement: Establishes international standards for intellectual property rights and grant equal rights to all member countries.	(Mueller-Langer, 2013b)
Policy instrument Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy.	
Strengthening Pharmaceutical Innovation in Africa (SPIA): Focus on reinforcing countries' capacity for policy formulation in the sectors of science and technology in order to enhance pharmaceutical innovations in SSA.	(Manu, 2014)
The Global Strategy and Plan of Action on Public Health, Innovation, and Intellectual Property (GSPA - PHI): Aim to promote thinking on the innovation and access of medicines, while enhancing sustainability in the R&D of diseases that disproportionately affect LMICs.	(Manu, 2014)
Priority review voucher Law under which companies that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.	
Priority Review Voucher (PRV): Law under which companies that receive FDA approval for a novel drug or vaccine targeting a list of NTDs and paediatric diseases are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.	(Dimitri, 2012; Mueller-Langer, 2013b; Sachs-Barrable *et al.*, 2014; Berdud *et al.*, 2016; Starr *et al.*, 2016)
Priority Review Voucher by the European Medicines Agency (EMA) or European Commission: Similar to initial PRV, in context of Europe. The developer is awarded with a voucher when a drug for a neglected disease is developed. The voucher can then be used to enhance the process of any product by accelerating marketing authorization and pricing procedures.	(Starr *et al.*, 2016)
Trade, tariff adjustments. Adjustments made to the trading or the taxes and related costs associated with trading of manufactured drugs.	
Doha trade rounds: World Trade organization offers the opportunity for policy makers to improve the health equity in resource poor countries. Includes tariff reduction and the establishment of global harmonized trade codes.	(Mackey and Liang, 2012)
Hybrid strategies	
Collaboration network and consortiums A collaboration network refers to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity towards achieving a common goal.	

BRICSTB Research Network: Accelerate research and innovation through collaboration across the BRICS countries.	SME 2
Collaboration for Applied Health Research and Delivery Consultation (CAHRD): Bring together internal and external partners to shape the strategic direction of various diseases. Focusing on four areas namely: 1) lung health, 2) maternal & new-born health, 3) NTD, and 4) Health systems.	(Squire, 2015)
International Rare Diseases Research Consortium (IRDiRC): Maximizes resources and coordinate research efforts of rare diseases.	(Squire, 2015)
Great neglected diseases network (GND) Ken Warren and Rockefeller foundation: Created multidisciplinary teams, consisting of handpicked leading scientists (from both developed and developing countries). Work was investigator-initiated; compulsory annual meeting, where progress and developments was reported; knowledge shared.	(Keating, 2014)
London Declaration on Neglected tropical diseases: Organizations committed to increase the number of drug donations available to countries, increase bilateral funding, support non-governmental development organisations (NGDOs) and philanthropic financial commitment to NTD intervention and research.	(Starr *et al.*, 2016; Molyneux, 2017)
Liverpool School of Tropical Medicine (LSTM): Developing of new diagnostics, drugs and insecticides for the control of NTDs.	(Squire, 2015)
The Life Prize: An open collaboration approach, aims to pull funding, pool intellectual property, and push finance for R&D. (Unique to other collaboration approaches)	SME 2
PDE4NPD: Aim to develop new treatments for Neglected parasitic diseases.	(Kameda, 2014)
The NTD NGO Network (NNN): Global forum of NGO working to control or eliminate NGOs, working with governments through partnerships. Aim to be the unified voice on common issues to achieve NTD goals.	(Bailey *et al.*, 2019)
Coordination mechanism and platform Initiatives launched to coordinate R&D investments and activities. Operate to clarify investment priorities, increase transparency and diversify stakeholders to better align to R&D needs and investments.	
Coalition for African Research and Innovation (CARI): Setting of priorities and spurring innovation for meeting regional R&D needs	(Beyeler *et al.*, 2019)
WHO Global Observatory on Health R&D: Identifies global health R&D priorities by monitoring and analysing health R&D needs, collecting data and supporting coordination.	(Beyeler *et al.*, 2019)
Colloquium and Symposium An academic conference or seminar held, focussing on specifically one topic, in this case NDs, R&D in the field, operational research and access.	
Drugs for Communicable diseases: Stimulating development and securing availability, colloquium: Discuss incentivizing methods for the development of drugs that targets neglected diseases.	(Kameda, 2014)
New Medicines for Trypanosomiasis Infections (NMTrypl): A common drug-discovery platform that tests HIT compounds and complete safety testing.	Pierce *et al.*, 2017)
Policy and legislation Legislation includes laws constructed by governments; whereas policies must adhere to the law and comprises practical objectives and principles to guide decisions and actions within the pharmaceutical industry. Includes incentives such as drug acts to promote research in domestic markets.	
Orphan drug legislation combination with other interventions: Combination of orphan drug designation with interventions such as transferable patent exclusivity and transferable priority review. Include the possibility to shift for another drug from a standard to a priority or fast review process.	(Villa *et al.*, 2009)
Orphan Drug Act (ODA): Provides incentives (tax credits, FDA fees paid and grant opportunities) to promote research in and the production of drugs for rare diseases in domestic markets.	(Mueller-Langer, 2013b)
Drug status designation Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.	
Orphan Drug Designation Program (ODDP): Provides an orphan drug status to drugs and biologics that treat diseases defined as rare diseases by ODA.	(Sachs-Barrable *et al.*, 2014)
Joint venture Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures are associated with a specified end-date	

Oxford Emergent Tuberculosis Consortium (OETC): Joint-venture structure set up by a publicly funded University and a biopharmaceutical firm listed on the New York Stock Exchange.	(Li and Garnsey, 2014)
The Synaptic Leap (TSL): An open-source biomedical research community that aims to investigate diseases where "profit-driven research is failing".	(Weilbaecher, 2009)
Independent organization Independent organizations do not require the approval of a government agency for decision-making and / or financial planning. Can determine their own R&D agenda and main activities. Include for example advocating certain R&D priorities or providing evidence for informed decision-making.	
Global Forum for Health Research (GFHR): Initiated the 10/90 gap. Focus on improving global health and the health research sphere.	(Manu, 2014)
International Trachoma Initiative: Non-governmental organization dedicated solely to the elimination of trachoma. Aim is to collaborate with governmental and non-governmental agencies.	(Bartlett *et al.*, 2019)
Hybrid PPP This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive type included in this list of incentive types.	
Open-Source Drug Discovery Initiative (OSDD): Community of people, students, scientists and researchers who commits time to R&D drugs in an open-source mode for NTDs. (PPP and open-source)	(Weilbaecher, 2009; Hunter, 2011; Allarakhia and Ajuwon, 2012)
African Network for Drugs and Diagnostics Innovation (ANDI): Vision is to create a sustainable platform for R&D innovation in Africa to address Africa's own health needs. (PPP and open-source)	(Starr *et al.*, 2016; Molyneux, 2017)
The Paediatric Praziquantel (PEDPZQ) Consortium: NGO that contributes to reducing GBD of schistosomiasis by driving and implementing the development of a child friendly formulation for the disease. (PPP and open-source)	(Allarakhia and Ajuwon, 2012; Hussaarts *et al.*, 2017)
Cambia partnered with Queensland University of Technology: Establish a platform to promote patent system transparency worldwide. Funding from BMGF grant. (PPP, open-source initiative and the provision of grants)	(Johnson and Kar, 2014)
Tres Cantos Open Lab Foundation (TCOLF): Facilitate access to IP, industrial expertise, and technologies to stimulate research into NTDs. (PPP, open-source initiative and patent pool)	(Hunter, 2011)
WIPO Re:Search consortium: Organizations collaborate to share expertise, research and technology, with focus on drug, vaccine and diagnostic development.	(So and Ruiz-Esparza, 2012)
Novartis institute for Tropical Disease in Singapore: Research institute focused on doing research in tropical diseases. (PPP formed research institute)	(Towse *et al.*, 2012)
Research laboratories Research laboratories are scientifically orientated facilities equipped with the necessary equipment to complete the necessary experimental studies aimed at R&D of drugs. These can incentivize independent researchers and / or serve as laboratories for innovators without the newest technology.	
Astra Zeneca's TB Facility in Bangalore, India: Research facility that focus on finding new treatments for TB.	(Towse *et al.*, 2012)
Treaty Formal agreement between two or more states, subject to international law. A treaty can for example, enforce the coherence, fairness and efficiency of the R&D system.	
International Binding R&D Treaty: Improve the coherence, fairness, efficiency, and sustainability of the global R&D system.	(Moon *et al.*, 2012; Hoffman *et al.*, 2014)
Working Group Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings. Therefore, a group of individuals or entities can complete R&D collectively.	
Consultave Expert Working Group on Research and Development Financing and Coordination (CEWG): Examine the concerns of the lack of resources being devoted to NTDs. Builds on previous version of EWG.	(Hoffman *et al.*, 2014)
Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG-PHI): Aim is to improve and advance essential R&D for diseases that disproportionally affect developing countries.	(Manu, 2014)
The WHO Expert Working Group on R&D Financing (EWG): Stimulate R&D for type II and III diseases and satisfy the R&D needs of developing countries.	(Manu, 2014)
Mental Wellbeing and Stigma (MWS): Task group focused on NTD-related stigma and the mental wellbeing of those affected by NTDs.	(Bailey *et al.*, 2019)

Appendix F: Non-incentive-based interventions

The list of non-incentive-based solutions are provided together with the incentive-based interventions that is produced as output of the decision-support framework. The non-incentive-based interventions are not ranked from highest to lowest, however the system element importance, as rated in domain 1 (system demarcation) is added to each non-incentive-based intervention. The list of 43 interventions is categorized into ten categories (indicated in roman numerals), which corresponds to the categories of the system demarcation domain system elements.

I. DISEASE SETTING AND AFFECTING POPULATION

1. Country economic status		*For further reference*
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.	
Intervention considerations	The classification measures are described in Table 2.3	
	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.	

2. Burden fully characterized		*For further reference*
Meaning	The affected patients are diagnosed, being monitored and documented properly.	(Olmsted *et al.*, 2006; RAND Corporation, 2007; Novak *et al.*, 2013)
Relevance	Once the burden of a disease is fully characterized, consumer demand can be estimated. Consumer demand will have an influence on how profitable the perceived market is. Fully characterizing the burden also assists in the planning, distribution and implementation of control strategies.	
Intervention considerations	Diagnostic tools and technology, availability and access there of	
	Diagnostic intervention and intervention strategies	
	Availability of health facilities (option is to consider mobile health facilities)	
	Educate populations on disease side-effects, risks, and necessity of health interventions	
	Capture burden characterization data	

3. Physicians per 1000 population		*For further reference*
Meaning	The number of physicians available per capita / 1000 of people	(Al-Shamsi, 2017)
Relevance	The higher the availability of physicians in a country, the higher the likelihood that the population will have access to adequate care.	
Intervention considerations	Recruit international medical graduates	
	Modify postgraduate majors to allow physicians to enter the practice in areas of need	
	Shorten the preparatory under-graduate medical education years and introduce modern methods of teaching.	

II. EXISTING DRUG CHARACTERISTICS

4. Quality of existing drugs		*For further reference*
Meaning	Drugs should not pose significant health risks to patients and should be effective in treating the disease.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; van Olmen *et al.*, 2010; Dorlo *et al.*, 2012; Rauscher *et al.*, 2018)
Relevance	Patients depend on drugs for disease mitigation. If quality is not up-to-standard, then disease burden might increase or might not decrease.	
Intervention considerations	Repeat final clinical trial stages to monitor effects of medicine in a controlled environment	
	Remove drugs from market	
	Improve monitoring of ADR	
	Pharmacovigilance	
	Quality control of current manufacturing procedures	
	Enforce international clinical trial and manufacturing practices and regulations	

5. Availability of drugs for the desired population		*For further reference*
Meaning	Drugs are available in the right quantities, on the right time for patients to access.	(Jackson, 2010; Holt *et al.*, 2012; Niëns and Brouwer, 2013)
Relevance	If drugs are adequate but not available, then patients might not be effectively treated. Possible resistance to medicines.	
Intervention considerations	Supply chain management	
	Distribution networks	
	Inventory management at health facilities	
	Replenishment systems at health facilities	
	Burden characterization assists in inventory planning	

6. Affordability of current drugs to desired population		*For further reference*
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger *et al.*, 2012)
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.	
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs	
	Collaborate with other health delivery entities to form partnerships	
	Manufacture drugs nationally, instead of importing	

7. Appropriateness of drugs to the desired population		*For further reference*
Meaning	Drugs must target the disease intended for. Intervention must be understandably explained and not interfere with culture.	(Hotez, 2008; Jackson, 2010)
Relevance	If drugs are not appropriate, then patients won't use it or, if they use it, improvements in disease burden will not be made.	
Intervention considerations	Screen culture and explore possible cultural and ethical issues	
	Improve diagnostics of patients	
	Communication in understandable language for population group	
	Survey to understand the feelings of patients	

8. Acceptability of drugs to the desired population		*For further reference*
Meaning	Drugs are not acceptable because of cultural values norms or stigmas.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; Hotez, 2008; Jackson, 2010)
Relevance	If patients do not accept drugs, then intervention strategies go to waste.	
Intervention considerations	Educate people to reduce stigmas.	
	Educate people to understand potential of drugs.	
	Respect and honour the norms and values of the patient group.	

III. SERVICE DELIVERY

9. Comprehensiveness of services delivered		*For further reference*
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004; WHO, 2010b)
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.	
Intervention considerations	Education of prevention measures.	
	Address root-cause of disease (e.g. water and sanitation)	
	Investigate the needs of the affected population group	
	Address social needs of patients	
	Repeat prevention or mass drug administration interventions, if deemed necessary.	

10. Continuity of patients' access to health services		*For further reference*
Meaning	For health interventions where once-off treatment is not adequate, follow-up treatments must be scheduled and adhered to.	(Stevens, 2004; Jackson, 2010; Holt *et al.*, 2012)
Relevance	If follow-up treatments are not provided, then patient health might not improve as desired.	
Intervention considerations	Scheduling of follow-up interventions	
	Mobile health facilities	
	Track patient health records and data	
	Monitor and track patients	

11. Coordination of service delivery networks		*For further reference*
Meaning	Service delivery is done in an organized, timely, professional and appropriate manner.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; WHO, 2010a; Rauscher *et al.*, 2018)
Relevance	If service delivery is not coordinated properly, then some patients might be overlooked for treatment, not have access, or might miss the opportunity to meet with health care workers (if not properly communicated)	
Intervention considerations	Communication services	
	Scheduling of health workers	
	Monitor service delivery per area	
	Monitor drug distribution or mass drug administrations per region.	

IV. CONSUMER, COMPETITORS AND SUPPLIERS

13. Demand size or sales force (relates to disease burden)		*For further reference*
Meaning	The size of the burdened population, and patients who needs medicines, or intervention strategies.	(Olmsted *et al.*, 2006; RAND Corporation, 2007; Novak *et al.*, 2013)
Relevance	By determining the size of the burdened population, service delivery and intervention strategies can be planned more accurately. Also, service delivery waste can be reduced.	
Intervention considerations	Characterization of the burden of disease	
	Diagnostic interventions	
	Target repurposing	

14. The role of brand loyalty		
Meaning	Brand loyalty of consumers to certain brands / drugs means that consumers buy certain drugs, based on previous experience, or perceived value. (relevant to other brands).	(Griffiths, 2008; Panchal *et al.*, 2012)
Relevance	If a product does not have brand loyalty, it might have the necessary characteristics to mitigate disease, but patients are not using it as a result of not 'trusting' the drug.	
Intervention considerations	Awareness amongst physicians of the value of the drug	
	Build trust in the communities	
	Well planned market strategies	

15. Bargaining power of the suppliers (chemical entities)		*For further reference*
Meaning	The ability of suppliers to influence the prizing of the entities that they offer the pharmaceutical innovators and manufacturers.	(Whiteside, 2016)
Relevance	The stronger the bargaining power of the suppliers; the higher the prizes of resources, and the higher the total cost of drug interventions.	
Intervention considerations	Research alternative suppliers.	
	Support local suppliers.	
	Consider importing of goods.	
	Ensure quality of suppliers, if weak bargaining power.	

16. Existence of competitors		*For further reference*
Meaning	Competitors refer to other pharmaceutical innovators completing R&D in the same field, thus, targeting the same disease.	(Whiteside, 2016; Thakor and Lo, 2018)
Relevance	Strong competition exists because of intellectual property rights that are gained for new chemical entities innovated.	
Intervention considerations	Explore and compare for similar drugs being marketed as different products.	
	Competition is not always a bad thing (speeds up discovery)	
	Collaboration and open innovation	

V. GOVERNANCE AND LEADERSHIP

17. Political will and contribution to improve R&D for disease		*For further reference*
Meaning	The effort and contribution that the government of a country is willing to make towards R&D of diseases.	(Emmanuel and Emmanuel, 1996; Sheldon, 1998; Brinkerhoff, 2003; WHO, 2018d)
Relevance	Governments should be obligated to make significant efforts to reduce disease burden within a country	
Intervention considerations	Enforce SDGs	
	Ministry of Health audit	
	Policy reform	
	Political accountability systems	

18. Effective national budget allocation		*For further reference*
Meaning	The financial plan of a country should include planning and financial allocations to the health and health care of citizens.	(Emmanuel and Emmanuel, 1996; Becker, 2015; WHO, 2018a)
Relevance	The health care of a country is the responsibility of its government. Without budget allocation, health care advancement is less likely.	
Intervention considerations	Implement SDGs	
	Policy reform	
	Strategic resource allocation options	
	Global health governance	

19. Regulation of strategic health policy		*For further reference*
Meaning	The goals, visions, priorities and budgetary decisions of a country needs to be regulated, to be in line with health needs.	(Mackey and Liang, 2012; Nagpal *et al.*, 2013; WHO, 2018e)
Relevance	If the strategic plans and actions to undertake and achieve are not taken, then the health of the country will lack improvement.	
Intervention considerations	Global health governance	
	Strategic political interventions	
	Domestic, private, and global policy interventions	

20. Adequate supply of the health service		*For further reference*
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Manjit Kaur; Sarah Hall, 2002; RAND Corporation, 2007; Jacobs *et al.*, 2012)
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.	
Intervention considerations	Strategic service delivery	
	Burden characterization	
	Health supply management	

21. Monitoring of the actual health system and system performance		*For further reference*
Meaning	The observation and measurement of health system performance.	(WHO, 2010a; International Federation *et al.*, 2015; Jones *et al.*, 2015; Newman *et al.*, 2016)
Relevance	By observing and measuring performance of the health system, problems can be located faster and more easily.	
Intervention considerations	Information systems and data handling	
	Pharmacovigilance	
	Reporting networks	
	Personnel training	
	Accountability networks and schedules	

VI. PROFITABILITY AND MARKET FORCES

22. Current investment capital and returns		*For further reference*
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Bates *et al.*, 2015; Payne *et al.*, 2015; Ho *et al.*, 2016; Vischer *et al.*, 2017)
Relevance	This factor refers to the current ROI being profitable or not, if not then more investment in a similar research area is not likely.	
Intervention considerations	Financial analysis	
	Cost analysis of activities	
	Reduce indirect and operational costs	

23. Stakeholder demand		*For further reference*
Meaning	Stakeholder demand refer to whether the public desires, and needs the product being developed.	(Whiteside, 2016; Thakor and Lo, 2018)
Relevance	The higher the demand for the products being delivered, the greater the perceived potential ROI.	
Intervention considerations	Target market analysis	
	Marketing strategies	
	Inform governments and the public that require this drug.	
	Pricing of the product	

24. Established marketing and distribution network		*For further reference*
Meaning	The marketing and distribution of drugs are important, to inform patients, and provide access and availability.	(Radulescu, 2012)
Relevance	Distribution adds to effective service delivery; and marketing creates and enlarges the market demand.	
Intervention considerations	Marketing strategies	
	Effective distribution networks	
	Supply chain management	
	Coordination of service delivery, inventory management and distribution services	

VII. RESEARCH AND DEVELOPMENT PROCESS

25. Consistency and recommendations on choosing metrics for clinical trials		*For further reference*
Meaning	Clinical trials are the most timeous procedure of drug R&D, using the correct metrics are essential in innovation productivity.	(Clifton *et al.*, 2015; Zhou *et al.*, 2015; Gupta *et al.*, 2016; Moatti *et al.*, 2016; Mayo *et al.*, 2017)
Relevance	Guidelines and regulations should be followed to advance in clinical trial phases. If not consistent then clinical trials might be trivial.	
Intervention considerations	Structured regulations and policy recommendations	
	Standardized clinical trial metrics	
	Market authorization regulation	
	Capture data of clinical trial methods and metric outputs	

26. Transparency of clinical trial information		*For further reference*
Meaning	Clinical trial information is openly available, reliable and does not entail any suspicious information.	(Tsourounis *et al.,* 2015; Shaw and Ross, 2015; Campa *et al.*, 2016; Li *et al.*, 2016; Šolić *et al.*, 2017)
Relevance	Transparent clinical trial information assures that products being developed adhere to safety, efficacy and regulatory requirements.	
Intervention considerations	Annual, and unannounced firm audits	
	Ethical conduct	
	Education on misconduct and legal consequences	
	Adhere to international clinical trial authority agency regulations	

27. Accountability of clinical trial information		*For further reference*
Meaning	Clinical trial information should be trustworthy	(Tsourounis *et al.,* 2015, Shaw and Ross, 2015; Campa *et al.*, 2016; Li *et al.*, 2016; Šolić *et al.*, 2017)
Relevance	There should be clear accountability for the information of clinical trials.	
Intervention considerations	Annual, and unannounced organization audits	
	Ethical conduct	
	Education on misconduct and legal consequences	
	Adhere to international clinical trial authority agency regulations	

28. Accessibility of clinical trial information		*For further reference*
Meaning	The clinical trial information should be made available (within the market exclusivity agreements)	(Tsourounis *et al.,* 2015; Shaw and Ross, 2015; Campa *et al.*, 2016; Li *et al.*, 2016; Šolić *et al.*, 2017)
Relevance	Secrecy on critical clinical trial information not allowed, especially if it alters the safety and efficacy of the drugs.	
Intervention considerations	Annual, and unannounced organization audits	
	Ethical conduct	
	Education on misconduct and legal consequences	
	Adhere to international clinical trial authority agency regulations	

29. The use of innovative clinical trial tools and technology		*For further reference*
Meaning	Advanced tools and technologies exist for performing clinical trials.	(McKinsey&Company, 2017)
Relevance	Modern technology and tools assist in clinical trial and drug discovery processes and might enhance the R&D process.	
Intervention considerations	Research on tools and technology available	
	Reliability of current tools and technology used in clinical trials	
	Break-even of getting new equipment, tools and technologies	
	Cost-benefit analysis of getting new equipment, tools and technologies	

30. Struggling to prove efficacy		*For further reference*
Meaning	The ability of pharmaceutical innovators to prove that the drug fulfils the intended result.	(Hay *et al.*, 2014; Ho *et al.*, 2016; PhRMA, 2016; von Ranke *et al.*, 2016)
Relevance	Drugs should target the intended disease and be effective in treating the patients.	
Intervention considerations	Clinical trial information quality	
	Clinical trial design	
	Tools, technology and equipment used for clinical trials	
	Adhere to international regulation standards	

31. Legal and ethical regulations for clinical trials too difficult		*For further reference*
Meaning	Extensive laws and regulations exist for the development of drugs.	(Califf and Sugarman, 2015; Cheng and Xie, 2017; Salas, 2017)
Relevance	A lot of difficulty is experienced in bridging legal and ethical barriers in drug R&D.	
Intervention considerations	Collaborate with bigger pharmaceutical organizations	
	Availability of third parties to adhere to regulations and laws	
	Complete annual audits	
	Ensure data transparency, accuracy and accountability	

32. Safety assessments standards		*For further reference*
Meaning	Safety assessment standards should be adhered to, to quantify and measure risks involved in the drug being developed.	(Singh and Loke, 2012; Hay *et al.*, 2014; PhRMA, 2016)
Relevance	Drugs that does not adhere to safety standards might pose a health risk to patients.	
Intervention considerations	Health authority standards and regulations	
	Clinical trial practices and designs	
	Randomized controlled trials	
	Global health governance	

33. Adaptive clinical trials occurrence		*For further reference*
Meaning	Clinical trials that involves observing participant outcomes and adjusting drug parameters in accordance.	(Baylor College of Medicine, 2009; Gokhale and Gokhale, 2016)
Relevance	Without adaptive clinical trials, important observations cannot be made; and drug safety not improved to the extent necessary.	
Intervention considerations	Amount of participants part of adaptive clinical trials	
	Procedures of adaptive clinical trials	
	Data capturing	
	Health authority standards and regulations	

34. Recruitment and retention of participants		*For further reference*
Meaning	Clinical trials require participants to perform drug safety and adequacy tests.	(Jennings *et al.*, 2015; Hammer *et al.*, 2016; Thacker *et al.*, 2016; Kurt *et al.*, 2017)
Relevance	Effort should be done to recruit the right number of participants for clinical trial tests	
Intervention considerations	Marketing strategies	
	Incentivize participants	
	Ensure safety of participants	
	Build trustworthy relationships with participants	

36. Racial differences in participation in clinical trial		*For further reference*
Meaning	A variety of ethnicity groups, races and both genders' response on the drugs needs to be tested	(Baylor College of Medicine, 2009; Kurt *et al.*, 2017)
Relevance	Given that drugs can be used by anyone, tests should be performed on various people to test for any difference in reactions or dosage requirements.	
Intervention considerations	Marketing strategies	
	Incentivize participants	
	Build trustworthy relationships with participants	

36. Relationships between innovators and participants		*For further reference*
Meaning	Innovators should strive to have a professional, and trustworthy relationship with participants	(Califf and Sugarman, 2015; Tsukamoto *et al.*, 2016; Kurt *et al.*, 2017; Salas, 2017)
Relevance	If the relationship between innovators and participants is not appropriate; then participants might not agree to complete more trials.	
Intervention considerations	Build trust with participants, by following standard clinical trial procedures	
	Adhere to safety and regulation standards	
	Monitor participants closely	
	Capture data	

37. Physician participation		*For further reference*
Meaning	Qualified medical practitioners should be present in clinical trial tests on humans.	(Baylor College of Medicine, 2009)
Relevance	Qualified physicians will be able to monitor the health and wellbeing of patients in clinical trials, as well as respond if ADR occur.	
Intervention considerations	Incentivize physicians to participate	
	Provide proper training to physicians	
	Adhere to correct clinical trial procedures	

38. Skilled workforce		*For further reference*
Meaning	Workforce, part of drug R&D process should be skilled to adequately perform tasks.	(International Labour Office, 2010)
Relevance	If workforce is not skilled, preventable problems in the R&D process might arise.	
Intervention considerations	Train workforce (workshops, training programs)	
	Encourage mentorship in work environment	
	Ethical conduct	

VIII. MANUFACTURING SYSTEMS

39. Existence of manufacturing plants		*For further reference*
Meaning	Manufacturing plants exists to perform adequate drug manufacturing.	(WHO, 2011b, 2016)
Relevance	If no manufacturing plants exists, then producing drugs on large scale might be difficult.	
Intervention considerations	Encourage/ Incentivize SME drug manufacturers	
	Consider international manufacturing organizations	

40. Drug manufacturing adheres to regulatory requirements		*For further reference*
Meaning	Drug manufacturing should adhere to regulatory requirements to ensure safety.	(Burnham *et al.*, 2015; J. Wechsler, 2015; Koeberle and Schiemenz, 2017)
Relevance	Unregulated manufacturing practices poses potential risks to the drugs.	
Intervention considerations	Audit Manufacturing organizations	
	Global manufacturing practices	
	Comply to current good manufacturing practices	
	Unannounced visits by regulatory authorities to manufacturing facilities	

41. Appropriate technology used for the manufacturing of drugs		*For further reference*
Meaning	A lot of technologies are available to manufacture drugs, some are advised by regulatory agencies.	(WHO, 2011a, 2011b)
Relevance	Appropriate technology might improve the safety, productivity and quality of the drugs being manufactured.	
Intervention considerations	Comply to current good manufacturing practices	
	Research technology that is available	
	Complete cost-benefit analysis to ensure new technologies are a strategic choice	
	Ensure compliance of all regulations and policies	

VIII. MANUFACTURING SYSTEMS

42. Health data generation		*For further reference*
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja *et al.*, 2017; Fatt and Ramadas, 2018)
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.	
Intervention considerations	Use adequate health information system	
	Ensure all data is captured accurately	
	Ensure backups of health data	
	Ensure safety of, and the network security of the stored health data	

43. Communication and use of public health data		*For further reference*
Meaning	Analysing, synthesising and validating health data	(WHO, 2010a)
Relevance	By evaluating health data, important measures can be implemented to satisfy growing needs, or gaps within the health system.	
Intervention considerations	Establish national sets of indicators with targets and accurate reporting which will inform health sector reviews and improve the planning of future interventions	
	Assess the health systems performance, to determine the success of current interventions	
	Adjust health system operation, based on accurate data.	
	Communicate health statistics to the public for awareness.	

Appendix G: Final decision-support framework

The final decision-support framework is presented in this Appendix. Fictional values are used in the solution set, and the supplementary materials, to display what the diagrams would look like. This appendix is made up of:

(i) Domain 1 System demarcation
(ii) Background logic 1AB
(iii) Domain 2 Enabler profile
(iv) Background logic 2
(v) Domain 3 Innovator profile
(vi) Background logic 3
(vii) Domain 4 Consumer profile
(viii) Background logic 4
(ix) Background logic 5
(x) Domain 5 Solution set
(xi) Supplementary page 1
(xii) Supplementary page 2
(xiii) Supplementary page 3
(xiv) Supplementary page 4

Domain 1 system demarcation

	DOMAIN 1: SYSTEM DEMARCATION					System evaluation	
	System elements	2	1	0	Aspect to address	Measure [0|1|2]	Sourced from section
Disease setting and affected population							
1	Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)		Chapter 3.6.2
2	Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact		Chapter 3.6.2
3	Burden fully characterized	< 40% of population within 5% of health facility	40% - 60% of population within 5% of health facility	> 60% of population within 5% of health facility	Non-incentive-based solutions (I)		Chapter 3.4.1.1 &3.6.2
4	Physicians per 1000 population	¡ 1 per 1 000	1 - 2 physicians per 1 000 population	¿ 2 physicians per 1 000 population	Non-incentive-based solutions (I)		SME 4
Existing drug characteristics							
5	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact		Chapter 3.6
6	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)		Chapter 3.6
7	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact		Chapter 2.1.2
8	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)		Chapter 2.2.5
9	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access		Chapter 2.2.5
10	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)		Chapter 2.2.5
11	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)		Chapter 2.2.5
12	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (Respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)		Chapter 2.2.5
13	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access		Chapter 3.6.2
Service delivery							
14	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)		Chapter 2.2.3
15	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)		Chapter 2.2.3
16	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)		Chapter 2.2.3
17	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)		Chapter 2.2.3
Consumers, Competitors, and suppliers							
18	Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)		Chapter 3.4.3 & 3.7.3
19	The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)		Chapter 3.7.3
20	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)		Chapter 3.4.3
21	Existence of competitors	No competitors	Some competitors	A lot of competition	Non-incentive-based solutions (V)		Chapter 3.4.3
22	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility		Chapter 3.4.3
23	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation		Chapter 3.4.3
24	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation		Chapter 3.4.3
Governance and leadership							
25	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)		Chapter 3.6.2
26	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership		Chapter 3.6.2
27	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership		Chapter 3.6.2
28	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership		Chapter 3.6.2
29	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)		Chapter 2.1.2
30	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)		Chapter 2.1.2
31	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership		Chapter 2.2.3
32	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)		Chapter 2.2.5
33	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)		Chapter 2.2.3
Profitability and market forces							
34	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces		Chapter 2.1 & 3.6.2
35	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)		Chapter 3.6.2
36	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)		Chapter 2.1.2
37	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)		Chapter 3.4.3
38	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces		Chapter 3.4.3 & 3.6.2
39	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership		Chapter 3.6.2
Research and development process							
40	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials		Chapter 2.1.2
41	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)		Chapter 2.1.2
42	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)		Chapter 2.1.2
43	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)		Chapter 2.1.2
44	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)		Chapter 2.1.2
45	Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials		Chapter 2.1.2
46	Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials		Chapter 2.1.2
47	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials		Chapter 2.1.2
48	Quality of clinical trials	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable	Good clinical trial quality	9. R&D and clinical trials		Chapter 2.1.2
49	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials		Chapter 3.6.2
50	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)		Chapter 2.1.2
51	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)		Chapter 2.1.2
52	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)		Chapter 2.1.2
53	Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)		Chapter 2.1.2
54	Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)		Chapter 2.1.2
55	Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)		Chapter 2.1.2
56	Racial differences in participation in clinical trial	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)		Chapter 2.1.2
57	Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)		Chapter 2.1.2
58	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)		Chapter 2.1.2
59	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)		Chapter 3.4.3
60	R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials		Chapter 2.1.3
61	Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials		Chapter 2.1.2 & 2.1.3
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)		Chapter 2.1.2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)		Chapter 2.1.2
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)		Chapter 3.4.3
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs		Chapter 3.4.3
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)		Chapter 2.2.3
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)		Chapter 2.2.3

Background Logic 1AB

	BACKGROUND LOGIC 1A&B: CRITERIA MATRIX	1. Profitability and market forces			2. Implementation feasibility and security				3. Green and sustainability			4. Population impact and access				5. Participation and cooperation					6. Governance and leadership							7. Rewards focus						8. Impact on R&D process and clinical trials							
		Improve NPV	Delink revenue from sales volume	Improve product export potential	Minimizes barriers to implementation	Minimize disruptive effects to population	Affordable to implement the incentive	Provide R&D project insurance	Ensure conservation of resources in R&D process	Encourage efficient innovation	Green R&D of drugs	Potential to reduce burden of disease	Encourage R&D of a drug/novel drug	Improve consumer access	Enable mass drug administration	Enables participation of small and medium organization	Encourage large firm participation	Facilitates cooperation and synergy	Platform for coordinating innovators	Allow competition among parallel experiments	Promote equitable health-focused governance	Promote transparency and accountability	Advances the priority of disease on health agenda	Advance proper functioning of domestic policy	Regulatory oversight to promote R&D	Regulatory exclusivity provisions for R&D	Resources to develop drug government financed	Payoff to innovators based on cost-effectiveness	Reward innovation	Financing timed across drug lifecycle	Provide long term R&D financing	Provide sustainable financing	Provide public subsidies for clinical trials	Reduce clinical trial risk involved	Assist in registration and monitor of trials	Globalize clinical trial methods	Reduce clinical trials activation difficulty	Enhance or prompt the quality of clinical trials	Assist in expensive clinical trial regulation	Improves R&D productivity	Enlarge number of clinical trials registered
1	**Grants:** Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting	1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	1	0	1	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0
2	**Open-source initiative:** Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets have the ability to benefit all participants.	1	1	0	1	1	1	0	0	0	0	1	0	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1
3	**Patent pool:** Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.	1	1	1	0	0	1	0	0	0	0	1	1	1	0	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
4	**Public-private partnership:** Public-private partnerships is any arrangement between one or more public and private entities. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	1	0	0	1	1	1	1	0	1	1	1	0	1	0	1
5	**Tax credits:** Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.	1	0	0	1	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0
6	**Advanced market commitments:** Advanced market commitments are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
7	**Differential pricing:** Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
8	**Patent buyouts:** IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.	1	0	0	0	0	0	1	0	0	0	1	1	0	0	1	1	0	0	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
9	**Pooled fund:** When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.	0	1	0	1	0	1	1	1	1	0	1	1	1	1	1	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0
10	**Prize fund:** Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.	1	1	0	1	0	1	0	1	1	0	1	1	1	0	1	0	0	0	1	0	1	1	0	0	0	0	1	1	1	0	0	0	0	0	1	0	1	0	0	1
11	**Rating system:** Pharmaceutical organizations are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.	0	0	0	0	0	1	0	1	1	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0
12	**Intellectual property and market exclusivity:** Intellectual property refers to the right that the innovator receives when a new innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.	1	0	1	0	0	1	1	0	0	0	1	1	0	0	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
13	**Policy instrument:** Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy. Instruments can also include altering and enforcing domestic policies.	0	0	1	1	1	1	0	1	1	1	1	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0	1
14	**Priority review voucher:** Law under which companies that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.	1	1	0	1	0	1	0	0	0	0	1	1	0	0	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0
15	**Trade, tariff adjustments:** Adjustments made to the trading or the taxes and required costs associated with trading of specified manufactured drugs.	1	0	1	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	1	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
16	**Collaboration and consortiums:** A collaboration network refer to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a goal.	0	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	0	1	0	1	1	0	1	1	1	0	1	1	1	0
17	**Colloquium and symposium:** An academic conference or seminar held, focussing on one topic.	0	0	0	0	0	1	0	0	1	0	1	0	0	0	1	1	1	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0
18	**Policy and legislation:** Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.	0	0	1	1	1	0	0	0	1	1	1	0	1	1	1	1	0	0	0	1	1	0	1	1	0	1	0	0	0	0	0	0	0	1	0	1	1	1	1	0
19	**Drug status designation:** Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.	1	1	1	1	0	0	1	0	0	0	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	**Joint venture:** Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.	1	0	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	1
21	**Independent organization:** Independent organizations does not require the approval of a government agency for decision-making and financial planning.	1	1	0	1	0	0	0	0	0	0	1	1	1	0	1	1	1	1	0	1	1	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0	0
22	**Hybrid public-private partnership:** This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention, the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	0	1	1
23	**Research laboratories:** Research laboratories are scientifically orientated facilities equipped with equipment to complete experiments aimed at R&D of drugs.	1	0	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	1	1	1
24	**Treaty:** Formal agreement between two or more political authorities, subject to international law.	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	1	1	1	1	1	0	1	0	0	0	0	0	0	1	0	0	1	1	0	1	1
25	**Working Group:** Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.	1	0	1	1	0	1	1	0	0	0	1	1	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	1	1	0	0	0
26	**Coordination mechanism and platform:** Initiatives to coordinate R&D investments and activities. Operate to clarify priorities, increase transparency, and diversify stakeholders.	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1

Domain 2 Enabler profile

DOMAIN 2: ENABLER INQUIRY FORM	
OBJECTIVES	INTERNAL CAPABILITIES
1 Goal of the incentive strategy? (Inclusion)	1 Available funding. (Exclusion)
Improve the state of the R&D pipeline	Limited to an amount
Enable organizations to innovate easier	Full capacity
Gain market exclusivity over an innovation	No capacity
Advance the R&D field	2 Tranches to innovators? (Inclusion)
Deliver affordable and accessible treatment	Beginning once-off
Convey an important message	End once-off
Fulfil corporate social responsibility	Once output is provided
Increase bandwidth and network	Incrementally, based on output
De-risk R&D process	Incrementally, based on timing
Political obligations	Incrementally, as innovator requires
2 Which innovators are targeted? (Inclusion)	3 Ability to influence policy? (Inclusion)
Large pharmaceutical organizations (private)	Clinical trial regulation policies
SMEs (private)	Market authorization policies
Governmental institutions	Market exclusivity policies
Independent scientists	Pricing policies
Academic institutions	Tax credit policies
NGO organizations	National/international intellectual property policies
Everyone	National policies and legislation
3 Intention for the consumers? (Exclusion)	International trade law
Provide drug	Access and expertise? (Inclusion)
Multi-purpose drug	4 Access to key data
Play a role in improved access	Access to compounds
Implement mass drug administrations	Access to intellectual property
Deliver regime treatment	Technology expertise and access
4 Desired relationship with innovators? (Inclusion)	R&D expertise
Once-off occasion	
Limited to a number of years	
Milestone related	
Engage at given time instances	
Collaborate and build a partnership	
5 Role and Responsibility willing to play? (Exclusion)	
Fund R&D	
Partially fund R&D	
Facilitate collaboration between innovators	
Collaborate with innovator	
Facilitate in regulatory process	
Provide market exclusivity	
Adjust policies and regulations	
Provide market certainty	

Background Logic 1AB

Background logic 2: Enabler Matrix	1. Goal of the incentive strategy										2. Which innovators are targeted?							3. Intention for the patients?					4. Desired relationship with innovator?					5. Role & responsibility willing to play?								1. Available funding?			2. Funding timing?			3. Ability to influence /provide guidance in policies?									4. Access to aspects?				
	Improve the state of the R&D pipeline	Enable organizations to innovate easier	Gain market exclusivity over an innovation	Advance the R&D field & body of knowledge	Deliver affordable and accessible treatment	Convey an important message	Fulfil corporate social responsibility	Increase bandwidth and network	De-risk R&D process	Political obligations	Large pharmaceutical organizations(private)	SMEs (private)	Governmental institutions	Independent scientists	Academic institutions	NGO organizations	Everyone	Provide drug/novel drug	Multi-purpose drug	Play a role in improved access	Deliver regime treatment	Implement mass drug administrations	Once-off occasion	Limited to a number of years	Milestone related	Engage at given time instances	Collaborate and build a partnership	Fund R&D	Partially fund	Facilitate collaboration between innovators	Collaborate with innovator	Facilitate in regulatory process	Provide market exclusivity	Adjust policies and regulations	Provide market certainty	Limited to an amount	Full capacity	No capacity	Beginning once-off	End once-off	Once output provided	Incrementally, based on output	Incrementally, based on timing	Incrementally, as innovator requires	Clinical trial regulation policies	Market authorization policy	Market exclusivity policies	Pricing policies	Tax credit policies	National policies and legislations	National/International intellectual property	International trade law	Access to key data	Access to compounds	Access to intellectual property	Technology expertise and access	R&D expertise
Push interventions																																																						
1 Grant	1	0	0	1	0	0	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
2 Open-source initiative	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
3 Patent Pool	1	0	1	0	1	0	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1	0	0
4 PPP	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5 Tax credits	1	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Outcome-based pull strategies																																																						
6 Advanced market commitments	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	1	0	1	0	0	0	0	1	0
7 Differential pricing	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
8 Patent buyouts	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	1	0	1	1	1	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1	0
9 Pooled fund	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0
10 Prize fund	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
11 Rating system	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lego-regulatory pull strategies																																																						
12 Intellectual property and market exclusivity	1	0	1	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0	1	1	0	0	1	0	0	0	0	0	1	0
13 Policy instrument	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
14 Priority review voucher	1	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	1	0	0	1	1	0	0	0	1	0	0	0	0	1	0
15 Trade, tariff adjustments	1	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0	0
Hybrid strategies																																																					
16 Collaboration network and consortiums	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	1	0	1	1
17 Colloquium and symposium	0	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	1	0	1	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
18 Policy and legislation	0	0	1	0	1	0	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	1	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
19 Drug status designation	1	0	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	0	0	0
20 Joint venture	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
21 Independent organization	0	0	0	1	0	0	1	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1
22 Hybrid PPP	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
23 Research laboratories	1	1	0	1	0	0	1	0	0	1	0	1	1	1	1	1	0	1	1	0	1	0	0	1	0	1	1	0	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
24 Treaty	1	1	1	0	1	0	0	1	0	1	0	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1
25 Working Group	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	1	1	1	0	0	0	1	0	1	1	1	1	0	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	1	1
26 Coordination mechanism*	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1

Domain 3 Innovator matrix

DOMAIN 3: INNOVATOR INQUIRY FORM	
OBJECTIVES	**INTERNAL CAPABILITIES**
1 Reason for performing R&D for the disease?	**1 Nature of innovator stakeholder?**
Profit maximization	Small to medium organization (includes start-up)
Corporate social responsibility	Large pharmaceutical organization
Not for profit	Not-for-profit organization
Profit improvement	Governmental institution
Political obligations	Academic institution
2 Focus area of R&D and intention for patients?	Independent scientist (no organization linked)
R&D of drug	**2 Capacity to provide own funding?**
R&D of multi-purpose drug	No capacity
Play a role in improved access	Limited to an amount
Drug repurposing	Full capacity
Deliver regime treatment	**3 R&D limitations?**
3 Require from the enabler?	Don't have research laboratory
Fund all R&D costs	Don't have adequate equipment
Partially fund R&D	Lack of information (knowledge) on disease
Collaboration with enabler	Cumbersome nature of clinical trial regulations
Adjust policies and regulations	Shortage of finances
Facilitate regulatory process	Policies or regulatory limitations
Provide market exclusivity	No market certainty
Provide market certainty	**4 Authorization standards adhered to?**
Provide a collaboration platform	None
Provide risk insurance or security	Accredited authorisation organization
Improve export potential	
4 Preference or required funding timing?	
Beginning once-off	
End once-off	
Incrementally based on output	
Incrementally based on timing	
Incrementally as required	
Once output provided	
Don't require any funding	

Background Logic 3 Innovator matrix

	1. Reason for performing R&D for the disease?	Profit maximization	Corporate or social responsibility	Not for profit	Profit improvement	Political obligations	2. Focus area of R&D and intention for patients?	R&D of drugs / novel drugs	Develop regime treatment	R&D a multi-purpose drug/vaccine	Play a role in improved access	Drug repurposing	3. Require from enabler / incentive intervention	Cover all R&D costs	Partly cover R&D costs	Collaboration with enabler	To adjust policies and regulations	To facilitate in the regulatory process	To provide market certainty	To provide market exclusivity	Collaboration platform	Risk insurance or security	Improve export potential	4. Preference or required funding timing?	Beginning once-off	End once-off	Incrementally based on output	Incrementally based on timing	Incrementally as required / incrementally	Once output provided	Do not require any funding	1. Nature of organization?	Large pharmaceutical organizations (private)	Small-and medium enterprise (private)	NGO	Governmental institution	Academic Institution	Scientist (no company)	2. Capacity to provide own funding?	No capacity	Limited to an amount	Full capacity	3. R&D limitations?	Don't have research laboratory	Don't have adequate equipment	Lack of information (knowledge) on disease	Cumbersome nature of clinical trial regulations	Shortage of finances	Policies or regulation limitations	No market certainty	4. Which Authorization standards adhered to?	None	Accredited authorisation organization
Push interventions																																																					
1	Grant		0	1	1	1	1		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		1	0	1	1	0	0	0		0	1	1	1	1	1		1	1	1		0	0	0	0	1	0	0		0	1
2	Open-source initiative		0	1	1	1	1		0	0	0	0	1		0	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	0		0	0	1	1	0	0	0		1	1
3	Patent Pool		0	1	1	1	0		1	1	1	1	1		0	0	0	0	0	0	1	1	0	1		0	0	0	0	1	0	1		1	1	1	1	0	0		0	0	0		0	0	0	0	0	0	0		0	1
4	PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
5	Tax credits		1	0	0	1	0		1	1	1	0	1		0	1	0	1	0	0	0	0	0	0		0	0	0	1	0	1	1		1	1	0	1	1	0		0	0	0		0	0	0	0	0	0	0		0	0
Outcome-based pull incentives																																																					
6	Advanced market commitments		1	1	0	1	1		1	1	1	1	1		0	0	0	0	0	1	0	0	1	0		0	1	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		0	1
7	Differential pricing		0	1	1	1	1		1	1	1	1	1		0	1	0	1	0	0	0	0	0	1		0	0	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	0		0	0
8	Patent buyouts		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	1	1	0	1	0		0	1	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	0	0		0	1
9	Pooled fund		0	1	1	0	1		1	1	1	1	1		1	1	0	0	0	0	0	1	1	0		1	1	1	1	1	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		1	1
10	Prize fund		1	1	1	1	0		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		0	1	1	0	0	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		0	1
11	Rating system		0	1	1	0	1		1	1	1	1	0		0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	1		1	1	1	1	1	0		0	0	1		0	0	0	0	0	0	0		1	1
Lego-regulatory pull strategies																																																					
12	Intellectual property and market exclusivity		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	0	1	0	1	1		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		0	1
13	Policy instrument		0	1	1	0	1		0	0	0	1	0		0	0	0	1	1	0	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	0	1		0	0	0	0	0	1	0		1	1
14	Priority review voucher		1	0	1	1	0		1	1	1	0	0		0	1	0	0	1	0	0	0	0	0		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	1	0	1	0		1	1
15	Trade, tariff adjustments		1	1	1	1	1		1	1	1	1	0		0	1	0	1	0	1	1	0	1	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		0	0	0	0	1	1	0		1	1
Hybrid strategies																																																					
16	Collaboration network and consortiums		0	1	1	0	1		1	1	1	1	1		1	1	1	0	0	0	0	1	1	1		0	0	1	1	1	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
17	Colloquium and symposium		0	1	1	0	0		0	0	0	0	0		0	0	1	0	1	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	1	1	0	0	0		1	1
18	Policy and legislation		0	1	1	0	1		0	1	0	1	1		0	0	0	1	1	1	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		1	1
19	Drug status designation		1	1	1	1	0		1	1	1	1	1		0	1	0	1	0	1	0	0	1	1		0	0	0	0	0	0	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		1	1
20	Joint venture		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	1	1	1	1	1	0		1	1	1	1	1	1		0	1	1		1	1	1	1	1	0	0		1	1
21	Independent organization		1	1	1	1	0		1	1	1	1	1		1	0	1	0	1	1	0	1	0	0		1	1	1	1	1	0	1		1	1	1	0	0	1		0	0	1		1	1	1	1	0	0	0		1	1
22	Hybrid PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	1	1		1	1
23	Research laboratories		1	1	0	1	1		1	1	1	0	1		0	0	1	0	0	0	0	0	0	0		0	0	0	0	0	0	1		0	1	1	1	1	1		0	0	1		1	1	0	0	0	0	0		1	1
24	Treaty		0	0	0	1	1		1	1	1	1	1		1	1	0	1	1	1	1	1	1	1		1	1	0	1	0	0	1		0	0	0	1	0	0		1	1	1		0	0	1	1	1	1	0		1	1
25	Working Group		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	0	1	1	1	0	1		0	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
26	Coordination mechanism		1	1	1	0	1		1	1	1	1	1		0	1	1	0	0	0	0	1	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	0		1	1

Domain 4 Consumer profile

DOMAIN 4: CONSUMER REQUIREMENTS	
END CONSUMER (patient)	
1 **Socio-economic inequalities**	
Require differential pricing	
Must eliminate all financial risk	
2 **Contextual treatment criteria**	
Accommodates contextual treatment criteria	
PROCUREMENT: PUBLIC / PRIVATE (FOR-/ NOT FOR PROFIT)	
3 **Affordability**	
Require differential pricing	
4 **End-price profit margins**	
Any profit margins allowed	
Restricted profit margins	
No profit	
5 **Availability and accessibility**	
IP regulation allows procurement of drugs to target area	
Existing drugs not allowed in target area	
Drug status designation required	

BACKGROUND LOGIC 4: CONSUMER MATRIX	END-CONSUMER					PROCURERS (PUBLIC / PRIVATE)								
	1. Socio-economic inequalities	Require differential pricing	Must eliminate all financial risk	2. Contextual treatment criteria	Addresses contextual treatment criteria	3. Affordability	Require differential pricing	4. End-price profit margins	Any profit margins allowed	Restricted profit margins	No profit	5. Availability and accessibility	IP regulation allows procurement of drugs to target area	Existing drugs not allowed in target area	Drug status designation required
Push intervention															
1 Grant		0	0		1		0		0	0	0		0	0	0
2 Open-source initiative		0	0		1		0		0	1	1		1	0	0
3 Patent pool		0	0		1		0		0	0	0		1	1	0
4 PPP		1	1		1		1		0	1	0		1	0	1
5 Tax credits		0	0		1		0		0	1	0		0	0	1
Outcome-based pull strategies															
6 Advanced market commitments		0	0		1		0		1	1	0		0	1	0
7 Differential pricing		1	1		0		1		0	1	0		0	0	0
8 Patent buy-outs		0	0		1		0		1	1	0		1	1	0
9 Pooled fund		0	0		1		0		0	0	0		0	0	0
10 Prize fund		0	0		1		0		0	0	0		0	0	0
11 Rating system		0	0		1		0		0	0	1		0	1	1
Lego-regulatory pull strategies															
12 Intellectual property		0	0		1		0		1	1	0		1	1	0
13 Policy instrument		1	1		1		1		1	1	1		1	1	1
14 PRV		0	0		1		0		0	1	0		0	0	0
15 Trade, tariff adjustments		1	1		0		1		1	1	1		1	1	1
Hybrid strategies															
16 Collaboration network and consortiums		0	0		1		0		0	0	1		0	0	0
17 Colloquium and symposium		0	0		1		0		0	0	1		0	0	0
18 Policy and legislation		0	0		1		0		1	1	1		1	1	0
19 Drug status designation		1	1		1		1		0	0	1		1	1	1
20 Joint venture		0	1		1		0		0	1	1		1	1	0
21 Independent organization		0	1		1		0		1	0	1		0	1	0
22 Hybrid between PPP and other mechanisms		1	1		1		1		1	1	1		1	1	1
23 Research laboratories		0	0		0		0		1	0	1		0	0	0
24 Treaty		1	0		0		1		0	1	1		1	1	0
25 Working group		0	0		1		0		0	1	1		0	1	0
26 Coordination mechanism		0	0		1		0		0	1	1		0	1	0

Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	BL	1		1	3		2	2	2	3		2	3	2	2	2	2		1	3	3	4	1		2	2	4	4	4		1	2	3		2	3		3	2	1	4	3		1	1	1	1
	Cluster 1: Profitability and market forces	Delink revenue from sales volume		Incentive improves product export potential	Improve product export potential (Incentive ability)	Improve export potential (Innovator require)	Incentive allows market exclusivity over an innovation	Gain market exclusivity over an innovation (Enabler goal)	Provide market exclusivity (Enabler ability)	Market exclusivity policies (Enabler ability to alter)	Provide market exclusivity (Innovator require)	Incentive provides market certainty	Provide market certainty (Enabler role)	Provide market certainty (Innovator require)	Incentive involves/requires national/international intellectual property policies (Enabler ability)	Incentive involves/requires tax credit policies (Enabler ability)	Incentive involves/requires pricing policies (Enabler ability)	Incentive involves/requires international trade law (Enabler ability)	Incentive improves NPV of stakeholders	Improve NPV of stakeholders	Profit improvement (Innovator goal)	Profit maximization (Innovator goal)	Any profit margins allowed (Consumer require)	Minimizes barriers to implementation (implementation of incentive)	Cluster 2Facilitate registration of drug / approval for use	Incentive involves/requires market authorization policies (Enabler ability)	Incentive involves/requires national policies and legislations (Enabler ability)	Existing drugs not allowed in target area (Consumer availability)	Drug status designation required (Consumer availability)	IP regulation allows procurement of drugs to target area (Consumer availability)	Cluster 3: Ability to influence nature of drug that is developed	Incentive encourage R&D of a drug/intervention	Encourage R&D of a drug/intervention (Incentive ability)	Provide drug (Enabler goal)	R&D of drug (Innovator goal)	Incentives stimulates multi-purpose drug R&D	Multi-purpose drug (Enable goal)	R&D of multi-purpose drug (Innovator goal)	Incentive allows the delivery of regime treatment	Deliver regime treatment (Innovator goal)	Deliver regime treatment (Enabler goal)	Payoff to innovators based on cost-effectiveness	Contextual treatment criteria can be addressed by incentive (Consumer requirements)	Incentive allows drug repurposing (Innovator goal)	Cluster 4: Improved governance	Promote equitable health-focused governance (Incentive ability)	Promote transparency and accountability (Incentive ability)	Advances the priority of disease on health agenda (Incentive ability)	Advance proper functioning of domestic policy (Incentive ability)
Push mechanisms																																														
Grant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Open-source initiative		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1		0	0	0	0	1		0	0	0	0	0	0	0	0	0	0	1	1		1	1	1	1
Patent pool		1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0		0	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	1		1	1	0	0
PPP		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1		1	1	0	1	1		1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1
Tax credits		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	0	1		0	0	0	1	0		1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Outcome-based pull strategies																																														
Advanced market commitments (AMC)		1	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	1	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1		0	0	1	0
Differential pricing		1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	0	1		0	0	1	0
Patent buy-outs		0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0		1	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	0		0	0	1	0
Pooled fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Prize fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	1	1	1		0	1	1	0
Rating system		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	1	1	0		1	1	1	1	1	1	1	1	1	0	1	0		1	1	1	1
Lego-regulatory pull strategies																																														
Intellectual property		0	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0		0	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	0		0	0	1	0
Policy instrument		0	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	1	1		1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	1	0		1	1	0	1
PRV		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1		1	1	0	0	0		1	1	1	1	1	1	1	1	1	0	1	0		0	0	1	0
Trade, tariff adjustments		0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0		1	1	1	1	1		1	1	1	1	1	1	1	1	1	0	0	0		1	0	1	1
Hybrid strategies																																														
Collaboration network and consortiums		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	0
Colloquium and symposium		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	1	0		0	1	1	1
Policy and legislation		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1		1	1	1	0	1		0	0	0	0	0	0	0	1	1	0	0	1		1	1	0	1
Drug status designation		1	1	1	1	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	0	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	0	1	1		0	0	1	0
Joint venture		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	0	1		0	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Independent organization		1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	0
Hybrid between PPP and other mechanisms		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1
Research laboratories		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	0	1		0	1	1	0
Treaty		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1		1	1	1	0	1		1	1	1	1	1	1	1	1	1	0	0	1		1	1	1	1
Working group		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	0	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1		0	0	1	0
Coordination mechanism		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0

Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 5: Population impact and access	Incentive improves consumer access	Improve consumer access (Incentive ability)	Play a role in improved access (Enabler goal)	Play a role in improved access (Innovator goal)	Incentive enables mass drug administration	Enable mass drug administration (Incentive ability)	Implement mass drug administrations (Enabler goal)	Incentive aims to reduce burden of disease in area	Incentive aims to minimize disruptive effects to population	Incentive allows for differential pricing (Consumer requirement)	Incentive allows differential pricing (End-consumer requirement)	Incentive allows differential pricing (Procurer requirement)	Deliver affordable and accessible treatment (Enabler goal)	Incentive eliminates all financial risk (Consumer requirement)
			1	2	3		1	2	1	1		4	4	2	4
Push mechanisms															
Grant		1	1	1	1	1	1	1	1	0	0	0	0	0	0
Open-source initiative		0	0	0	0	0	0	0	1	1	0	0	0	1	0
Patent pool		1	1	1	1	0	0	0	1	0	0	0	0	1	0
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tax credits		0	0	0	0	1	1	1	1	0	0	0	0	0	0
Outcome-based pull strategies															
Advanced market commitments (AMC)		1	1	1	1	1	1	1	1	1	0	0	0	0	0
Differential pricing		1	1	1	1	1	1	1	1	0	1	1	1	1	1
Patent buy-outs		0	0	0	0	0	0	0	1	0	0	0	0	0	0
Pooled fund		1	1	1	1	1	1	1	1	0	0	0	0	0	0
Prize fund		1	1	1	1	0	0	0	1	0	0	0	0	0	0
Rating system		1	1	1	1	0	0	0	1	0	0	0	0	1	0
Lego-regulatory pull strategies															
Intellectual property		0	0	0	0	0	0	0	1	0	0	0	0	0	0
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1
PRV		0	0	0	0	0	0	0	1	0	0	0	0	1	0
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hybrid strategies															
Collaboration network and consortiums		1	1	1	1	1	1	1	1	0	0	0	0	1	0
Colloquium and symposium		0	0	0	0	0	0	0	1	0	0	0	0	0	0
Policy and legislation		1	1	1	1	1	1	1	1	1	0	0	0	1	0
Drug status designation		1	1	1	1	1	1	1	1	0	1	1	1	1	1
Joint venture		1	1	1	1	1	1	1	1	0	0	0	0	0	1
Independent organization		1	1	1	1	0	0	0	1	0	0	0	0	0	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Research laboratories		0	0	0	0	0	0	0	1	1	0	0	0	0	0
Treaty		1	1	1	1	1	1	1	1	1	1	1	1	1	0
Working group		1	1	1	1	1	1	1	1	0	0	0	0	1	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	0	0	0	1	0

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 6: Limited enabler resource investment	Affordable to implement the incentive	Incentive allows resources to develop drugs to be government financed	Incentive allows payoff to innovator to be in the beginning, once-off	Incentive allows payoff to innovator to be in the beginning, once-off (Enabler requirement)	Incentive allows payoff to innovator to be in the beginning, once-off (Innovator requirement)	Incentive allows payoff to innovator to be at the end, once-off	Incentive allows payoff to innovator to be at the end, once-off (Enabler requirement)	Incentive allows payoff to innovator to be at the end, once-off (Innovator requirement)	Incentive allows payoff to innovator to be incrementally, based on output	Incentive allows payoff to innovator to be incrementally, based on output (Enabler requirement)	Incentive allows payoff to innovator to be incrementally, based on output (innovator requirement)	Incentive does not require enabler funding (Enabler no capacity)	Incentive does not require enabler funding (Enabler has no capacity to fund)	Innovator does not require any funding from enabler, or incentive (Innovator requirement)	Incentive requires/allows the enabler to partially fund R&D	Incentive requires/allows the enabler to partially fund R&D (Enabler requirement)	Incentive requires/ allows innovator to partially fund R&D (*Innovator requirement*)	Incentive payout to innovator is a once-off occasion (Enabler requirement)	Incentive payout to innovator occurs once output is delivered (Innovator requirement)	Incentive allows innovator payouts to be limited to a number of years	Incentive allows innovator payouts to be milestone related	Incentive allows enabler to engage with innovator at given time instances	Incentive allows enabler funding to be limited to an amount
		1	1		2	3		2	3		2	3		2	3		2	3	2	3	2	2	2	2
Push mechanisms																								
Grant		1	1	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	1	0	1	1	0	1
Open-source initiative		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Patent pool		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1	1	0	0
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1
Tax credits		0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	0	1	0
Outcome-based pull strategies																								
Advanced market commitments (AMC)		1	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0
Differential pricing		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1	1	0	0	0
Patent buy-outs		0	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	0	0	1
Pooled fund		1	0	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1
Prize fund		1	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	1	0	1
Rating system		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	0	1	0	1	0
Lego-regulatory pull strategies																								
Intellectual property		1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1	1	1	0	0
Policy instrument		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	1	0
PRV		1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	1	1	0
Trade, tariff adjustments		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	0	0	0	1	0
Hybrid strategies																								
Collaboration network and consortiums		1	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0
Colloquium and symposium		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	1	0	0	0	1	0
Policy and legislation		0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	1	0
Drug status designation		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0
Joint venture		1	0	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1
Independent organization		0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	1	1	0	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1
Research laboratories		0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1	0	1	0
Treaty		1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	0	1	1	1	1
Working group		1	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0
Coordination mechanism		1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	0	1	0	1	1

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 7: Encourage competition in the innovation process	Incentive encourages large firm participation	Incentive encourages large firm participation	Incentive allows large pharmaceutical organization (private) participation (Enabler identity)	Incentive aimed at incentivising large pharmaceutical organization (Innovator identity)	Incentive allows competition among parallel experiments	Incentive enlarges the number of clinical trials registered	Incentive targets all organizations to participate (Enabler target)
			1	2	3	1	1	2
Push mechanisms								
Grant		0	0	0	0	0	0	0
Open-source initiative		1	1	1	1	0	1	0
Patent pool		1	1	1	1	0	0	0
PPP		1	1	1	1	0	1	1
Tax credits		1	1	1	1	0	0	0
Outcome-based pull strategies								
Advanced market commitments (AMC)		1	1	1	1	0	0	1
Differential pricing		1	1	1	1	0	0	1
Patent buy-outs		1	1	1	1	0	0	1
Pooled fund		0	0	0	0	0	0	1
Prize fund		0	0	0	0	1	1	1
Rating system		1	1	1	1	1	0	1
Lego-regulatory pull strategies								
Intellectual property		1	1	1	1	1	0	1
Policy instrument		1	1	1	1	0	1	1
PRV		1	1	1	1	1	0	1
Trade, tariff adjustments		1	1	1	1	0	0	1
Hybrid strategies								
Collaboration network and consortiums		1	1	1	1	0	0	1
Colloquium and symposium		1	1	1	1	0	0	1
Policy and legislation		1	1	1	1	0	1	1
Drug status designation		1	1	1	1	1	0	1
Joint venture		1	1	1	1	0	1	0
Independent organization		1	1	1	1	0	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	0	1	0
Research laboratories		0	0	0	0	0	1	0
Treaty		0	0	0	0	0	1	0
Working group		0	0	0	0	0	0	0
Coordination mechanism		1	1	1	1	0	1	1

Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	**Cluster 8: Overcome barriers to innovator participation in R&D process**	**Incentive allows small and medium organizations to be incentivized**	Incentive enables participation of small and medium organizations	Incentive enables participation of small and medium organizations (Enabler target)	Incentive enables participation of small and medium organizations (Innovator identity)	**Incentive allows governmental institutions to be incentivized**	Incentive allows governmental institutions to be incentivized (Enabler target)	Incentive allows governmental institutions to be incentivized (Innovator identity)	**Incentive allows independent scientists to be incentivized**	Incentive allows independent scientists to be incentivized (Enabler target)	Incentive allows independent scientists to be incentivized (Innovator identity)	**Incentive allows academic institutions to be incentivized**	Incentive allows academic institutions to be incentivized (Enabler target)	Incentive allows academic institutions to be incentivized (Innovator identity)	**Incentive allows NGO organizations to be incentivized**	Incentive allows NGO organizations to be incentivized (Enabler target)	Incentive allows NGO organizations to be incentivized (Innovator identity)	**Incentive financing is timed across drug lifecycle**	**Incentive provides long term R&D financing**	**Incentive provides sustainable financing for innovator**	**Incentive provides R&D project insurance**	Incentive provides R&D project insurance	Incentive provides risk insurance or security (Innovator requirement)	**Incentive de-risks the R&D process**	**Incentive requires/allows enabler to fund R&D**	Incentive allows enabler to fund R&D (Enabler goal)	Incentive requires enabler to fund all R&D costs (Innovator requirement)	**Incentive allows enabler to fully fund R&D (Enabler full capacity)**	Incentive allows enabler to fully fund R&D (Enabler full capacity)	Incentive requires enabler to completely fund R&D (Innovator no ability)	**Incentive requires enabler to partially fund R&D (Innovator ability)**	Incentive requires enabler to partially fund R&D (Innovator requirement)	Incentive requires enabler to partially fund R&D (Innovator ability)	**Incentive allows funding to be incremental, as innovator requires**	Incentive allows funding to be incremental, as innovator requires (Enabler ability)	Incentive allows funding to be incremental, as innovator requires (Innovator requirement)	**Incentive allows funding to be incremental, based on timing**	Incentive allows funding to be incremental, based on timing (Enabler ability)	Incentive allows funding to be incremental, based on timing (Innovator requirement)	**Incentive does not provide any funding (Innovator has full capacity to provide own funding)**	**Incentive allows enabler to increase bandwidth and network (Enabler goal)**	**Incentive utilizes enabler's ability to influence intellectual property (Enabler ability)**	**Incentive requires/ utilizes enabler's access to key data**	Incentive utilizes enabler's access to key data (Enabler ability)	Incentive provides innovator with information (knowledge) on disease (Innovator requirement)	**Incentive utilizes enabler's access to compounds (Enabler ability)**	**Incentive requires/ utilizes enabler technology expertise and access**	Incentive requires/ utilizes enabler technology expertise and access	Incentive provides innovator access to adequate equiptment (Innovator requirement)	Incentive provides innovator with access to research laboratory (innovator requirement)	**Incentive requires/ utilizes enablers R&D expertise**	Incentive requires/ utilizes enablers R&D expertise	Incentive aids innovator with cumbersome nature of clinical trial regulations (innovator requirement)	**Incentive addresses innovator's policy or regulatory limitations (innovator requirement)**	**Incentive provides innovator with market certainty (innovator requirement)**	**Innovator does not adhere to any authorization standards (innovator nature)**	**Innovator has accredited authorisation organization (innovator nature)**	**Incentive rewards innovation**
			1	2	3		2	3		2	3		2	3		2	3	1	1	1		1	2	2		2	3		2	3		3	3		2	3		2	3	3	2	2		2	3	2		2	3	3		2	3	3	3	3	3	1
Push mechanisms																																																										
Grant		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Open-source initiative		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	1	0
Patent pool		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0
Tax credits		1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Outcome-based pull strategies																																																										
Advanced market commitments (AMC)		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1
Differential pricing		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Patent buy-outs		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1
Pooled fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Prize fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	1	1	1	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1
Rating system		1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Lego-regulatory pull strategies																																																										
Intellectual property		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
PRV		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1
Hybrid strategies																																																										
Collaboration network and consortiums		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Colloquium and symposium		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	1	1	1	0	0	1	1	0
Policy and legislation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
Drug status designation		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Joint venture		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Independent organization		1	1	1	1	0	0	0	0	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Research laboratories		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	0
Treaty		0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0	1	1	0
Working group		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0

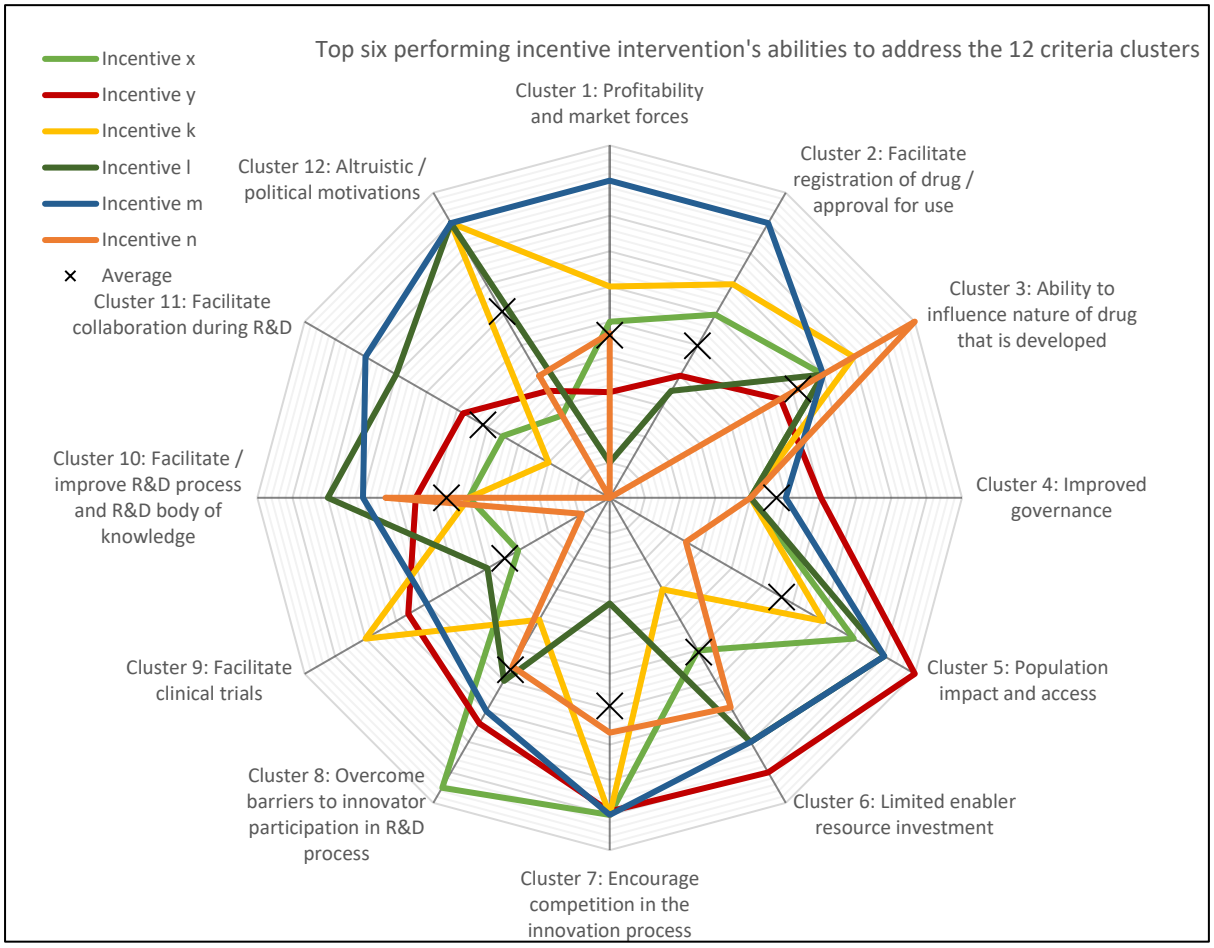
Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING		1	1	1	1	1	1	1	2			1	1	1	1	1	1	2	2	2				1	2	2		2	3			1	3			2	3			2	3			2			2	3	3		4	4
	Cluster 9: Facilitate clinical trials	**Incentive allows provision of public subsidies for clinical trials**	**Incentive reduces clinical trial risk involved**	**Incentive assist in registration and monitor of trials**	**Incentive globalizes clinical trial methods**	**Incentive reduces clinical trial activation difficulty**	**Incentive enhances or prompt the quality of clinical trials**	**Incentive aids in clinical trial regulation**	**Clinical trial regulation policies (Enablers ability to influence)**		**Cluster 10: Facilitate / improve R&D process and R&D body of knowledge**	**Incentive aims to/ allows improvement of R&D productivity**	**Incentive provides regulatory oversight to promote R&D**	**Incentive provides regulatory exclusivity provisions for R&D**	**Incentive encourages efficient innovation**	**Incentive ensures the conservation of resources in R&D process**	**Incentive requires/ allows green R&D of drugs**	**Incentive enables organizations to innovate easier (Enabler goal)**	**Incentive advances the R&D field & body of knowledge (Enabler goal)**	**Incentive can improve the state of the R&D pipeline (Enabler goal)**		**Cluster 11: Facilitate collaboration during R&D**	**Incentive facilitates cooperation and synergy between all stakeholders**	Facilitates cooperation and synergy between all stakeholders	Incentive facilitates collaboration between innovators (Enabler goal)	**Incentive allows enabler to collaborate and build a partnership/s (Enabler goal)**	**Incentive allows enabler to collaborate with innovator**	Incentive allows enabler to collaborate with innovator (Enabler goal)	Incentive allows innovator to collaborate with enabler (Innovator requirement)	**Incentive provides a platform for coordinating innovators**	Incentive provides a platform for coordinating innovators	Incentive provides a collaboration platform (Innovator requirement)	**Incentive allows/ requires enabler to facilitate in regulatory process**	Incentive allows/ requires enabler to facilitate in regulatory process (Enabler ability)	Incentive allows/ requires enabler to facilitate innovator in regulatory process (Innovator requirement)	**Incentive requires enabler to adjust policies and regulations**	Enabler has ability to adjust policies and regulations	Innovator requires enabler to adjust policies and regulations (should be allowed by incentive)		**Cluster 12: Altruistic / political motivations**	**Incentive convey an important message (Enabler goal)**	**Incentive allows corporate social responsibility to be fulfilled**	Incentive allows enabler to fulfil corporate social responsibility (Enabler goal)	Incentive allows innovator to fulfil corporate social responsibility (Innovator goal)	**Incentive allows enabler to fulfil political obligations**	Incentive allows enabler to fulfil political obligations (Enabler goal)	Incentive allows innovator to fulfil political obligations (innovator goal)	**Incentive allows not for profit R&D (Innovator goal)**	**Incentive allows not for profit/ restricted profit margins for drug procurer**	Incentive enables/ allows restricted profit margins for drug procurers	Incentive enables no profit margins for drug procurers
Push mechanisms																																																		
Grant		0	0	0	0	1	0	0	0			0	1	0	0	0	0	0	1	1			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	1	1	1	1	1	1	1	0	0	0
Open-source initiative		0	1	1	1	0	0	0	0			1	0	0	0	0	0	0	1	1	1			1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0		1	1	1	1	1	1	1	1	1	1	1
Patent pool		0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	0	1			0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	0		0	1	1	1	0	0	0	1	0	0	0
PPP		1	0	1	1	1	0	1	1			0	0	0	0	0	0	0	1	1	1			1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0		1	1	1	1	1	1	1	1	1	1	0
Tax credits		1	0	0	0	0	0	0	1			0	1	1	0	0	0	0	0	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1			0	0	0	0	0	0	0	0	1	1	0
Outcome-based pull strategies																																																		
Advanced market commitments (AMC)		0	0	0	0	0	0	0	0			0	0	0	1	1	0	0	0	1				0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	0	1	1	0
Differential pricing		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1			1	1	1	1	1	1	1	1	1	1	0
Patent buy-outs		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	1	1	0
Pooled fund		0	1	0	0	0	0	0	0			0	0	0	1	1	0	1	0	1				1	1	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	1	0	0	0
Prize fund		0	0	0	1	0	1	0	0			0	0	0	1	1	0	1	1	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	1	1	1	0	0	0	1	0	0	0
Rating system		0	0	0	0	0	1	0	0			1	1	1	1	1	1	0	1	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			1	1	1	1	1	1	1	1	0	0	1
Lego-regulatory pull strategies																																																		
Intellectual property		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	1	1	0
Policy instrument		0	0	1	1	0	1	1	1			0	1	0	1	1	1	0	1	0				0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	1	1	1			0	1	1	1	1	1	1	1	1	1	1
PRV		0	0	0	0	1	0	1	1			0	0	1	0	0	0	0	1	1				0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0			1	0	0	0	0	0	0	1	1	1	0
Trade, tariff adjustments		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1			0	1	1	1	1	1	1	1	1	1	1
Hybrid strategies																																																		
Collaboration network and consortiums		0	1	1	1	0	1	1	0			1	0	0	1	1	0	1	1	1				1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0			1	1	1	1	1	1	1	1	0	0	1
Colloquium and symposium		0	0	0	1	0	1	0	0			1	1	0	1	0	0	1	1	0				1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0			1	1	1	1	0	0	0	1	0	0	1
Policy and legislation		1	0	1	1	1	1	0	1			0	1	0	1	0	1	0	0	0				0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	1	1	1			0	1	1	1	1	1	1	1	1	1	1
Drug status designation		0	0	0	0	0	0	0	1			0	0	1	0	0	0	0	1	1				0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1			1	1	1	1	0	0	0	1	0	0	1
Joint venture		0	1	0	1	1	1	1	0			0	0	0	1	1	0	1	1	1				1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	1	1	1	1
Independent organization		0	0	0	0	0	1	0	0			0	0	0	0	0	0	0	1	0				1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0			0	1	1	1	0	0	0	1	0	0	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	0	1	1			0	1	0	0	0	0	1	1	1				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			0	1	1	1	1	1	1	1	1	1	1
Research laboratories		0	0	1	1	1	1	1	0			0	0	0	1	1	1	1	1	1				1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	0	0	0	1
Treaty		1	0	0	1	0	1	1	1			0	1	0	1	1	1	1	0	1				1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1			0	0	0	0	1	1	1	0	1	1	1
Working group		0	0	0	1	1	0	0	0			0	0	0	0	0	0	1	1	1				1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	1
Coordination mechanism		0	1	1	1	1	1	1	0			0	0	0	1	1	1	1	0	0				1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	1

Domain 5 solution set (1 of 2)

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
1	Grant														
2	Open-source initiative														
3	Patent pool														
4	PPP														
5	Tax credits														
6	Advanced market commitments														
7	Differential pricing														
8	Patents buy-outs														
9	Pooled fund														
10	Prize fund														
11	Rating system														
12	Intellectual property														
13	Policy instrument														
14	PRV														
15	Trade, tariff adjustments														
16	Collaboration network														
17	Colloquium and symposium														
18	Policy and legislation														
19	Drug status designation														
20	Joint venture														
21	Independent organization														
22	Hybrid PPP														
23	Research laboratories														
24	Treaty														
25	Working group														
26	Collaboration platform														

Domain 5 solution set (2 of 2)



Non-incentive-based interventions (1 of 8)

1. Country economic status		*For further reference*	
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)	-
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

2. Burden fully characterized		*For further reference*	
Meaning	The affected patients are diagnosed, being monitored and documented properly.	(Olmsted et al., 2006; RAND Corporation, 2007; Novak et al., 2013)	-
Relevance	Once the burden of a disease is fully characterized, consumer demand can be estimated. Consumer demand will have an influence on how profitable the perceived market is. Fully characterizing the burden also assists in the planning, distribution and implementation of control strategies.		
Intervention considerations	Diagnostic tools and technology, availability and access there of		
	Diagnostic intervention and intervention strategies		
	Availability of health facilities (option is to consider mobile health facilities)		
	Educate populations on disease side-effects, risks, and necessity of health interventions		
	Capture burden characterization data		

3. Physicians per 1000 population		*For further reference*	
Meaning	The number of physicians available per capita / 1000 of people	(Al-Shamsi, 2017)	-
Relevance	The higher the availability of physicians in a country, the higher the likelihood that the population will have access to adequate care.		
Intervention considerations	Recruit international medical graduates		
	Modify postgraduate majors to allow physicians to enter the practice in areas of need		
	Shorten the preparatory under-graduate medical education years and introduce modern methods of teaching.		

4. Quality of existing drugs		*For further reference*	
Meaning	Drugs should not pose significant health risks to patients and should be effective in treating the disease.	(van Olmen et al., 2010); (Dorlo et al., 2012); (Rauscher, Walkowiak and Djara, 2018); (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	-
Relevance	Patients depend on drugs for disease mitigation. If quality is not up-to-standard, then disease burden might increase or might not decrease.		
Intervention considerations	Repeat final clinical trial stages to monitor effects of medicine in a controlled environment		
	Remove drugs from market		
	Improve monitoring of ADR		
	Pharmacovigilance		
	Quality control of current manufacturing procedures		
	Enforce international clinical trial and manufacturing practices and regulations		

5. Availability of drugs for the desired population		*For further reference*	
Meaning	Drugs are available in the right quantities, on the right time for patients to access.	(Jackson, 2018) ; (Niëns and Brouwer, 2013), (Holt, Gillam and Ngondi, 2012)	-
Relevance	If drugs are adequate but not available, then patients might not be effectively treated. Possible resistance to medicines.		
Intervention considerations	Supply chain management		
	Distribution networks		
	Inventory management at health facilities		
	Replenishment systems at health facilities		
	Burden characterization assists in inventory planning		

Non-incentive-based interventions (2 of 8)

6. Affordability of current drugs to desired population		*For further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	-
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

7. Appropriateness of drugs to the desired population		*For further reference*	
Meaning	Drugs must target the disease intended for. Intervention must be understandably explained and not interfere with culture.	(Jackson, 2018), (Hotez, 2008)	-
Relevance	If drugs are not appropriate, then patients won't use it or, if they use it, improvements in disease burden will not be made.		
Intervention considerations	Screen culture and explore possible cultural and ethical issues		
	Improve diagnostics of patients		
	Communication in understandable language for population group		
	Survey to understand the feelings of patients		

8. Acceptability of drugs to the desired population		*For further reference*	
Meaning	Drugs are not acceptable because of cultural values norms or stigmas.	(Jackson, 2018) ; (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	-
Relevance	If patients do not accept drugs, then intervention strategies go to waste.		
Intervention considerations	Educate people to reduce stigmas.		
	Educate people to understand potential of drugs.		
	Respect and honour the norms and values of the patient group.		

9. Comprehensiveness of services delivered		*For further reference*	
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004), (WHO, 2010)	-
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.		
Intervention considerations	Education of prevention measures.		
	Address root-cause of disease (e.g. water and sanitation)		
	Investigate the needs of the affected population group		
	Address social needs of patients		
	Repeat prevention or mass drug administration interventions, if deemed necessary.		

10 Continuity of patients' access to health services [Check in Case study 1 Appendix]		*For further reference*	
Meaning	For health interventions where once-off treatment is not adequate, follow-up treatments must be scheduled and adhered to.	(Jackson, 2018, (Holt, Gillam and Ngondi, 2012, Stevens, 2004)	-
Relevance	If follow-up treatments are not provided, then patient health might not improve as desired.		
Intervention considerations	Scheduling of follow-up interventions		
	Mobile health facilities		
	Track patient health records and data		
	Monitor and track patients		

11. Coordination of service delivery networks		*For further reference*	
Meaning	Service delivery is done in an organized, timely, professional and appropriate manner.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; WHO, 2010a; Rauscher et al., 2018)	-
Relevance	If service delivery is not coordinated properly, then some patients might be overlooked for treatment, not have access, or might miss the opportunity to meet with health care workers (if not properly communicated)		
Intervention considerations	Communication services		
	Scheduling of health workers		
	Monitor service delivery per area		
	Monitor drug distribution or mass drug administrations per region.		

Non-incentive-based interventions (3 of 8)

12. Minimize waste of resources in service delivery		*For further reference*	
Meaning	Any resource that is not used or used in an effective or efficient manner, leads to waste and possible financial losses.	(Priya, Nandini and Selvamani, 2012)	-
Relevance	Given that most waste is preventable, resources could be used in a more effective manner.		
Intervention considerations	Monitor service delivery to identify and address waste.		
	Coordinate service delivery actions		
	Waste management		

13. Demand size or sales force (relates to disease burden)		*For further reference*	
Meaning	The size of the burdened population, and patients who needs medicines, or intervention strategies.	(Novak et al., 2013; RAND Corporation, 2007)	-
Relevance	By determining the size of the burdened population, service delivery and intervention strategies can be planned more accurately. Also, service delivery waste can be reduced.		
Intervention considerations	Characterization of the burden of disease		
	Diagnostic interventions		
	Target repurposing		
	The size of the burdened population, and patients who needs medicines, or intervention strategies.		

14. The role of brand loyalty		*For further reference*	
Meaning	Brand loyalty of consumers to certain brands / drugs means that consumers buy certain drugs, based on previous experience, or perceived value. (relevant to other brands).	(Griffiths, 2008; Panchal *et al.*, 2012)	-
Relevance	If a product does not have brand loyalty, it might have the necessary characteristics to mitigate disease, but patients are not using it as a result of not 'trusting' the drug.		
Intervention considerations	Awareness amongst physicians of the value of the drug		
	Build trust in the communities		
	Well planned market strategies		

15. Bargaining power of the suppliers (chemical entities)		*For further reference*	
Meaning	The ability of suppliers to influence the prizing of the entities that they offer the pharmaceutical innovators and manufacturers.	(Whiteside, 2016)	-
Relevance	The stronger the bargaining power of the suppliers; the higher the prizes of resources, and the higher the total cost of drug interventions.		
Intervention considerations	Research alternative suppliers.		
	Support local suppliers.		
	Consider importing of goods.		
	Ensure quality of suppliers, if weak bargaining power.		

16. Existence of competitors		*For further reference*	
Meaning	Competitors refer to other pharmaceutical innovators completing R&D in the same field, thus, targeting the same disease.	(Thakor and Lo, 2018; (Whiteside, 2016)	-
Relevance	Strong competition exists because of intellectual property rights that are gained for new chemical entities innovated.		
Intervention considerations	Explore and compare for similar drugs being marketed as different products.		
	Competition is not always a bad thing (speeds up discovery)		
	Collaboration and open innovation		

17. Political will and contribution to improve R&D for disease		*For further reference*	
Meaning	The effort and contribution that the government of a country is willing to make towards R&D of diseases.	(Brinkerhoff, 2003; (Emmanuel and Emmanuel, 1996; World Health Organization, 2018)	-
Relevance	Governments should be obligated to make significant efforts to reduce disease burden within a country		
Intervention considerations	Enforce SDGs		
	Ministry of Health audit		
	Policy reform		
	Political accountability systems		

Non-incentive-based interventions (4 of 8)

18. Effective national budget allocation		*For further reference*	
Meaning	The financial plan of a country should include planning and financial allocations to the health and health care of citizens.	(World Health Organization, 2018; Emmanuel and Emmanuel, 1996; Becker, 2015)	-
Relevance	The health care of a country is the responsibility of its government. Without budget allocation, health care advancement is less likely.		
Intervention considerations	Implement SDGs		
	Policy reform		
	Strategic resource allocation options		
	Global health governance		

19. Regulation of strategic health policy		*For further reference*	
Meaning	The goals, visions, priorities and budgetary decisions of a country needs to be regulated, to be in line with health needs.	(Liang and Mackey, 2012; World Health Organization, 2018; Nagpal, Sinclair and Garner, 2013)	-
Relevance	If the strategic plans and actions to undertake and achieve are not taken, then the health of the country will lack improvement.		
Intervention considerations	Global health governance		
	Strategic political interventions		
	Domestic, private, and global policy interventions		

20. Adequate supply of the health service		*For further reference*	
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Jacobs et al., 2012; RAND Corporation, 2007; Manjit Kaur; Sarah Hall, 2002)	-
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

21. Monitoring of the actual health system and system performance		*For further reference*	
Meaning	The observation and measurement of health system performance.	(WHO, 2010a; International Federation *et al.*, 2015; Jones *et al.*, 2015; Newman *et al.*, 2016)	-
Relevance	By observing and measuring performance of the health system, problems can be located faster and more easily.		
Intervention considerations	Information systems and data handling		
	Pharmacovigilance		
	Reporting networks		
	Personnel training		
	Accountability networks and schedules		

22. Current investment capital and returns		*For further reference*	
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Vischer et al., 2017; Bates et al., 2015; Ho, Zarrinpar and Chow, 2016; Payne et al., 2015)	-
Relevance	This factor refers to the current ROI being profitable or not, if not then more investment in a similar research area is not likely.		
Intervention considerations	Financial analysis		
	Cost analysis of activities		
	Reduce indirect and operational costs		

23. Stakeholder demand		*For further reference*	
Meaning	Stakeholder demand refer to whether the public desires, and needs the product being developed.	(Thakor and Lo, 2018; Whiteside, 2016)	-
Relevance	The higher the demand for the products being delivered, the greater the perceived potential ROI.		
Intervention considerations	Target market analysis		
	Marketing strategies		
	Inform governments and the public that require this drug.		
	Pricing of the product		

Non-incentive-based interventions (5 of 8)

24. Established marketing and distribution network		*For further reference*	
Meaning	The marketing and distribution of drugs are important, to inform patients, and provide access and availability.	(Ravn, 2012; Radulescu, 2012)	-
Relevance	Distribution adds to effective service delivery; and marketing creates and enlarges the market demand.		
Intervention considerations	Marketing strategies		
	Effective distribution networks		
	Supply chain management		
	Coordination of service delivery, inventory management and distribution services		

25. Consistency and recommendations on choosing metrics for clinical trials		*For further reference*	
Meaning	Clinical trials are the most timeous procedure of drug R&D, using the correct metrics are essential in innovation productivity.	(Gupta et al., 2016; Moatti et al., 2016; Mayo et al., 2017; Clifton, Kohrt and Peoples, 2015; Zhou et al., 2015)	-
Relevance	Guidelines and regulations should be followed to advance in clinical trial phases. If not consistent then clinical trials might be trivial.		
Intervention considerations	Structured regulations and policy recommendations		
	Standardized clinical trial metrics		
	Market authorization regulation		
	Capture data of clinical trial methods and metric outputs		

26. Transparency of clinical trial information		*For further reference*	
Meaning	Clinical trial information is openly available, reliable and does not entail any suspicious information.	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	-
Relevance	Transparent clinical trial information assures that products being developed adhere to safety, efficacy and regulatory requirements.		
Intervention considerations	Annual, and unannounced firm audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

27. Accountability of clinical trial information		*For further reference*	
Meaning	Clinical trial information should be trustworthy	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	-
Relevance	There should be clear accountability for the information of clinical trials.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

28. Accessibility of clinical trial information		*For further reference*	
Meaning	The clinical trial information should be made available (within the market exclusivity agreements)	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	-
Relevance	Secrecy on critical clinical trial information not allowed, especially if it alters the safety and efficacy of the drugs.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

29. The use of innovative clinical trial tools and technology		*For further reference*	
Meaning	Advanced tools and technologies exist for performing clinical trials.	(McKinsey&Company, 2017)	-
Relevance	Modern technology and tools assist in clinical trial and drug discovery processes and might enhance the R&D process.		
Intervention considerations	Research on tools and technology available		
	Reliability of current tools and technology used in clinical trials		
	Break-even of getting new equipment, tools and technologies		
	Cost-benefit analysis of getting new equipment, tools and technologies		

Non-incentive-based interventions (6 of 8)

30. Struggling to prove efficacy		*For further reference*	
Meaning	The ability of pharmaceutical innovators to prove that the drug fulfils the intended result.	(PhRMA, 2016)	-
Relevance	Drugs should target the intended disease and be effective in treating the patients.	(Hay et al., 2014)	
Intervention considerations	Clinical trial information quality	(von Ranke, Fierro and Antunes, 2016) (Ho, Zarrinpar and Chow, 2016)	
	Clinical trial design		
	Tools, technology and equipment used for clinical trials		
	Adhere to international regulation standards		

31. Legal and ethical regulations for clinical trials too difficult		*For further reference*	
Meaning	Extensive laws and regulations exist for the development of drugs.	(Califf and Sugarman, 2015), (Salas, 2017), (Tsukamoto et al., 2016), (Cheng and Xie, 2017), (Tsourounis et al., 2015)	-
Relevance	A lot of difficulty is experienced in bridging legal and ethical barriers in drug R&D.		
Intervention considerations	Collaborate with bigger pharmaceutical organizations		
	Availability of third parties to adhere to regulations and laws		
	Complete annual audits		
	Ensure data transparency, accuracy and accountability		

32. Safety assessments standards		*For further reference*	
Meaning	Safety assessment standards should be adhered to, to quantify and measure risks involved in the drug being developed.	(Singh and Loke, 2012)	-
Relevance	Drugs that does not adhere to safety standards might pose a health risk to patients.	(PhRMA, 2016)	
Intervention considerations	Health authority standards and regulations	(Hay et al., 2014)	
	Clinical trial practices and designs		
	Randomized controlled trials		
	Global health governance		

33. Adaptive clinical trials occurrence		*For further reference*	
Meaning	Clinical trials that involves observing participant outcomes and adjusting drug parameters in accordance.	(Gokhale and Gokhale, 2016)	-
Relevance	Without adaptive clinical trials, important observations cannot be made; and drug safety not improved to the extent necessary.	(Baylor College of Medicine, 2009)	
Intervention considerations	Amount of participants part of adaptive clinical trials	(Hay et al., 2014)	
	Procedures of adaptive clinical trials		
	Data capturing		
	Health authority standards and regulations		

34. Recruitment and retention of participants		*For further reference*	
Meaning	Clinical trials require participants to perform drug safety and adequacy tests.	(Kurt et al., 2017) (Hammer, Eckardt and Barton-Burke, 2016)	-
Relevance	Effort should be done to recruit the right number of participants for clinical trial tests		
Intervention considerations	Marketing strategies	(Jennings et al., 2015), (Thacker, T., Wegele, A.R., Pirio Richardson, 2016)	
	Incentivize participants		
	Ensure safety of participants		
	Build trustworthy relationships with participants		

35. Racial differences in participation in clinical trial		*For further reference*	
Meaning	A variety of ethnicity groups, races and both genders' response on the drugs needs to be tested	(Kurt, Semler, et al., 2017)	-
Relevance	Given that drugs can be used by anyone, tests should be performed on various people to test for any difference in reactions or dosage requirements.	(Baylor College of Medicine, 2009)	
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Build trustworthy relationships with participants		

36. Relationships between innovators and participants		*For further reference*	
Meaning	Innovators should strive to have a professional, and trustworthy relationship with participants	(Kurt, Semler, et al., 2017)	-
Relevance	If the relationship between innovators and participants is not appropriate; then participants might not agree to complete more trials.	(Tsukamoto et al., 2016)	
Intervention considerations	Build trust with participants, by following standard clinical trial procedures	(Califf and Sugarman, 2015) (Salas, 2017)	
	Adhere to safety and regulation standards		
	Monitor participants closely		
	Capture data		

Non-incentive-based interventions (7 of 8)

37. Physician participation		*For further reference*	
Meaning	Qualified medical practitioners should be present in clinical trial tests on humans.	(Baylor College of Medicine, 2009)	-
Relevance	Qualified physicians will be able to monitor the health and wellbeing of patients in clinical trials, as well as respond if ADR occur.		
Intervention considerations	Incentivize physicians to participate		
	Provide proper training to physicians		
	Adhere to correct clinical trial procedures		

38. Skilled workforce		*For further reference*	
Meaning	Workforce, part of drug R&D process should be skilled to adequately perform tasks.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001), International Labour Office, 2010)	-
Relevance	If workforce is not skilled, preventable problems in the R&D process might arise.		
Intervention considerations	Train workforce (workshops, training programs)		
	Encourage mentorship in work environment		
	Ethical conduct		

39. Existence of manufacturing plants		*For further reference*	
Meaning	Manufacturing plants exists to perform adequate drug manufacturing.	(World Health Organization, 2016), (WHO, 2011)	-
Relevance	If no manufacturing plants exists, then producing drugs on large scale might be difficult.		
Intervention considerations	Encourage/ Incentivize SME drug manufacturers		
	Consider international manufacturing organizations		

40. Drug manufacturing adheres to regulatory requirements		*For further reference*	
Meaning	Drug manufacturing should adhere to regulatory requirements to ensure safety.	(Koeberle and Schiemenz, 2017) (Burnham et al., 2015), (Wechsler, 2015)	-
Relevance	Unregulated manufacturing practices poses potential risks to the drugs.		
Intervention considerations	Audit Manufacturing organizations		
	Global manufacturing practices		
	Comply to cGMPs (Current good manufacturing practices)		
	Unannounced visits by regulatory authorities to manufacturing facilities		

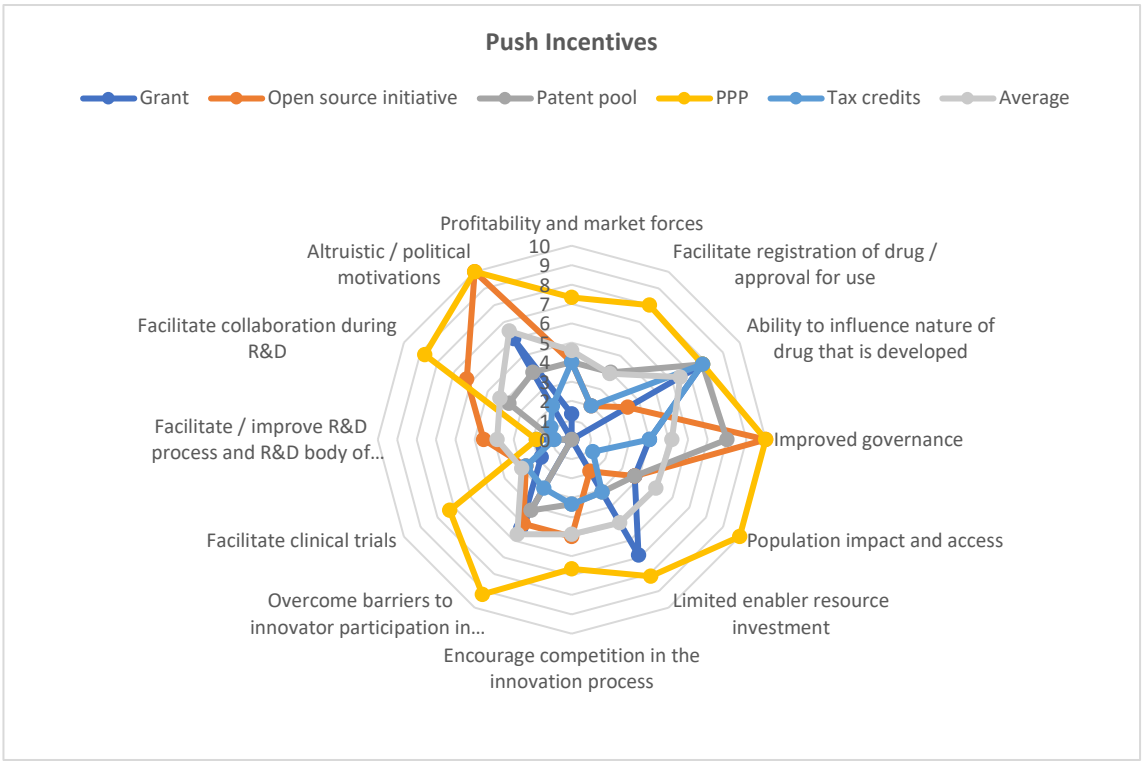
41. Appropriate technology used for the manufacturing of drugs		*For further reference*	
Meaning	A lot of technologies are available to manufacture drugs, some are advised by regulatory agencies.	(World Health Organization, 2011)	-
Relevance	Appropriate technology might improve the safety, productivity and quality of the drugs being manufactured.		
Intervention considerations	Comply to cGMPs		
	Research technology that is available		
	Complete cost-benefit analysis to ensure new technologies are strategic choices		
	Ensure compliance of all regulations and policies		

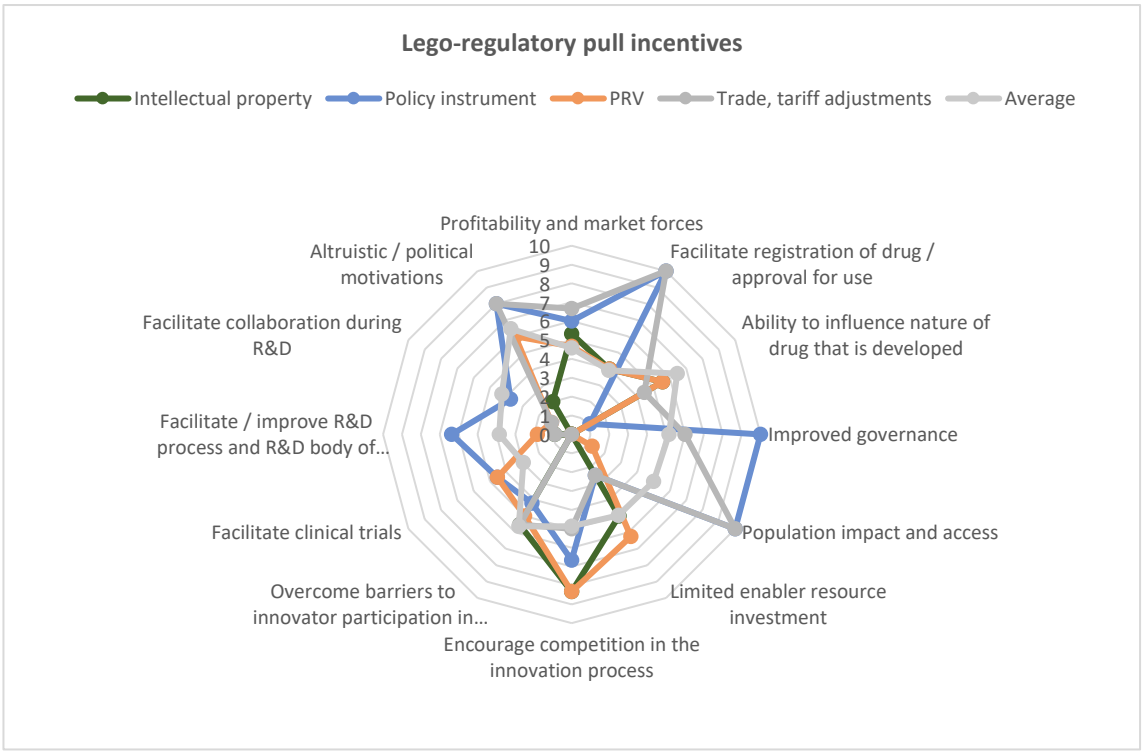
42. Health data generation		*For further reference*	
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	-
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

Non-incentive-based interventions (8 of 8)

43. Communication and use of public health data		*For further reference*	
Meaning	Analysing, synthesising and validating health data	(WHO, 2010a)	-
Relevance	By evaluating health data, important measures can be implemented to satisfy growing needs, or gaps within the health system.		
Intervention considerations	Establish national sets of indicators with targets and accurate reporting which will inform health sector reviews and improve the planning of future interventions		
	Assess the health systems performance, to determine the success of current interventions		
	Adjust health system operation, based on accurate data.		
	Communicate health statistics to the public for awareness.		

Supplementary material 1 (1 of 2)





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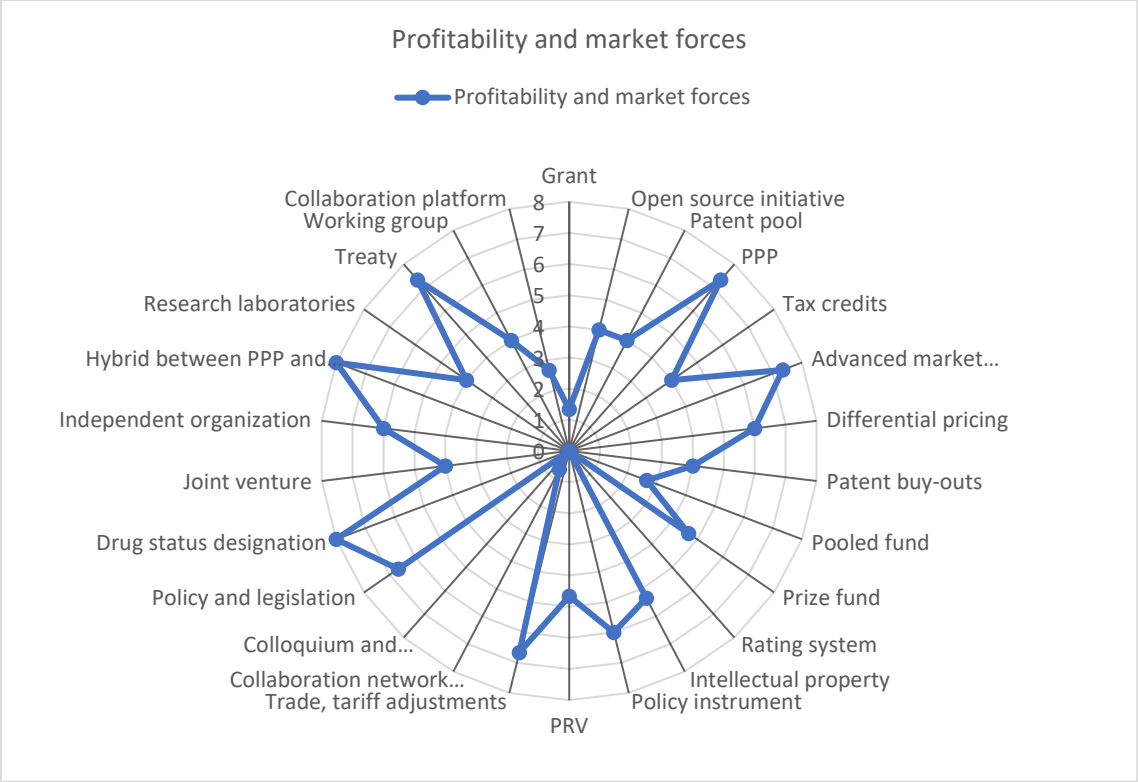

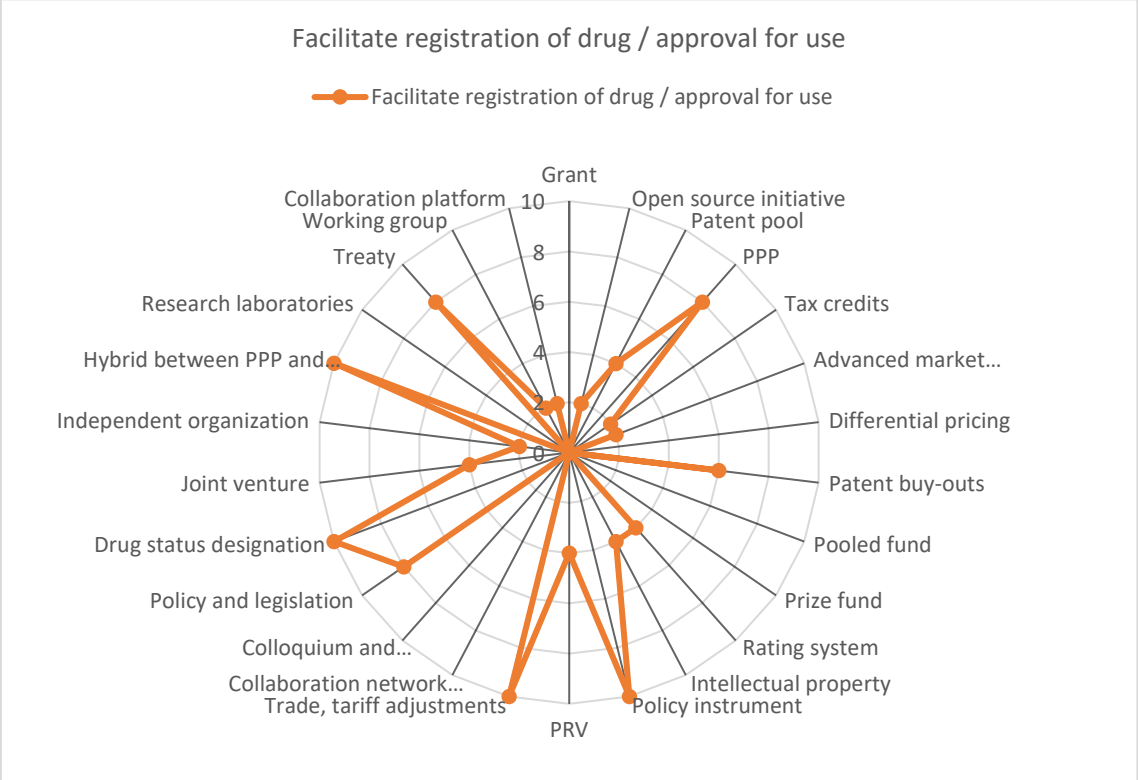

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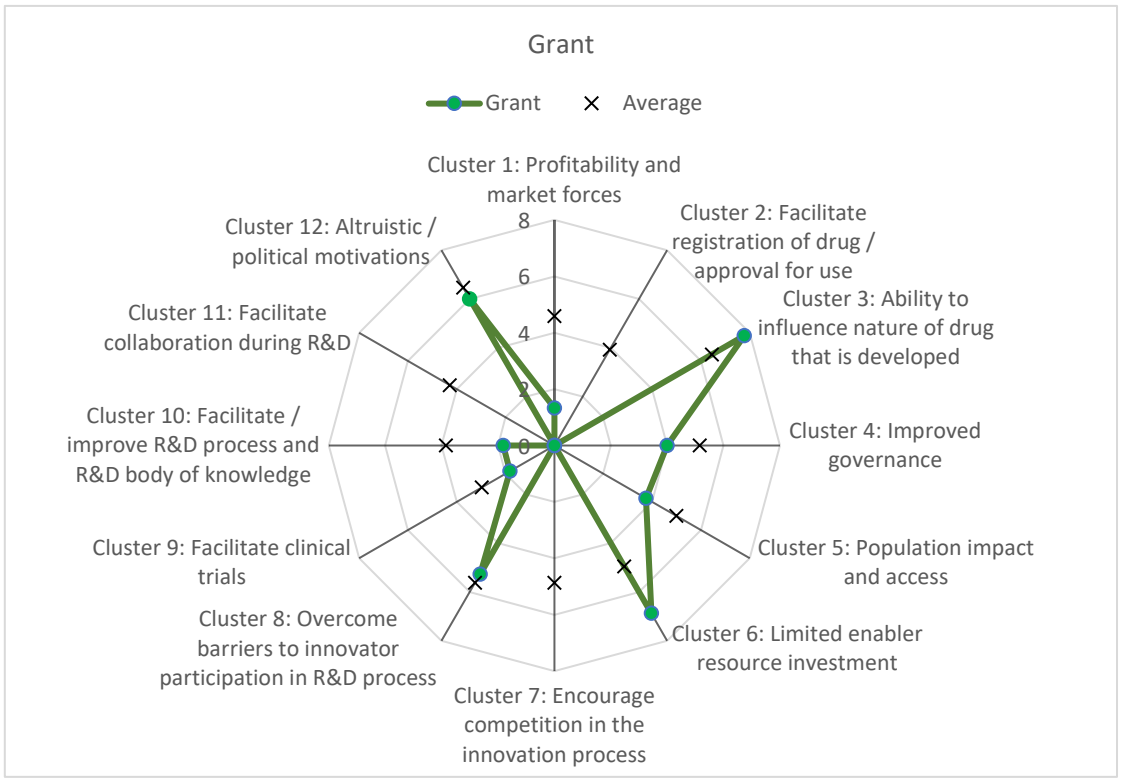
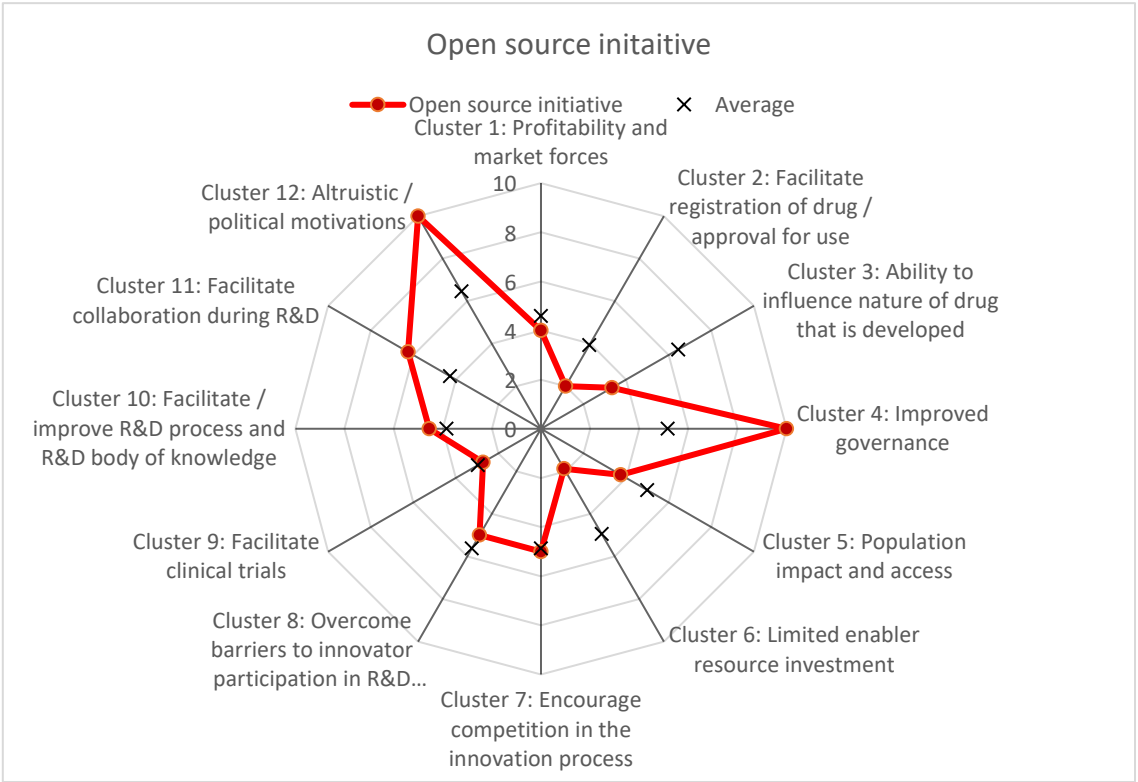
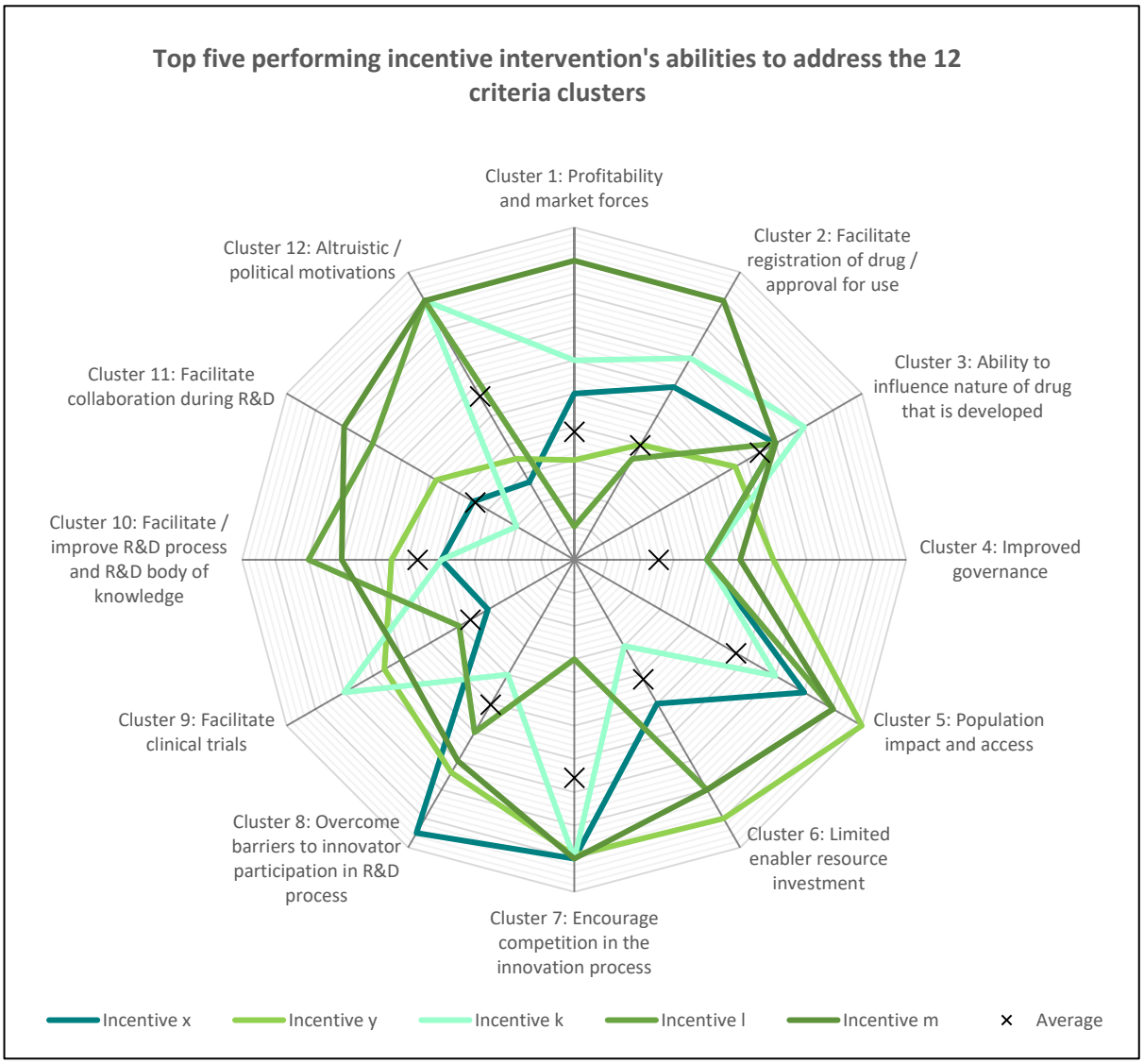




Supplementary material 4 (1 of 2)

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
1	Grant														
2	Open-source initiative														
3	Patent pool														
4	PPP														
5	Tax credits														
6	Advanced market commitments														
7	Differential pricing														
8	Patents buy-outs														
9	Pooled fund														
10	Prize fund														
11	Rating system														
12	Intellectual property														
13	Policy instrument														
14	PRV														
15	Trade, tariff adjustments														
16	Collaboration network														
17	Colloquium and symposium														
18	Policy and legislation														
19	Drug status designation														
20	Joint venture														
21	Independent organization														
22	Hybrid PPP														
23	Research laboratories														
24	Treaty														
25	Working group														
26	Collaboration platform														

Supplementary material 4 (2 of 2)



Appendix H: 12 Criteria clusters and sub-clusters

The criteria clusters, sub-clusters as well as decision-criteria categorized within each cluster are displayed in this Appendix.

	Sub-categories of Criteria clusters
	Cluster 1: Profitability and market forces
1.1	Delink revenue from sales volume
1.2	Incentive improves product export potential
1.3	Improve product export potential (Incentive ability)
1.4	Improve export potential (Innovator require)
1.5	Incentive allows market exclusivity over an innovation
1.5.1	Gain market exclusivity over an innovation (Enabler goal)
1.5.2	Provide market exclusivity (Enabler ability)
1.5.3	Market exclusivity policies (Enabler ability to alter)
1.5.4	Provide market exclusivity (Innovator require)
1.6	Incentive provides market certainty
1.6.1	Provide market certainty (Enabler role)
1.6.2	Provide market certainty (Innovator require)
1.7	Incentive involves/requires intellectual property policies (Enabler ability)
1.8	Incentive involves/requires pricing policies (Enabler ability)
1.9	Incentive involves/requires tax credit policies (Enabler ability)
1.10	Incentive involves/requires international trade law (Enabler ability)
1.11	Incentive improves NPV of stakeholders
1.11.1	Improve NPV of stakeholders
1.11.2	Profit improvement (Innovator goal)
1.12	Profit maximization (Innovator goal)
1.13	Any profit margins allowed (Consumer require)
1.14	Minimizes barriers to implementation (implementation of incentive)
	Cluster 2: Facilitate registration of drug / approval for use
2.1	Incentive involves/requires market authorization policies (Enabler ability)
2.2	Incentive involves/requires national policies and legislations (Enabler ability)
2.3	Existing drugs not allowed in target area (Consumer availability)
2.4	Drug status designation required (Consumer availability)
2.5	IP regulation allows procurement of drugs to target area (consumer availability)
	Cluster 3: Ability to influence nature of drug that is developed
3.1	Incentive encourage R&D of a drug/intervention
3.1.1	Encourage R&D of a drug/intervention (Incentive ability)
3.1.2	Provide drug (Enabler goal)
3.1.3	R&D of drug (Innovator goal)
3.2	Incentives stimulates multi-purpose drug R&D
3.2.1	Multi-purpose drug (Enable goal)
3.2.2	R&D of multi-purpose drug (Innovator goal)
3.3	Incentive allows the delivery of regime treatment
3.3.1	Deliver regime treatment (Innovator goal)
3.3.2	Deliver regime treatment (Enabler goal)
3.4	Payoff to innovators based on cost-effectiveness
3.5	Contextual treatment criteria can be addressed by incentive (Consumer requirements)
3.6	Incentive allows drug repurposing (Innovator goal)
	Cluster 4: Improved governance
4.1	Promote equitable health-focused governance (Incentive ability)
4.2	Promote transparency and accountability (Incentive ability)
4.3	Advances the priority of disease on health agenda (Incentive ability)
4.4	Advance proper functioning of domestic policy (Incentive ability)
	Cluster 5: Population impact and access
5.1	Incentive improves consumer access
5.1.1	Improve consumer access (Incentive ability)
5.1.2	Play a role in improved access (Enabler goal)
5.1.3	Play a role in improved access (Innovator goal)

5.2	**Incentive enables mass drug administration**
5.2.1	Enable mass drug administration (Incentive ability)
5.2.2	Implement mass drug administrations (Enabler goal)
5.3	**Incentive aims to minimize disruptive effects to population**
5.4	**Incentive allows for differential pricing (Consumer requirement)**
5.4.1	Incentive allows differential pricing (Consumer requirement)
5.4.2	Incentive allows differential pricing (Consumer requirement)
5.5	**Deliver affordable and accessible treatment (Enabler goal)**
5.6	**Incentive eliminates all financial risk (Consumer requirement)**
	Cluster 6: Limited enabler resource investment
6.1	**Affordable to implement the incentive**
6.2	**Incentive allows resources to develop drugs to be government financed**
6.3	**Incentive allows payoff to innovator to be in the beginning, once-off**
6.3.1	Incentive allows payoff to innovator to be in the beginning, once-off (Enabler requirement)
6.3.2	Incentive allows payoff to innovator to be in the beginning, once-off (Innovator requirement)
6.4	**Incentive allows payoff to innovator to be at the end, once-off**
6.4.1	Incentive allows payoff to innovator to be at the end, once-off (Enabler requirement)
6.4.2	Incentive allows payoff to innovator to be at the end, once-off (Innovator requirement)
6.5	**Incentive payoff to innovator incrementally, based on output**
6.5.1	Incentive allows payoff to innovator to be incrementally, based on output (Enabler requirement)
6.5.2	Incentive allows payoff to innovator to be incrementally, based on output (innovator requirement)
6.6	**Incentive does not require enabler funding (Enabler no capacity)**
6.6.1	Incentive does not require enabler funding (Enabler no capacity)
6.6.2	Innovator does not require any funding from enabler, or incentive (Innovator requirement)
6.7	**Incentive requires/allows the enabler to partially fund R&D**
6.7.1	Incentive requires/allows the enabler to partially fund R&D (Enabler requirement)
6.7.2	Incentive requires/ allows innovator to partially fund R&D (Innovator requirement)
6.7.3	Incentive pay-out to innovator is a once-off occasion (Enabler requirement)
6.7.4	Incentive pay-out to innovator occurs once output is delivered (Innovator requirement)
6.8	**Incentive allows innovator pay-outs, limited to number of years**
6.9	**Incentive allows innovator pay-outs, milestone related**
6.10	**Incentive allows enabler to engage with innovator at given time instances**
6.11	**Incentive allows enabler funding to be limited to an amount**
	Cluster 7: Encourage competition in the innovation process
7.1	**Incentive encourages large firm participation**
7.1.1	Incentive encourages large firm participation
7.1.2	Incentive allows large pharmaceutical organization (private) participation (Enabler identity)
7.1.3	Incentive aimed at incentivising large pharmaceutical organization (Innovator identity)
7.2	**Incentive allows competition among parallel experiments**
7.3	**Incentive enlarges the number of clinical trials registered**
7.4	**Incentive targets all organizations to participate (Enabler target)**
	Cluster 8: Overcome barriers to innovator participation in R&D process
8.1	**Incentive allows small and medium organizations to be incentivized**
8.1.1	Incentive enables participation of SMEs (Incentive ability)
8.1.2	Incentive enables participation of SME (Enabler target)
8.1.3	Incentive enables participation of SMEs (Innovator identity)
8.2	**Incentive allows governmental institutions to be incentivized**
8.2.1	Incentive allows governmental institutions to be incentivized (Enabler target)
8.2.2	Incentive allows governmental institutions to be incentivized (Innovator identity)
8.3	**Incentive allows independent scientists to be incentivized**
8.3.1	Incentive allows independent scientists to be incentivized (Enabler target)
8.3.2	Incentive allows independent scientists to be incentivized (Innovator identity)
8.4	**Incentive allows academic institutions to be incentivized**
8.4.1	Incentive allows academic institutions to be incentivized (Enabler target)
8.4.2	Incentive allows academic institutions to be incentivized (Innovator identity)
8.5	**Incentive allows NGO organizations to be incentivized**
8.5.1	Incentive allows NGO organizations to be incentivized (Enabler target)
8.5.2	Incentive allows NGO organizations to be incentivized (Innovator identity)
8.6	**Incentive provides sustainable financing for innovator**
8.7	**Incentive financing is timed across drug lifecycle**
8.8	**Incentive provides long term R&D financing**
8.9	**Incentive provides R&D project insurance**
8.9.1	Incentive provides R&D project insurance
8.9.2	Incentive provides risk insurance or security
8.10	**Incentive de-risks the R&D process**
8.11	**Incentive requires/allows enabler to fund R&D**
8.11.1	Incentive allows enabler to fund R&D (Enabler goal)
8.11.2	Incentive requires enabler to fund all R&D costs (Innovator requirement)

8.12	**Incentive allows enabler to fully fund R&D (Enabler full capacity)**
8.12.1	Incentive allows enabler to fully fund R&D (Enabler full capacity)
8.12.2	Incentive requires enabler to completely fund R&D (Innovator no ability)
8.13	**Incentive requires enabler to partially fund R&D (Innovator ability)**
8.13.1	Incentive requires enabler to partially fund R&D (Innovator requirement)
8.13.2	Incentive requires enabler to partially fund R&D (Innovator requirement)
8.14	**Incentive allows funding to be incremental, as innovator requires**
8.14.1	Incentive allows incremental funding, as innovator requires (Enabler ability)
8.14.2	Incentive allows funding to be incremental, as innovator requires (Innovator requirement)
8.15	**Incentive allows funding to be incremental, based on timing**
8.15.1	Incentive funding incremental, based on timing (Enabler ability)
8.15.2	Incentive funding incremental, based on timing (Innovator requirement)
8.16	**Incentive does not provide any funding (Innovator has full capacity to provide own funding)**
8.17	**Incentive allows enabler to increase bandwidth and network (Enabler goal)**
8.18	**Incentive utilizes enabler's ability to influence intellectual property (Enabler ability)**
8.19	**Incentive requires/ utilizes enabler's access to key data**
8.19.1	Incentive utilizes enabler's access to key data (Enabler ability)
8.19.2	Incentive provides innovator with information (knowledge) on disease (Innovator requirement)
8.20	**Incentive utilizes enabler's access to compounds (Enabler ability)**
8.21	**Incentive requires/ utilizes enabler technology expertise and access**
8.21.1	Incentive requires/ utilizes enabler technology expertise and access
8.21.2	Incentive provides innovator access to equipment (Innovator requirement)
8.21.3	Incentive provides innovator access to research laboratory (innovator requirement)
8.22	**Incentive requires/ utilizes enablers R&D expertise**
8.22.1	Incentive requires/ utilizes enablers R&D expertise
8.22.2	Incentive aids innovator with cumbersome nature of clinical trial regulations (innovator requirement)
8.23	**Incentive addresses innovator's policy or regulatory limitations (innovator requirement)**
8.24	**Incentive provides innovator with market certainty (innovator requirement)**
8.25	**Incentive rewards innovation**
	Cluster 9: Facilitate clinical trials
9.1	**Incentive allows provision of public subsidies for clinical trials**
9.2	**Incentive reduces clinical trial risk involved**
9.3	**Incentive assist in registration and monitor of trials**
9.4	**Incentive globalizes clinical trial methods**
9.5	**Incentive reduces clinical trial activation difficulty**
9.6	**Incentive enhances or prompt the quality of clinical trials**
9.7	**Incentive provides assistance in clinical trial regulation**
9.8	**Clinical trial regulation policies (Enablers ability to influence)**
	Cluster 10: Facilitate / improve R&D process and R&D body of knowledge
10.1	**Incentive aims to/ allows improvement of R&D productivity**
10.2	**Incentive provides regulatory oversight to promote R&D**
10.3	**Incentive provides regulatory exclusivity provisions for R&D**
10.4	**Incentive encourages efficient innovation**
10.5	**Incentive ensures the conservation of resources in R&D process**
10.6	**Incentive requires/ allows green R&D of drugs**
10.7	**Incentive enables organizations to innovate easier (Enabler goal)**
10.8	**Incentive can improve the state of the R&D pipeline (Enabler goal)**
10.9	**Incentive advances the R&D field & body of knowledge (Enabler goal)**
	Cluster 11: Facilitate collaboration during R&D
11.1	**Incentive facilitates cooperation and synergy between all stakeholders**
11.1.1	Facilitates cooperation and synergy between all stakeholders
11.1.2	Incentive facilitates collaboration between innovators (Enabler goal)
11.2	**Incentive allows enabler to collaborate and build a partnership/s (Enabler goal)**
11.3	**Incentive allows enabler to collaborate with innovator (Enabler goal)**
11.3.1	Incentive allows enabler to collaborate with innovator (Enabler goal)
11.3.2	Incentive allow collaboration with enabler (Innovator require)
11.4	**Incentive provides a platform for coordinating innovators**
11.4.1	Incentive provides a platform for coordinating innovators
11.4.2	Incentive provides a collaboration platform (Innovator requirement)
11.5	**Incentive allows/ requires enabler to facilitate in regulatory process**
11.5.1	Incentive allows/ requires enabler to facilitate in regulatory process (Enabler ability)
11.5.2	Incentive allows/ requires enabler to facilitate innovator in regulatory process (Innovator requirement)
11.6	**Adjust policies and regulations**
11.6.1	Adjust policies and regulations (Enabler ability)
11.6.2	Enabler should adjust policies and regulations (Innovator require)
	Cluster 12: Altruistic / political motivations
12.1	**Incentive conveys an important message (Enabler goal)**
12.2	**Incentive allows CSR to be fulfilled**

12.2.1	Incentive allows enabler to fulfil CSR (Enabler goal)
12.2.2	Incentive allows innovator to fulfil CSR (Innovator goal)
12.3	**Incentive allows enabler to fulfil political obligations**
12.3.1	Incentive allows enabler to fulfil political obligations (Enabler goal)
12.3.2	Incentive allows innovator to fulfil political obligations (innovator goal)
12.4	**Incentive allows not for profit R&D (Innovator goal)**
12.5	**Incentive allows not for profit/ restricted profit margins for drug procurers**
12.5.1	Incentive enables/ allows restricted profit margins for drug procurers
12.5.2	Incentive enables no profit margins for drug procurers

Appendix I: SME pre-read document phase 1

Before conducting one-on-one interviews with SMEs, a pre-read document with the most salient information was sent to allow the SME to grasp the fundamentals of the research. The pre-read also includes the preliminary decision-support framework, before any refinements were made.

VERIFICATION: PRE-READ

DECISION-SUPPORT FRAMEWORK FOR FINDING INCENTIVES TO ENHANCE PHARMACEUTICAL R&D RESOURCE ALLOCATION

Nicola Hanekom
September 2019

Foreword

This document serves as pre-read material for the subject matter expert (SME) before consultation with the author. This document introduces the aim of the overall research, as well as the method used to establish the development of the decision-support framework. Finally, an overview of the framework that has been developed is presented, along with a concise breakdown of the different components and domains of the framework. Detailed descriptions of the framework components are included in the Appendices.

This document provides a list of all the verification questions that will form the basis of the semi-structured interview with each SME. This verification round will also be used as a framework refining step in the research, where the suggestions of SMEs will be incorporated, to the furthest extent feasible, into the framework.

Table of Contents

1. Introduction

The intention of this document is to provide brief background information on the overall problem addressed by this research. The document further investigates the concept of verification, and background on the requirement specifications to be verified. This is followed by an overview of the framework, its domains and functions and its output intention.

1.1 Problem statement and background

This research aims to provide a means for any entity to establish a set of incentive interventions that are suited to the characteristics of the instance environment, the stakeholders, and the desired drug cost and quality. This is achieved through the development of a decision-support framework that proposes a shortlisted set of incentive interventions that are well-suited to the specific instance. This document forms part of a larger research, where the following research objectives were addressed:

i Investigate the drug research and development (R&D) pipeline;
ii Establish elements affecting the drug R&D pipeline;
iii Investigate market attractiveness within the pharmaceutical R&D environment; and
iv Establish existing incentive interventions within the neglected disease drug R&D environment.

The emphasis of this study is on neglected diseases. Where neglected diseases are defined as diseases for which inadequate treatment options, or a lack of treatment options are available (MSF, 2001). These diseases mostly occur in developing countries. As the multinational drug industry is highly competitive, it delivers drugs based on economic market forces (Trouiller *et al.*, 2002). From the perspective of both public- and private organizations, the market for neglected diseases is not sufficiently attractive to attain the necessary resources to effectively address such diseases. This lack of resource investment leads to an absence of drugs for the treatment of these diseases in the developing world. Various incentive interventions, with divergent underlying means, have been proposed and / or implemented to encourage resource allocation toward research and development (R&D) of drugs for neglected diseases. Not all incentive interventions are equally likely to be effective for a given instance. Factors that influence whether an incentive intervention is more or less likely to be effective include: (i) taking the conflicts of interest between stakeholders into account (Granville and Trushin, 2010); (ii) not only encourage participation, but also providing an incentive to deliver a high quality drug at a low cost (Granville and Trushin, 2010); and (iii) creating an attractive and supportive environment for investment in R&D for neglected diseases (Renwick *et al.*, 2016).

1.2 Aim of the decision-support framework

The decision-support framework is intended to facilitate any governmental, private or public body, aiming to encourage investment in R&D of drugs for a disease that is currently experiencing neglect. The framework outcome is to provide a set of recommended solutions (incentivising interventions) based on (i) the current pharmaceutical R&D demarcation of the environment being addressed; (ii) the needs, abilities, and limitations of the enabling organization or body; and (iii) the abilities of the incentive interventions to address the priority improvement areas of the scenario under investigation.

1.3 Aim and methodology of verification

Verification is the process of establishing the accuracy of the proposed solution (Oxford University Press, 2019). During this round of verification, the focus is on confirming that no relevant aspect has been omitted from the developed decision-support framework and that the framework functions effectively in proposing an appropriate set of incentive interventions as a solution to the scenario under consideration. Feedback that is gathered through this round of verification will be used to refine and improve the framework before proceeding to a case study application.

1.4 Components and concepts included in the decision-support framework

Table 0.1: Elements of the decision-support framework.

The framework encompasses various elements with several data variables that emerge and flow through the framework. A summary of the terminology that is used in the framework description is provided in Table 1.

Variable or Acronym	*Definition*
Domain	The framework comprises four domains. Each domain requires input data, performs functions and delivers output that is either used by other domains or directly informs the final solution.
Background Logic (BL)	The BL processes are hardcoded and run in the background of the domains, with the aim of analyzing and interpreting the data used in the domains.
Context-specific (CS) criteria	Criteria from the system demarcation domain that should be addressed by the incentive-based intervention.
Combined list of intervention criteria (CLIC)	Criteria that the incentive-based intervention should adhere to. This set of criteria includes context-specific as well as context-non-specific criteria (sourced from literature).
Context specific-and non-specific (CSNS) score	A score metric that indicates the ability of each incentive intervention to satisfy the CLIC.
Enabler criteria (EC)	The characteristics relevant to the specific enabler.
Enabler profile (EP) score	Score metric indicating the ability of each incentive intervention to satisfy the enabler criteria (EC).
Overall feasibility (OF) score	A score metric that combines the CSNS and EP scores for each incentive intervention. This metric indicates the overall feasibility per intervention.

2. Overview of the Decision-support framework

The decision-support framework overview is discussed, together with a concise summary of the various components, including the operationalization of each.

2.1 Overarching view of the framework

The framework consists of four domains and three background logic functions. Figure 1 depicts the overarching view.

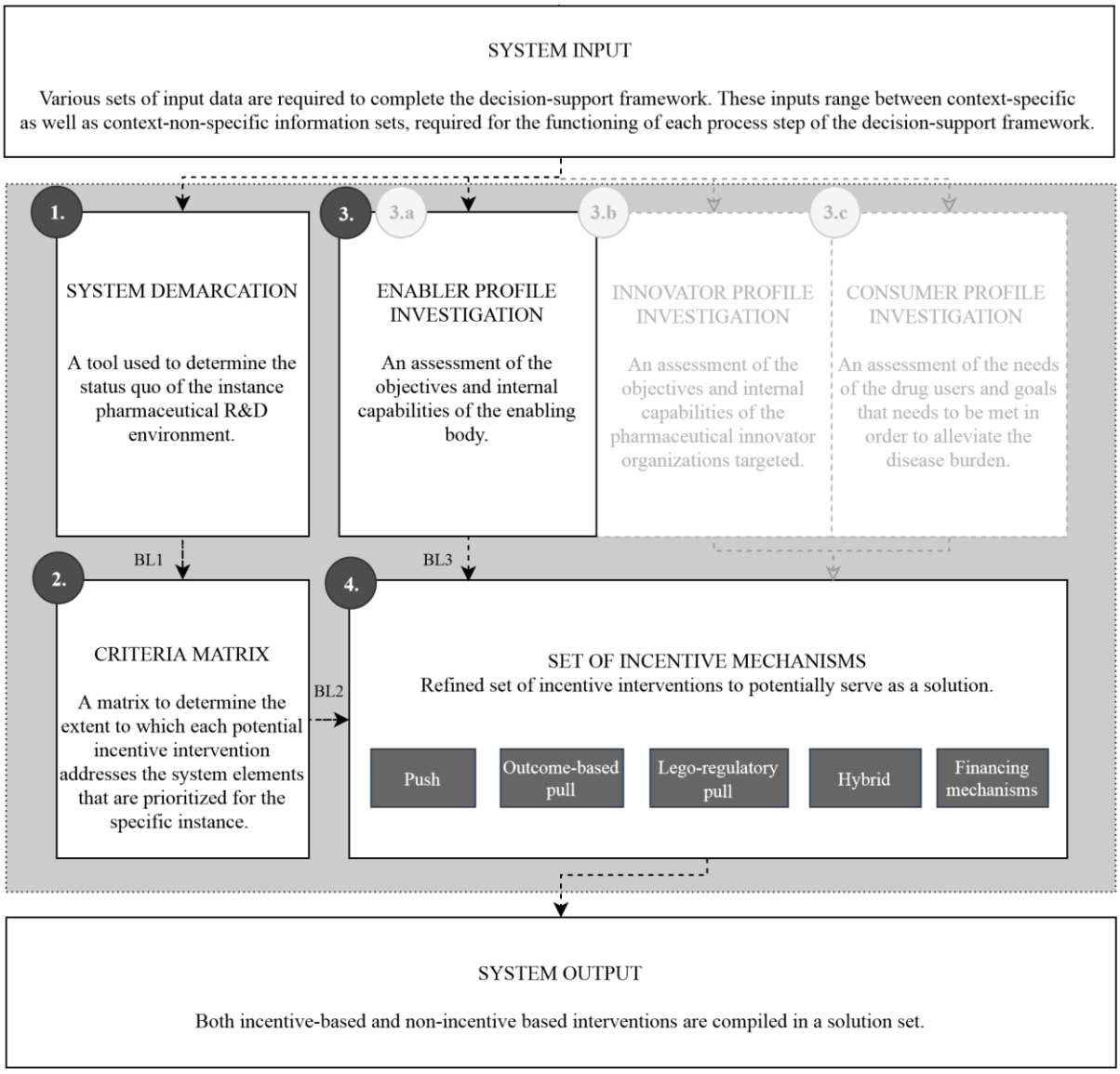


Figure 0.1: Overarching view of the decision-support framework.

(1) BL: Background Logic

2.2 Framework operationalization and description

The first step in the framework is concerned with documenting a holistic overview of the pharmaceutical R&D environment for the scenario being investigated (Domain 1). This is achieved through a set of questions that are intended to guide the user to systematically consider all relevant contextual factors.
The system demarcation questions are categorized into the following ten pharmaceutical R&D environment categories (sourced from literature; refer to Appendix B.1 for the detailed list of system criteria):

1. Disease setting and affected population
2. Existing drug characteristics
3. Service delivery
4. Consumers, competitors, and suppliers
5. Governance and leadership
6. Profitability and market forces
7. Research and development process
8. Manufacturing systems
9. Sustainability
10. Health information systems

Secondly, by evaluating the state of the R&D environment, the priority improvement areas of the current landscape can be identified, and, thirdly, classified as being suited to be addressed by either an incentive-based intervention or a non-incentive-based intervention (Domain 1). Though proposing non-incentive-based interventions is not intended as one of the primary aims of the decision-support framework, it is recognised that not all of the challenges that exist with regard to a lack of investment in R&D can be appropriately addressed through incentive mechanisms alone. Therefore, the framework incorporates 40 non-incentive-based interventions that have been identified from literature as well as background logic identifying which of these non-incentive-based interventions to propose for a given scenario. (Seven of the 40 system elements in the non-incentive-based intervention are listed in Appendix A.10.)

Based on the classification of the priority areas, the *context-specific* (CS) criteria is formulated consisting of all the incentive-based intervention criteria (Background Logic 1). The CS criteria serves as one of the three bases on which the shortlisted set of incentive interventions that are recommended by the framework is selected. The second base for selecting the shortlisted set of interventions is grounded in what is suggested in literature to be essential for any incentive intervention to be successful (Background Logic 1). Consequently, a set of criteria is constructed which consists of context-specific (based on the R&D system demarcation), as well as context non-specific (based on literature describing successful incentive interventions) criteria; this list is called the *combined list of intervention criteria* (CLIC). This list (CLIC) is seen as a critical set of requirements that the incentive intervention solution must satisfy. Refer to Appendix A.11.

A set of incentive interventions was established by performing a structured literature review. A set of 105 incentive interventions, grouped into 27 incentive strategies were identified, and categorized as either: (i) push incentives; (ii) lego-regulatory pull; (iii) outcome-based pull; (iv) hybrid; or (v) mechanisms to finance incentives. Refer to Appendix A.9 for the complete list of 105 incentive strategies, with definitions of each. The CLIC is then evaluated (in the background) against the abilities of the 27 incentive interventions to determine the extent to which each incentive intervention can address the CLIC. This is done in Domain 2 with a type of 'score metric' allocated to each incentive intervention. The score metric is called the *context specific-and non-specific* (CSNS) score.

Given that the incentive interventions are now 'scored', the third and final base influencing the selection of the solution set should be considered, namely the objectives, the capabilities and limitations of the stakeholders (Domain 3).

In its current form, only one stakeholder profile is included in the framework, namely that of the enabler (thus the entity that wants to incentivize R&D/ provides the funds). As indicated, the intention is to also incorporate profiles of the innovator (thus the entity that is being incentivised to perform R&D work) as well as the consumer (thus the intended consumers of the drugs) in future iterations of the framework.
The objectives and capabilities of the enabler profile are obtained, by providing the enabler with an enquiry form, to be completed. The questions in the enquiry form are grouped into the following categories:
Objectives:

1. Goal of the incentive strategy?
2. Which innovators are targeted?
3. Intention for the consumers
4. Desired relationship with the innovators
5. Role and responsibility willing to play

Internal capabilities:

1. Funding capacity
2. Desired funding timing
3. Ability to influence policy

The limitations of specifically the enabler will have a great influence on the feasibility of a given incentive intervention. The effect that the stakeholder profiles has on the solution set is then evaluated by means of a score metric (Background Logic 3). This score metric is called the *Enabler Profile* (EP) score. Therefore, each incentive mechanism will be allocated a score, indicating the incentive intervention's ability to satisfy the objectives and adhere to the limitations of the enabler.
Finally, the output of the framework is a shortlisted set of incentive-based and non-incentive-based interventions (Domain 4), covering eight focus areas (Appendix A.7), that are recommended feasible options for the specific instance, namely:

1. Profitability and market forces
2. Leadership and governance
3. Population access and impact
4. Impact R&D process and clinical trials
5. Implementation feasibility and security
6. Green and sustainability
7. Reward focus
8. Participation and cooperation

The incentive-based solutions will have a combined score-metric (indicating each incentive intervention's alignment to the CLIC as well as the enabler profile criteria). This score is called the *Overall Feasibility* (OF) score.
Refer to Appendix A.8 for an overall framework process flow, as well as the variable flow of the framework.

3. Concluding remarks

The developed framework, consequently, analyzes the current pharmaceutical R&D environment, receives input from the enabling stakeholder, as well as uses what literature suggests, to provide a means of enabling or simplifying the decision-making process involved in choosing an incentive intervention for encouraging R&D in drugs for neglected diseases. The framework comprises four domains and three background logic processes. The output of this framework is a proposed set of incentive interventions that have been identified as being suitable to requirements of the specific scenario, based on information gathered from literature. In addition, a set of non-incentive-based interventions that are likely to make a contribution to the scenario under consideration are also proposed. The set of suggested interventions will each satisfy a different focus area, or set of focus areas, consequently no one optimal solution exists.

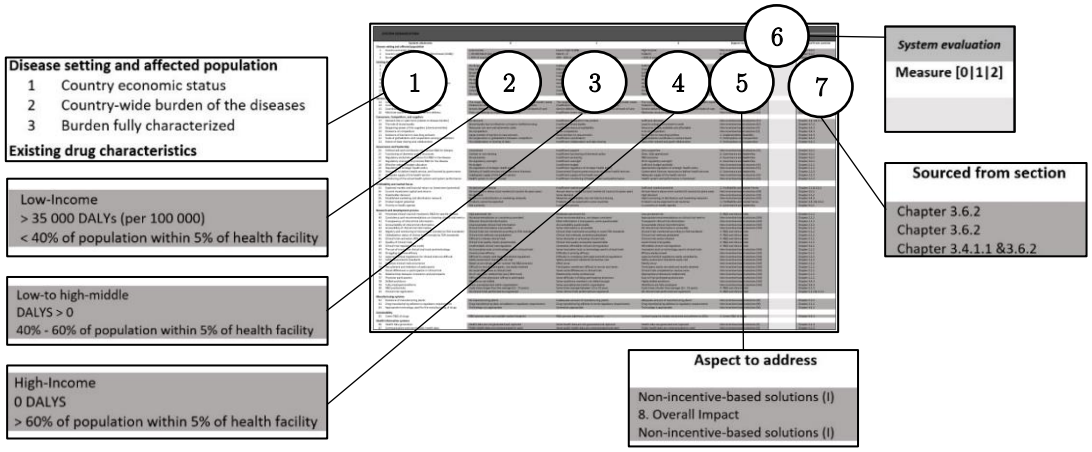
The decision-support framework described in this verification document is the initial version of the framework. The intention is to update and improve the framework, based on feedback received from SMEs.

Appendix A: Framework domain components

This section briefly discusses the operationalization of each domain and framework function.

Appendix A.1. Domain 1: System demarcation

The system demarcation domain is developed to draft a holistic understanding of the pharmaceutical R&D environment based on the scenario that will be investigated. Each of the system elements will be ranked, by the user, on a scale of [0, 1 or 2] – based on the state of the environment under investigation. Where 0 refer to the least ideal; and 2 refer to the ideal 'typical' state. The system elements (also called context-specific criteria) of the system demarcation comes from various sources, including: (i) a structured literature review identifiying 'factors that influences the R&D pipeline', and (ii) common trends of the R&D pipeline; (iii) the building blocks of the WHO health systems framework; (iv) properties of an attractive market identified in literature; structured literature review results on (v) factors improving market attractiveness, as well as (vi) factors reducing market attractiveness; finally a disease specific structured literature review provided disease-specific factors that lead to diseases becoming (vii) more; and (viii) less attractive in terms of drug R&D.
Evident in the system demarcation domain, is the differentiation made between system elements addressable by either incentive-based interventions or non-incentive-based interventions. The two sets of system elements follow different paths as of the system demarcation. Where the non-incentive based interventions are provided in a list format (part of the solution set), with no further scoring or rankings. A concise list of non-incentive based interventions are developed for every system element that is not addressable by incentive-based interventions, which is provided as part of the solution set (Domain 4). However, system elements addressable by incentive interventions are discussed in detail in the rest of the decision-support framework domains.Figure 2 depicts the system demarcation component breakdown. Appendix B.1. contains the detailed system demarcation view.



Domain components	
1. System demarcation elements	5. Aspect to address (incentive/non-incentive based)
2. "Not ideal typical" state of system elements	6. System evaluation (operationalization)
3. "Average" state of system elements	7. Sourced from section
4. "Ideal typical" state of system elements	

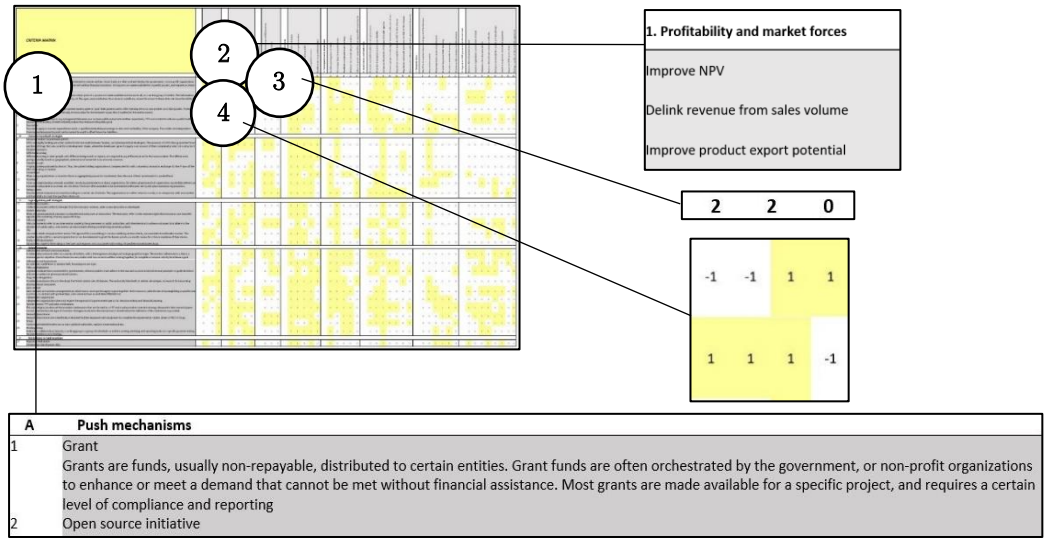
Figure 0.2: System demarcation components breakdown. 7

Appendix A.2. Background Logic 1: Criteria evaluation

Background logic 1 (BL 1) occurs between Domains 1 and 2. The purpose of this function is to merge the output of the system demarcation (Domain 1, this is also referred to as context-specific (CS) criteria), as well as criteria that is suggested as being critical for the success of an incentive intervention in literature (this is also referred to as context-non-specific criteria). The output of this function is a list of 27 criteria divided into 8 categories that serves as the input to Domain 2. Each criterion has a rating of 0 (lowest), 1 or 2 (highest), indicating the importance of addressing the criteria. This merged, rated list of criteria is called the *combined list of intervention criteria* (CLIC) and is presented in the columns of the table presented in Appendix A.11 and in Appendix B.2 (columns).

Appendix A.3. Domain 2: Criteria matrix

The criteria matrix provides the user with the ability to obtain a holistic overview of a comprehensive set of available incentive interventions, as well as an indication of the extent to which each incentive intervention can address the CLIC list constructed in BL 1. This indication of the extent to which each incentive intervention can address the various criteria is hardcoded and has been derived based on information on the various incentive interventions that is provided in literature. Two values are used to indicate whether an incentive intervention is able to address a criterion, namely -1, when the incentive intervention cannot address the criterion, and +1 when the criterion can be addressed by the incentive intervention.The criteria matrix is a matrix that consists of 104 incentive interventions (rows), divided into 27 incentive intervention categories, which falls under five incentive strategies, namely: (i) push; (ii) outcome-based pull; (iii) lego-regulatory pull; (iv) hybrid; and (v) interventions to fund incentives. The incentive interventions were identified in a structured literature review, which aimed to identify all incentive strategies available or suggested to encourage R&D in neglected diseases. The columns of the matrix are a list of criteria sourced from the BL 1 process, namely the CLIC list. Figure 3 depicts a breakdown of the criteria matrix components. Refer to Appendix B.2 for a view of the criteria matrix.



Domain components	
1. Incentive interventions	3. Rating for each CLIC
2. CLIC list (divided into 8 categories)	4. Incentive ability to address CLIC

Figure 0.3: Criteria matrix component breakdown.

Appendix A.4. Background Logic 2: Criteria scoring

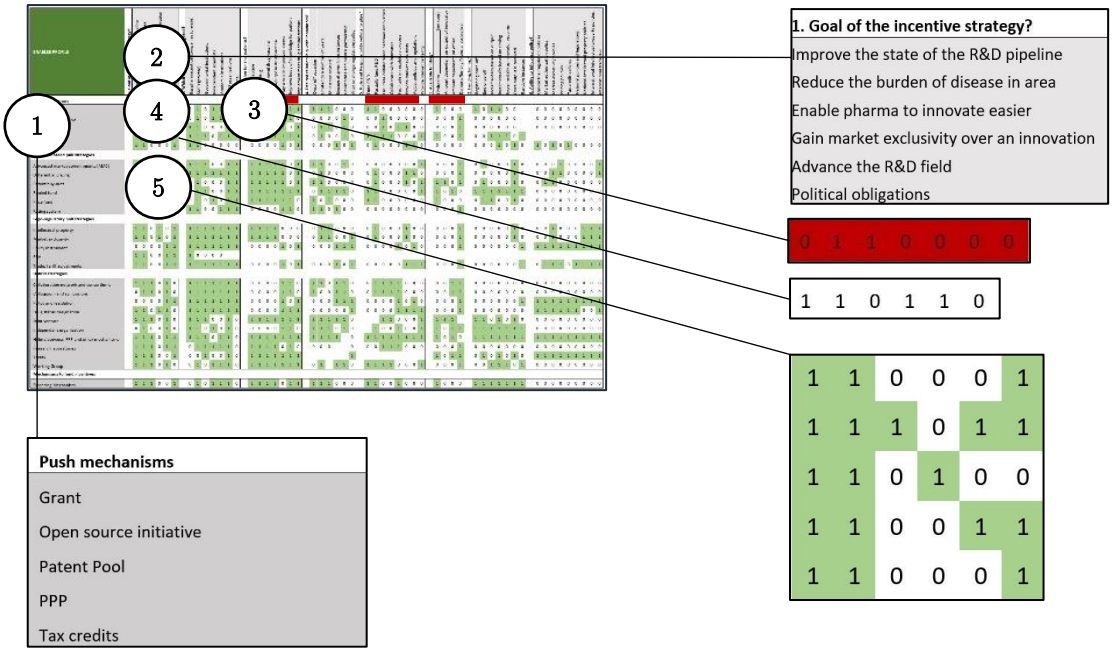
The aim of the BL 2 function is to process the ratings from Domains 1 and 2, into a holistic score metric for each incentive intervention. The score is used to, firstly, rank the incentive interventions and secondly, identify a recommended solution set based on the highest scores. This score will be referred to, as the *context specific- and non-specific* (CSNS) score. The CSNS score of each incentive intervention is calculated with a simple multiplication calculation. Where the CLIC list rated 0, 1 or 2 (BL 1) is multiplied by the list of incentive interventions, rated +1 or -1 (Domain 2).
The CSNS score for each incentive is calculated as in Equation 1:

$$CSNS\ score\ (per\ incentive\ j) = \sum_{i=1}^{28}(x_j^i \times y^i)\,, for\ j = [1,27] \qquad (1)$$

Where 'i' refers to the CLIC criterion (columns of the table in Appendix B.2), and 'j' refers to the incentive interventions (rows of the table in Appendix B.2); x refers to the rating of the incentive intervention's ability to satisfy the criterion; and y refers to the priority rating of the criterion. The output of BL 2 is a list of all the incentive interventions with a CSNS score indicating the ability to which the incentive satisfies the CLIC list. This output is used in Domain 4 to identify the final recommended solution set.

Appendix A.5. Domain 3: Enabler profile interpretation

The pharmaceutical status-quo is not the only determinant that affects what is required from an incentive intervention to be effective in encouraging R&D. This research also considers the enabling stakeholder involved, whom will act as the initiator of the incentive intervention. As discussed previously, although it is proposed that it would be beneficial to take the perspective of three stakeholders (namely the enabler, the innovator and the consumer) into consideration, only the enabler profile has been fully developed to date. The enabler stakeholder refers to the organization or entity aiming to incentivize a pharmaceutical innovator to devote resources to R&D in a desired field. The enabler has the ability to either (i) empower the innovator to innovate, by providing some or other resource; or to (ii) encourage the innovator to innovate by offering some kind of (potential) benefit.
The enabler is required to complete an 'inquiry form' (Figure 5), that is predefined with a short list of objectives and internal capabilities. The output of the enabler profile is the enabler matrix, indicating which objectives and internal capabilities are relevant to the scenario, and this serves as input for BL 3.
The enabler matrix consists of 27 incentive interventions (as the rows, this is the same set of rows as the ones in the criteria matrix), and 54 enabler profile objectives and internal capabilities (as the columns). The five domain components are described in Figure 4. Refer to Appendix B.3 for the overview of the enabler matrix.



Domain components	
1. Incentive interventions	4. Inclusion criteria rating
2. EC elements	5. Incentive ability to address EC
3. Exclusion criteria rating	

Figure 0.4: Enabler matrix components breakdown.

The objectives and internal capabilities of the enabler profile, were derived from the structured literature review that identified incentive interventions for drug R&D. The possible objectives and internal capabilities were established by investigating all possibilities from the 27 incentive interventions. These provide an overview of the enabler profile and give a clear indication of what their objectives and capacity restrictions are, which provides valuable input in the feasibility of the incentive interventions, this set of criteria is called the Enabler criteria (EC) relevant (therefore the criteria of the enabler profile, that is relevant to this specific enabler. The enabler profile investigation is depicted in Figure 5.

ENABLER PROFILE INVESTIGATION			
Objectives			
1 Goal of the incentive strategy? (PREFERRED)	Improve the state of the R&D pipeline		IN
	Reduce the burden of disease in area		IN
	Enable pharma to innovate easier		IN
	Gain market exclusivity over an innovation		IN
	Advance the R&D field		IN
	Political obligations		IN
2 Which innovators are targeted? (PREFERRED)	Big pharmaceutical companies (private)		IN
	SMEs (private)		IN
	Governmental institutions		IN
	Independent scientists		IN
	Academic institutions		IN
	NGO organizations		IN
	Everyone		IN
3 Intention for the consumers? (EXCLUSION CRITERIA)	Provide vaccine		EX
	Provide drug		EX
	Provide novel drug/vaccine		EX
	Multi-purpose drug/vaccine		EX
	Play a role in improved access		EX
	Implement mass drug administrations		EX
	Improve body of knowledge for consumer benefit		EX
4 Desired relationship with innovators? (PREFERRED)	Once-off occasion		IN
	Limited to a number of years		IN
	Milestone related		IN
	Engage at given time instances		IN
	Collaborate and build a partnership		IN
	Alter or change regulation/policy		IN
5 Role and Responsibility willing to play? (EXCLUSION CRITERIA)	Fund R&D		EX
	Partially fund R&D		EX
	Facilitate collaboration between innovators		EX
	Collaborate with innovator		EX
	Facilitate in regulatory process		EX
	Provide market exclusivity		EX
	Adjust policies and regulations		EX
	Provide market certainty		EX
Internal capabilities			
1 Available funding (EXCLUSION CRITERIA)	Limited to _____(amount)		EX
	Amount dependent on output of innovator		EX
	Amount dependent on other:		EX
2 Funding timing (PREFERRED)	Beginning once-off		IN
	End once-off		IN
	Incrementally based on output		IN
	Incrementally based on timing		IN
	Incrementally as innovator requires		IN
	Once output is received		IN
3 Ability to influence policy (PREFERRED)	Clinical trial regulation policies		IN
	Market authorization policy		IN
	Market exclusivity policies		IN
	Pricing policies		IN
	Tax credit policies		IN
	National policies and legislations		IN
	National Intellectual property policies		IN
	International Intellectual property policies		IN
	International trade law		IN

Figure 0.5: Enabler profile inquiry form.

Appendix A.6. Background Logic 3: Enabler scoring

BL 3 processes information that has been provided by the enabler (Domain 3) together with hard-coded information on the ability of each potential incentive intervention to satisfy the criteria that have been defined in the enabler matrix, to assign a score to each incentive intervention that serves as input to be considered when recommending the final short list of interventions.

Based on the enabler matrix (Domain 3, refer to Appendix B.3), a set of inclusion criteria as well as a set of exclusion criteria is formulated. The inclusion criteria refer to criterions dependent on the enabler's preferences, rather than on definite constraints. An exclusion criterion is an indication of a constraint that is based on the enabler's ability (e.g. a regulatory limitation that prevents funds from being offered in the form of a reward for a drug discovery).

The score per incentive intervention, based on the enabler profile, is called the *Enabler profile score* (EP-score). The EP-score is calculated by taking the sum product of the EC ability (ability of incentive to adhere to the criteria formulated by the enabler, this is derived from literature and is hard-coded) and the EC relevance (indication whether the criteria is relevant to the enabler, this is based on the enable matrix) for every incentive row (j). This is similar to the calculation of the CSNS-scoring. Equation 2 indicates the EP-score calculation.

$$EP\ score\ (per\ incentive\ j) = \frac{\sum_{i=1}^{54}\left(EC\ ability_j^i \times EC\ relevant^i\right)}{\sum_{i=1}^{54}(EC\ relevant^i)}, for\ j = [1,27] \qquad (2)$$

The EP-score provides an indication of how well each potential intervention fulfils the inclusion criteria that have been defined based on the stakeholder preferences. For potential incentive interventions that do not address exclusion criteria, an EP score of zero is allocated. This score of zero ensures that the infeasible incentive interventions are excluded from the final set of feasible incentive interventions. The enabler matrix consists of the incentive interventions as rows, and the enabler profile criteria (derived from Appendix A.2) as columns. This matrix indicates the binary ability of the incentive intervention to adhere to / satisfy the enabler criteria (represented with either a 0 or a 1). The matrix also indicates with either a 1 or 0, whether the criterion is relevant to the enabler (row 2 of enabler matrix).

Appendix A.7. Domain 4: Solution set

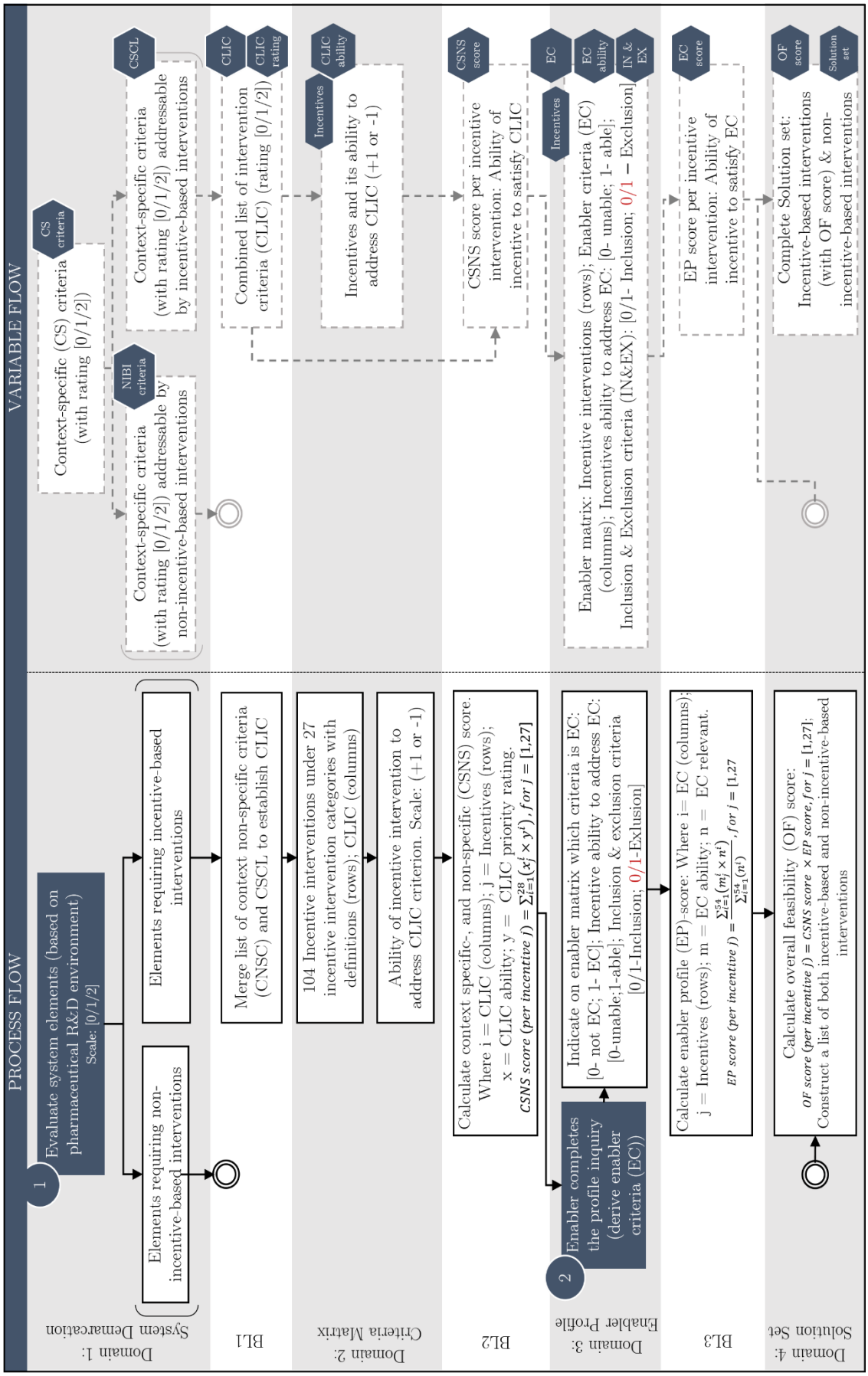
This domain involves compiling a set of solutions, with each solution being feasible to intervene the R&D environment and incorporate the limitations and capabilities of the enabler. The information for this domain is primarily sourced from BL 2 and BL 3. The development of the solution set of incentive interventions is based on a scoring process. The scoring is built on the CSNS-scoring (BL 2), as well as on the EP-scoring (BL 3) and is called the o*verall feasibility score* (OF-score). The OF -score is a combined measure for each incentive intervention (j), determined by multiplying the CSNS-score with the EP-score, resulting in a measure that quantifies the ability of the incentive to satisfy the requirements of the current R&D environment, as well as the preferences and limitations of the enabler. Equation 3 indicates how the OF-score is determined.

$$OF\ score\ (per\ incentive\ j) = CSNS\ score\ \times EP\ score, for\ j = [1,27] \qquad (3)$$

The OF-score is used as reference to measure the compliance of the incentives to the scenario being investigated. In addition to the recommended set of incentive interventions, a set of non-incentive related interventions are also provided. These are recommended for addressing system elements that cannot be addressed by incentive interventions. The solution set focus areas are the pharmaceutical R&D problem spheres that the incentives have the potential to address (depicted in Figure 6). These focus areas are derived from the context specific (system demarcation) and literature-based criteria, by grouping and categorizing the criteria according to the areas of the R&D industry that it addresses.

Figure 0.6: Solution set focus areas.

Appendix A.8. Framework process and variable flow



Appendix A.9. Incentive-based interventions

The complete list of 105 incentive-based interventions that are proposed, already implemented or ongoing are depicted here. The interventions are divided into 27 categories. All categories and interventions are briefly defined.

Push strategies
Grant Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting
USA Small Business Innovation and Research award programme: Provide grants to small businesses engaged in the R&D of NTD.
The Global Health Investment Fund (GHIF): Finance primarily late-stage R&D innovations for poverty related diseases.
Office of Orphan Product Development (OOPD): Aim to advance the evaluation and development of products that demonstrate potential for diagnostics or treatment of rare diseases and conditions by providing grants.
Open-source initiative Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets could benefit all participants.
PLOS open access journal: Open access journal devoted to NTDs of the world.
ChEMBL Neglected tropical disease database: Open access repository of data for the development of NTD medicinal chemistry.
Tropical Disease Initiative (TDI): A decentralized, internet-based, community-wide effort for tropical diseases, including NTDs.
MalariaGEN (Malaria Genomic Epidemiology Network): Researchers from 20 countries collaborate to R&D technology and control efforts for Malaria.
GNTD database: A database of 12 000 survey locations aimed at NTDs.
D3 (Distributed Drug Discovery): A strategy to accelerate the discovery of drugs to treat neglected diseases where multiple stakeholders engage to improve R&D capacity and capital development.
Leishmaniasis Research Network (redeLeish Network): The network operates through a Web Forum, and promote the exchange of information, enhances the consensus of clinical trial designs, encourage debates on the disease and enables collaborative research projects.
Wide in Silico Docking on Malaria (WISDOM): Links known chemical compounds with structural data from the Malaria parasite by the means of a network.
Patent pool Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.
Pool for Open Innovation Against Tropical neglected diseases: Donation of essential patents and know-hows to drive R&D on NTDs.
Malaria Vaccine Patent Pool: Allow access to multiple antigens, simplifies licensing transactions, and lowers the transaction costs.
GSKs Patent Pool for NTD: The pharmaceutical company GSK will share its patented knowledge used to develop medicines for NTDs.
PPP Public-private partnerships is any arrangement between one or more public and private entities respectively. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.
AERAS Global TB Vaccine Foundation (AERAS): Work through partnerships, to develop new, and effective TB vaccines.
Anti-Parasitic Drug Discovery in Epigenetics (A-ParaDDisE): Target-based strategy for the R&D of novel drug leads against certain NTDs.
Anti-Wolbachia Consortium (A-Wol): Develop drugs for specific NTD by developing products that targets the intracellular bacterium. The consortium comprises of both industry and academic partners.
Coalition for Epidemic Preparedness Innovations (CEPI): The fund would support emerging pandemic threats as well as NTD pathogens, while ensuring a market for product sales. Thus, focus on gaps in product R&D which results from market failures.
Council on Health Research and Development (COHRED): Global NGO with goal to maximize the research of diseases primarily occurring in LMICs.
Critical Path to TB Drug regimens (CPTR): Brings leading pharmaceutical and other drug developers in partnership to support the necessary infrastructure to facilitate the successful R&D of TB drug treatments.
Dengue Vaccine Initiative (DVI): Conduct policy and access-related activities to create an enabling environment for the introduction of dengue vaccine (e.g. decision making).
DNDi partnered with GSK: Partnership to develop drugs for NTD.
Drugs for Neglected Diseases Initiative (DNDi): NGO R&D organization that is committed to the R&D of improved or novel treatments for NTD.
European Developing Countries Clinical Trial Partnership (EDCTP): Funds clinical research to accelerate development of R&D for HIV, Malaria, TB, and other infectious diseases. Focus on Phase II and phase III trials.
Fixed-Dose Artesunate Combination Therapy (FACT) project consortium: Various entities are brought together for enhancing the development of anti-malarial treatments.
Foundation for Innovative New Diagnostics (FIND): International NGO that enable the R&D of much-needed diagnostic tests for poverty-related diseases.
Genzyme's Humanitarian Assistance for Neglected Diseases program (HAND): Work with partnerships or developing world institutions to R&D products from early stage of pipeline through clinical trial phases.
Global Alliance for TB drug development: NGO dedicated to R&D for improved TB medicines.
Global Alliance for Vaccines and Immunisation (GAVI): Partnership funds R&D and the supply of vaccines to developing countries.
Global Health Innovative Technology Fund (GHIT): Provides funding to support neglected infectious disease R&D collaborations between Japanese and global pharmaceutical organizations.
GSK and Brazil's Oswaldo Cruz Foundation (Fiocruz): Technology transfer partnership between a health institution and vaccine manufacturer.
Infectious Disease Research Institute (IDRI): NGO that conducts global health research on infectious diseases, with partners.
Innovative Vector consortium (IVCC): Not for profit, aim to develop and deliver new vector control tools.
Institute for One World Health (IOWH): NGO develops safe, effective, affordable medicines to people with diseases of the developing world.
KINDReD: Promote R&D of novel drug molecules against NTDs.
Macrofilaricide Drug Accelerator (MacDA): Bring entities together to advance R&D for drugs that are capable of killing the adult forms of the onchocerciasis and lymphatic filariasis parasites.
Medicines for Malaria Venture (MMV): The basic mission of the organization was to discover, develop and deliver safe and effective anti-malarial agents.
Novartis and Institute of Microbiology and Epidemiology in Beijing: R&D and distribution of antimalarial drug.
NTD NGDO Network: A global forum for non-governmental development organizations. Facilitate partnerships among group members.
PATH Malaria Vaccine Initiative (MVI): Program that works via partnerships in private and public sector to enable the development of vaccines.
PDP+ Fund: Raise funding by product development and the coordination of funding to many PDPs.
Roll Back Malaria (RBM): Mobilises action against Malaria (funding, scale up control and conduct resource mobilization).
Sanofi-Aventis and DNDi: Develop and manufacture drugs against and treat African trypanosomiasis and Malaria.
South-African Tuberculosis Vaccine Initiative (SATVI): Innovate and assist research for TB vaccinations and vaccination strategies.

Stop TB partnership Working group on new Vaccines: Works to develop a second-generation vaccine for TB, effective for all populations and age groups.
Therapeutics for Rare and Neglected Diseases (TRND) Program: Supports pre-clinical R&D of drug compounds that are intended to treat rare or neglected diseases.
UK Department for International Development (DFID): Funds R&D by PDPs. Includes both product development and operational research.
United States Agency for International Development Neglected Tropical Diseases (USAID NTD) Program: The NTD Program invests in priority research needs for NTD control and elimination to guide improved mapping, stop treatment decision-making and create sustainable disease surveillance.
Uniting to Combat NTDs: Dedicated partners to perform R&D to combat NTDs.
WHO Special Program for Research and Training in Tropical Diseases (WHO/TDR): Support for R&D in Chagas and similar diseases. Assists in establishing PDPs for R&D of drugs for NTDs.
WIPO Re:Search consortium: Organizations collaborate to share expertise, research and technology, with specific focus on drug, vaccine and diagnostic development.
Tax credits Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.
Vaccines for the New Millennium Act of 2001: Allows companies a 30% tax credit for pursuing R&D in vaccines for HIV/AIDS, Malaria and TB.
Pull strategies
Outcome-based pull strategies
Advanced market commitments (AMC) AMCs are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.
AMC programme for pneumococcal vaccines: Involve a guarantee by donors to purchase a successful vaccine at a fixed price for a fixed number of doses.
Advanced Market Commitment Scheme (AMC): Under the AMC, sponsors will make legally binding commitment to either fully or partially finance the purchase of a certain vaccine for poor countries, for a pre-specified price, for a fixed number of individuals.
Advanced Purchase Commitment, G8 Summit Italy 2009: Governments of five major countries announced a partnership with the BMG Foundation to commit $1.5 billion to purchase pneumococcal disease vaccines tailored for developing countries. The vaccines are yet to be developed.
Differential pricing Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.
Value-based differential pricing: Increase returns on R&D and expand overall access to medicines in LMIC.
Patent buy-outs IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.
Patent buyouts suggested by (Granslandt et. al. (2001)): Donors purchase IP rights to deliver products to developing countries.
Pooled fund When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.
Fund for Research into Neglected Diseases (FRIND): Allocate stepwise funding to only the most promising compound, will also focus on funding late stage product development.
Prize fund Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.
Health Impact Fund (HIF): Pay-for-performance scheme for new medicines. Pharmaceutical companies would be free to abandon monopoly pricing, and register products with HIF, which would reward them for the health impact.
Priority Medicines and Vaccines Prize Fund (PMV/pf): Lumpsum prize money. 90% of the prize money will go to the winning entrant; whereas the other 10% will go to the other entrants who did not win.
Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis: The total prize will be awarded to the entrant, once the entrant provides a satisfactory diagnostic test.
Prize Fund to Support Innovation and Access for Donor Supported Markets: Prizes to reward participation in a qualified, voluntary patent pool.
Drugs for Neglected Diseases Working Group (DND-WG): Aim to launch or fund drug development pilot projects.
Licensed Products Prize Fund (LP/pf) for Donors: Developers will be rewarder with cash prizes, if they voluntarily license their innovations for TB, Malaria and HIV/AIDS to a patent pool.
Rating system Pharmaceutical companies are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.
Access to Medicine Index: An international NGO that ranks pharmaceutical organizations based on making medicines, vaccines and diagnostics more accessible to LMICs.
Global Health Impact Rating system: Objective and output based rating system will rate companies on their R&D results and charitable contributions.
Lego-regulatory pull strategies
Intellectual property Intellectual property refers to the right that the innovator receives, when an innovation is developed.
Transferable IP Rights (TIPRs): Companies are awarded an IP extension for a product of their choice, should they successfully being a neglected disease product into the market and ensure product delivery in target population.
Market exclusivity When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.
TRIPS agreement: Intervention that reward companies that develop and reach market approval for a drug for a neglected disease. The intervention would grant developers a tradable right to an extended period of patent life for another product of their choice for a specified period in high-income markets.
Policy instrument Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy.
Strengthening Pharmaceutical Innovation in Africa (SPIA): Focus on reinforcing countries' capacity for policy formulation in the sectors of science and technology in order to enhance pharmaceutical innovations in SSA.
The Global Strategy and Plan of Action on Public Health, Innovation, and Intellectual Property (GSPA - PHI): Aim to promote thinking on the innovation and access of medicines, while enhancing sustainability in the R&D of diseases that disproportionately affect LMICs.
PRV Law under which companies that receive FDA approval for a novel drug or vaccine satisfying certain criteria, are awarded a transferable voucher.

This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.
Priority Review Voucher (PRV): Law under which companies that receive FDA approval for a novel drug or vaccine targeting one of 16 NTDs are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.
Priority Review Voucher by the European Medicines Agency (EMA) or European Commission: Similar to initial PRV, in context of Europe. The developer is awarded with a voucher when a drug for a neglected disease is developed. The voucher can then be used to enhance the process of any product by accelerating marketing authorization and pricing procedures.
Trade, tariff adjustments Adjustments made to the trading or the taxes and required costs associated with trading of manufactured drugs.
Doha trade rounds: World Trade organization offers the opportunity for policy makers to improve the health equity in resource poor countries. Includes tariff reduction and the establishment of global harmonized trade codes.
Hybrid strategies
Collaboration network and consortiums A collaboration network refers to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a common goal.
The 3P Project: An open collaboration approach, aims to pull funding, pool intellectual property and push finance for R&D. (Unique to other collaboration approaches)
Collaboration for Applied Health Research and Delivery Consultation (CAHRD): Bring together internal and external partners to shape the strategic direction of various diseases. Focusing on four areas namely: 1) lung health, 2) maternal & new-born health, 3) NTD, and 4) Health systems.
International Rare Diseases Research Consortium (IRDiRC): Maximizes resources and coordinate research efforts of rare diseases.
Great neglected diseases network (GND) Ken Warren and Rockefeller foundation: Created multidisciplinary teams, consisting of handpicked leading scientists (from both developed and developing countries). Work was investigator-initiated; compulsory annual meeting, where progress and developments was reported; knowledge shared.
London Declaration on Neglected tropical diseases: Organizations committed to increase the number of drug donations available to countries, increase bilateral funding, support non-governmental development organisations (NGDOs) and philanthropic financial commitment to NTD intervention and research.
Liverpool School of Tropical Medicine (LSTM): Developing of new diagnostics, drugs and insecticides for the control of NTDs.
PDE4NPD: Aim to develop new treatments for Neglected parasitic diseases.
Colloquium and Symposium An academic conference or seminar held, focussing on one topic.
Drugs for Communicable diseases: Stimulating development and securing availability, colloquium: Discuss incentivizing methods for the development of drugs that targets neglected diseases.
New Medicines for Trypanosomiasis Infections (NMTrypl): A common drug-discovery platform that tests HIT compounds and complete safety testing.
Policy and legislation Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.
Cost-Effectiveness model: Policy option to be considered by decision makers in the allocation of limited donor funding to incentivise R&D of vaccines.
Orphan drug legislation combination with other interventions: Combination of orphan drug designation with interventions such as transferable patent exclusivity and transferable priority review. Include the possibility to shift for another drug from a standard to a priority or fast review process.
Orphan Drug Act (ODA): Provides incentives (tax credits, FDA fees paid and grant opportunities) to promote research in and the production of drugs for rare diseases in domestic markets.
Drug status designation Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.
Orphan Drug Designation Program (ODDP): Provides an orphan drug status to drugs and biologics that treat diseases defined as rare diseases by ODA.
Joint venture Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.
Merck's Hilleman Research Laboratory: Vaccine R&D organization focus on diseases including NTD.
Oxford Emergent Tuberculosis Consortium (OETC): Joint-venture structure set up by a publicly funded University and a biopharmaceutical firm listed on the New York Stock Exchange.
The Synaptic Leap (TSL): An open-source biomedical research community that aims to investigate diseases where "profit-driven research is failing".
Wellcome trust Joint Venture: Aim to spur development for a range of vaccines for developing countries.
Independent organization Independent organizations does not require the approval of a government agency for decision-making and financial planning.
Global Forum for Health Research (GFHR): Initiated the 10/90 gap. Focus on improving global health and the health research sphere.
Hybrid between PPP and other interventions This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention; the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.
European Vaccine Initiative (EVI): Innovative solution for disease control to tackle neglected diseases and to ensure public health system preparedness. (PPP and grant)
Open-source Drug Discovery Initiative (OSDD): Community of people, students, scientists and researchers who commits time to R&D drugs in an open-source mode for NTDs. (PPP and open-source)
African Network for Drugs and Diagnostics Innovation (ANDI): Vision is to create a sustainable platform for R&D innovation in Africa to address Africa's own health needs. (PPP and open-source)
The Paediatric Praziquantel (PEDPZQ) Consortium: NGO that contributes to reducing GBD of schistosomiasis by driving and implementing the development of a child friendly formulation for the disease. (PPP and open-source)
Cambia partnered with Queensland University of Technology: Establish a platform to promote patent system transparency worldwide. Funding from BMGF grant. (PPP, open-source initiative and the provision of grants)
Tres Cantos Open Lab Foundation (TCOLF): Facilitate access to IP, industrial expertise and technologies to stimulate research into NTDs. (PPP, open-source initiative and patent pool)
UNITAID Medicine's Patent Pool: The Grant focuses on negotiating voluntary license to enable the manufacturing of HIV, Hepatitis C, and TB medicines for LMICs. (PPP, patent pool and grant)
Novartis institute for Tropical Disease in Singapore: Research institute focused on doing research in tropical diseases. (PPP formed research institute)

Research laboratories Research laboratories are scientifically orientated facilities equipped with the necessary equipment to complete the necessary experimental studies aimed at R&D of drugs.
Astra Zeneca's TB Facility in Bangalore, India: Research facility that focus on finding new treatments for TB.
Treaty Formal agreement between two or more states, subject to international law.
International Binding R&D Treaty: Improve the coherence, fairness, efficiency, and sustainability of the global R&D system.
Working Group Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.
Consultave Expert Working Group on Research and Development Financing and Coordination (CEWG): Examine the concerns of the lack of resources being devoted to NTDs. Builds on previous version of EWG.
Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG-PHI): Aim is to improve and advance essential R&D for diseases that disproportionally affect developing countries.
The WHO Expert Working Group on R&D Financing (EWG): Stimulate R&D for type II and III diseases and satisfy the R&D needs of developing countries.
Interventions to fund incentives
Financing mechanism Interventions that finances R&D.
Global Fund to Fight AIDS, TB, and Malaria (GFATM): Finance R&D of Aids,TB, Malaria, and NTDs.

Appendix A.10. Non-incentive-based solutions

The non-incentive-based solutions originate from the system demarcation system elements, that cannot be incentive interventions. For each system element, a brief meaning, the relevance to being addressed and a few possible intervention considerations are provided. 40 System elements are considered, this Appendix does however, merely serve an informative means to provide examples of seven of the system elements.

II. EXISTING DRUG CHARACTERISTICS

3 **Quality of existing drugs**

		For further reference
Meaning	Drugs should not pose significant health risks to patients and should be effective in treating the disease.	(van Olmen et al., 2010); (Dorlo et al., 2012); (Rauscher, Walkowiak and Djara, 2018) (Dorlo et al., 2012) (Institute of Medicine & Committee on Quality of Health Care in America, 2001)
Relevance	Patients depend on drugs for disease mitigation. If quality is not up-to-standard, then disease burden might increase or might not decrease.	
Intervention considerations	Repeat final clinical trial stages to monitor effects of medicine in a controlled environment	
	Remove drugs from market	
	Improve monitoring of adverse drug reactions (ADR)	
	Pharmacovigilance	
	Quality control of current manufacturing procedures	
	Enforce international clinical trial and manufacturing practices and regulations	

III. SERVICE DELIVER

7 **Comprehensiveness of services delivered**

		For further reference
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004) (WHO, 2010)
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.	
Intervention considerations	Education of prevention measures.	
	Address root-cause of disease (e.g. water and sanitation)	
	Investigate the needs of the affected population group	
	Address social needs of patients	
	Repeat prevention or mass drug administration interventions, if deemed necessary.	

VI. GOVERNANCE AND LEADERSHIP

15 **Effective national budget allocation**

		For further reference
Meaning	The financial plan of a country should include planning and financial allocations to the health and health care of citizens.	(World Health Organization, 2018) (Emmanuel and Emmanuel, 1996) (Becker, 2015)
Relevance	The health care of a country is the responsibility of its government. Without budget allocation, health care advancement is less likely.	
Intervention considerations	Implement SDGs	
	Policy reform	
	Strategic resource allocation options	
	Global health governance	

16 **Regulation of strategic health policy**

		For further reference
Meaning	The goals, visions, priorities and budgetary decisions of a country needs to be regulated, to be in line with health needs.	(Liang and Mackey, 2012) (World Health Organization, 2018) (Nagpal, Sinclair and Garner, 2013)
Relevance	If the strategic plans and actions to undertake and achieve are not taken, then the health of the country will lack improvement.	
Intervention considerations	Global health governance	
	Strategic political interventions	
	Domestic, private, and global policy interventions	

VIII. RESEARCH AND DEVELOPMENT PROCESS

23 **Transparency of clinical trial information**

		For further reference
Meaning	Clinical trial information is openly available, reliable and does not entail any suspicious information.	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis *et al.* (2015) (Šolić et al., 2017) (Li et al., 2016)
Relevance	Transparent clinical trial information assures that products being developed adhere to safety, efficacy and regulatory requirements.	
Intervention considerations	Annual, and unannounced firm audits	
	Ethical conduct	
	Education on misconduct and legal consequences	
	Adhere to international clinical trial authority agency regulations	

24 **Accountability of clinical trial information**

		For further reference
Meaning	Clinical trial information should be trustworthy	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)
Relevance	There should be clear accountability for the information of clinical trials.	
Intervention considerations	Annual, and unannounced organization audits	
	Ethical conduct	
	Education on misconduct and legal consequences	
	Adhere to international clinical trial authority agency regulations	

IX. MANUFACTURING SYSTEMS

Appendix A.11. Combined list of intervention criteria (CLIC)

This CLIC is the output of Background Logic 1 and represents the columns of the criteria matrix (Domain 2). This list is a combination of the context-specific (CS) criteria (from domain 1) and the context-non-specific criteria (CNSC) (identified in literature).

1. Profitability and market forces

1. Improve NPV
2. Delink revenue from sales volume
3. Improve product export potential

2. Implementation feasibility and security

4. Minimizes barriers to implementation
5. Minimize disruptive effects to population
6. Affordable to implement the incentive
7. Provide R&D project insurance

3. Green and sustainability

8. Ensure conservation of resources in R&D process
9. Encourage efficient innovation
10. Green R&D of drugs

4. Population impact and Access

11. Potential to reduce burden of disease
12. Encourage R&D of a drug or intervention
13. Encourage novel drug R&D
14. Improve consumer access
15. Enable mass drug administration

5. Participation and cooperation

16. Enables participation of SMEs
17. Encourage large firm participation
18. Facilitates cooperation and synergy
19. Platform for coordinating innovators
20. Allow for great competition among parallel experiments

6. Governance and leadership

21. Promote equitable health-focused governance
22. Promote transparency and accountability
23. Advances the priority of disease on health agenda
24. Advance proper functioning of domestic policy structures
25. Regulatory oversight to promote R&D for the disease
26. Regulatory exclusivity provisions for R&D of the disease
27. Resources to deliver health service are financed by government

7. Rewards focus

28. Payoff to innovators based on drug cost-effectiveness
29. Reward innovation
30. Financing timed across drug lifecycle
31. Provide long term R&D financing
32. Provide sustainable financing
33. Provide public subsidies for clinical trials

8. Impact on R&D process and clinical trials

34. Reduce clinical trial risk involved
35. Assist in registration and monitor of trials
36. Globalize clinical trial methods
37. Reduce clinical trials activation difficulty
38. Enhance or prompt the quality of clinical trials
39. Assist in expensive clinical trial regulation
40. Improve R&D productivity
41. Enlarge the number of clinical trials registered

						System evaluation	
	System elements	**2**	**1**	**0**	**Aspect to address**	**Measure [0|1|2]**	**Sourced from section**
Disease setting and affected population							
1	Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)		Chapter 3.6.2
2	Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact		Chapter 3.6.2
3	Burden fully characterized	< 40% of population within 5% of health facility	40% - 60% of population within 5% of health facility	> 60% of population within 5% of health facility	Non-incentive-based solutions (I)		Chapter 3.4.1.1 &3.6.2
Existing drug characteristics							
4	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact		Chapter 3.6
5	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)		Chapter 3.6
6	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact		Chapter 2.1.2
7	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)		Chapter 2.2.5
8	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access		Chapter 2.2.5
9	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)		Chapter 2.2.5
10	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)		Chapter 2.2.5
11	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (Respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)		Chapter 2.2.5
12	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access		Chapter 3.6.2
Service delivery							
13	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)		Chapter 2.2.3
14	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)		Chapter 2.2.3
15	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)		Chapter 2.2.3
16	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)		Chapter 2.2.3
Consumers, Competitors, and suppliers							
17	Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)		Chapter 3.4.3 & 3.7.3
18	The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)		Chapter 3.7.3
19	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)		Chapter 3.4.3
20	Existence of competitors	No competitors	Some competitors	A lot of competition	Non-incentive-based solutions (V)		Chapter 3.4.3
21	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility		Chapter 3.4.3
22	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation		Chapter 3.4.3
23	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation		Chapter 3.4.3
Governance and leadership							
24	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)		Chapter 3.6.2
25	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership		Chapter 3.6.2
26	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership		Chapter 3.6.2
27	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership		Chapter 3.6.2
28	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)		Chapter 2.1.2
29	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)		Chapter 2.1.2
30	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership		Chapter 2.2.3
31	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)		Chapter 2.2.5
32	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)		Chapter 2.2.3
Profitability and market forces							
33	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces		Chapter 2.1 & 3.6.2
34	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)		Chapter 3.6.2
35	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)		Chapter 2.1.2
36	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)		Chapter 3.4.3
37	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces		Chapter 3.4.3 & 3.6.2
38	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership		Chapter 3.6.2
Research and development process							
39	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials		Chapter 2.1.2
40	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)		Chapter 2.1.2
41	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)		Chapter 2.1.2
42	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)		Chapter 2.1.2
43	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)		Chapter 2.1.2
44	Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials		Chapter 2.1.2
45	Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials		Chapter 2.1.2
46	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials		Chapter 2.1.2
47	Quality of clinical trials	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable	Good clinical trial quality	9. R&D and clinical trials		Chapter 2.1.2
48	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials		Chapter 3.6.2
49	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)		Chapter 2.1.2
50	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)		Chapter 2.1.2
51	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)		Chapter 2.1.2
52	Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)		Chapter 2.1.2
53	Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)		Chapter 2.1.2
54	Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)		Chapter 2.1.2
55	Racial differences in participation in clinical trial	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)		Chapter 2.1.2
56	Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)		Chapter 2.1.2
57	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)		Chapter 2.1.2
58	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)		Chapter 3.4.3
59	Fully employed workforce	Some unemployment within organization	Some unemployment within organization	Workforce are fully employed	Non-incentive-based solutions (VIII)		Chapter 3.4.3
60	R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials		Chapter 2.1.3
61	Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials		Chapter 2.1.2 & 2.1.3
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)		Chapter 2.1.2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)		Chapter 2.1.2
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)		Chapter 3.4.3
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs		Chapter 3.4.3
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)		Chapter 2.2.3
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)		Chapter 2.2.3

CRITERIA MATRIX		**1. Profitability and market forces**	Improve NPV	Delink revenue from sales volume	Improve product export potential	**2. Implementation feasibility and security**	Minimizes barriers to implementation	Minimize disruptive effects to population	Affordable to implement the incentive	Provide R&D project insurance	**3. Green and sustainability**	Ensure conservation of resources in R&D process	Encourage efficient innovation	Green R&D of drugs	**4. Population impact and Access**	Potential to reduce burden of disease	Encourage R&D of a drug/intervention	Encourage novel drug R&D	Improve consumer access	Enable mass drug administration	**5. Participation and cooperation**	Enables participation of SMEs	Encourage large firm participation	Facilitates cooperation and synergy	Platform for coordinating innovators	Allow for great competition among parallel experiments	**6. Governance and leadership**	Promote equitable health-focused governance	Promote transparency and accountability	Advances the priority of disease on health agenda	Advance proper functioning of domestic policy structures	Regulatory oversight to promote R&D for the disease	Regulatory exclusivity provisions for R&D of the disease	Resources to deliver health service, government financed	**7. Rewards focus**	Payoff to innovators based on drug cost-effectiveness	Reward innovation	Financing timed across drug lifecycle	Provide long term R&D financing	Provide sustainable financing	Provide public subsidies for clinical trials	**8. Impact on R&D process and clinical trials**	Reduce clinical trial risk involved	Assist in registration and monitor of trials	Globalize clinical trial methods	Reduce clinical trials activation difficulty	Enhance or prompt the quality of clinical trials	Assist in expensive clinical trial regulation	Improves R&D productivity	Enlarge number of clinical trials registered
A	**Push interventions**		**2**	**2**	**0**		**2**	**2**	**2**	**2**		**2**	**2**	**0**		**0**	**0**	**0**	**2**	**0**		**2**	**2**	**2**	**2**	**2**		**2**	**2**	**0**	**0**	**0**	**0**	**0**		**2**	**2**	**2**	**2**	**2**	**2**		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	Grant Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting		1	-1	-1		-1	-1	1	1		-1	-1	-1		1	1	-1	-1	1		1	1	-1	-1	-1		-1	1	1	-1	1	-1	1		-1	-1	-1	1	-1	-1		-1	-1	-1	1	-1	-1	-1	-1
2	Open-source initiative Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets have the ability to benefit all participants.		1	1	-1		1	1	1	-1		-1	-1	-1		1	1	-1	-1	-1		1	-1	1	1	-1		1	1	1	1	-1	-1	-1		-1	-1	-1	-1	-1	-1		1	1	1	-1	-1	-1	1	1
3	Patent pool Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.		1	1	1		-1	-1	1	-1		-1	-1	-1		1	-1	1	1	-1		1	1	1	1	-1		1	1	-1	-1	-1	-1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
4	PPP Public-private partnerships is any arrangement between one or more public and private entities respectively. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.		1	-1	1		1	1	1	-1		-1	-1	-1		1	1	1	1	-1		1	1	1	1	1		1	1	1	1	-1	-1	1		-1	-1	1	1	1	1		-1	1	1	1	-1	1	-1	1
5	Tax credits Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.		1	-1	-1		1	-1	-1	-1		-1	-1	-1		1	1	-1	-1	-1		1	1	-1	-1	-1		-1	1	1	-1	1	1	1		-1	1	1	-1	-1	1		-1	-1	-1	-1	-1	-1	-1	-1
B	**Outcome-based pull strategies**																																																	
6	Advanced market commitments (AMC) AMCs are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.		1	1	-1		1	1	1	1		1	1	-1		1	1	1	1	1		-1	1	-1	-1	-1		-1	-1	1	-1	-1	-1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
7	Differential pricing Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.		1	1	1		1	-1	-1	-1		-1	-1	-1		1	1	1	1	1		-1	1	-1	-1	-1		-1	-1	1	-1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
8	Patent buy-outs IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.		1	-1	1		-1	-1	-1	1		-1	-1	-1		1	1	1	1	-1		1	-1	-1	-1	-1		-1	-1	1	-1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
9	Pooled fund When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.		-1	1	1		1	-1	1	1		1	1	-1		1	1	-1	1	1		1	-1	1	1	-1		-1	1	1	-1	-1	-1	-1		-1	-1	1	1	1	-1		1	-1	-1	-1	-1	-1	-1	-1
10	Prize fund Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.		1	1	-1		1	-1	1	1		1	1	-1		1	1	1	1	-1		1	-1	-1	-1	1		-1	1	1	-1	-1	-1	-1		1	1	1	-1	-1	-1		-1	-1	1	-1	1	-1	-1	1
11	Rating system Pharmaceutical companies are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.		-1	-1	1		-1	-1	1	-1		1	1	1		1	1	1	1	-1		1	1	-1	-1	1		1	1	1	1	1	1	-1		-1	-1	-1	-1	-1	-1		-1	-1	-1	-1	1	-1	1	-1
C	**Lego-regulatory pull strategies**																																																	
12	Intellectual property Intellectual property refers to the right that the innovator receives, when a new innovation is developed.		1	-1	-1		-1	-1	1	1		-1	-1	-1		1	1	1	-1	-1		-1	1	-1	-1	-1		-1	-1	1	-1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
13	Market exclusivity When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.		1	-1	-1		1	-1	1	1		-1	-1	-1		1	1	1	-1	-1		-1	1	-1	-1	-1		-1	-1	1	-1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
14	Policy instrument Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy. Instruments can also include altering and enforcing domestic policies.		-1	-1	1		1	1	1	-1		1	1	1		-1	1	-1	1	-1		1	1	-1	-1	-1		1	1	-1	1	1	-1	-1		-1	-1	-1	-1	-1	-1		-1	1	1	-1	1	1	-1	1
15	PRV Law under which companies that receive FDA approval for a novel drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.		1	1	-1		1	-1	1	-1		-1	-1	-1		1	1	1	-1	-1		-1	1	-1	-1	1		-1	-1	1	-1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	1	-1	1	-1	-1
16	Trade, tariff adjustments Adjustments made to the trading or the taxes and required costs associated with trading of specified manufactured drugs.		1	-1	1		-1	1	-1	-1		-1	-1	-1		1	1	1	-1	1		-1	1	-1	-1	-1		1	-1	1	1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
D	**Hybrid strategies**																																																	
17	Collaboration network and consortiums A collaboration network refers to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a goal.		1	-1	1		-1	-1	1	1		1	1	-1		1	-1	-1	1	1		1	1	1	1	-1		1	1	1	-1	-1	-1	-1		-1	1	-1	1	1	-1		1	1	1	-1	1	1	1	-1
18	Colloquium and Symposium An academic conference or seminar held, focussing on one topic.		-1	-1	1		-1	-1	1	-1		-1	1	-1		1	1	1	1	-1		1	1	1	1	-1		-1	1	1	1	1	-1	-1		-1	-1	-1	-1	-1	-1		-1	-1	1	-1	1	-1	1	-1
19	Policy and legislation Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.		-1	-1	1		1	1	-1	-1		-1	1	1		-1	1	-1	1	1		1	1	-1	-1	-1		1	1	-1	1	1	-1	1		-1	-1	-1	-1	-1	1		-1	1	1	1	1	-1	-1	1
20	Drug status designation Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.		1	1	1		1	-1	-1	-1		-1	-1	-1		1	1	1	1	1		1	1	1	-1	1		-1	-1	1	-1	-1	1	-1		-1	1	-1	-1	-1	-1		-1	-1	-1	-1	-1	-1	-1	-1
21	Joint venture Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.		1	-1	1		1	-1	1	1		1	1	-1		1	1	1	1	-1		1	1	1	1	-1		-1	1	1	-1	-1	-1	-1		-1	1	1	-1	-1	-1		1	-1	1	1	1	1	-1	1
22	Independent organization Independent organizations does not require the approval of a government agency for decision-making and financial planning.		-1	1	-1		1	-1	-1	-1		-1	-1	-1		1	1	1	1	-1		1	1	1	-1	-1		-1	1	1	1	1	-1	-1		-1	-1	-1	-1	1	-1		-1	-1	-1	-1	-1	-1	-1	-1
23	Hybrid between PPP and other interventions This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention; the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.		1	-1	1		1	1	1	1		-1	-1	-1		1	1	1	1	1		1	1	1	1	-1		1	1	1	1	-1	1	-1		-1	-1	1	1	1	1		1	1	1	1	-1	1	-1	1
24	Research laboratories Research laboratories are scientifically orientated facilities equipped with equipment to complete the experimental studies aimed at R&D of drugs.		-1	-1	1		1	1	-1	-1		1	1	1		1	1	1	1	-1		1	-1	1	1	-1		-1	1	1	-1	-1	-1	-1		-1	-1	-1	1	1	-1		-1	1	1	1	1	1	-1	1
25	Treaty Formal agreement between two or more political authorities, subject to international law.		-1	-1	1		1	1	1	-1		1	1	1		1	-1	-1	1	1		-1	-1	1	1	-1		1	1	1	1	-1	1	-1		-1	-1	-1	-1	-1	1		-1	-1	1	-1	1	1	-1	1
26	Working Group Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.		-1	-1	1		1	-1	1	1		-1	-1	-1		1	1	1	1	1		1	-1	1	1	-1		-1	-1	1	-1	-1	-1	-1		-1	-1	1	-1	1	-1		-1	-1	1	1	-1	-1	-1	-1
E	**Interventions to fund incentives**																																																	
27	Financing Intervention Interventions that finances R&D.		1	-1	-1		1	-1	-1	1		-1	-1	-1		1	1	-1	1	-1		1	-1	-1	-1	-1		-1	-1	1	-1	-1	-1	-1		-1	-1	1	1	1	-1		1	-1	-1	1	-1	1	-1	-1

ENABLER PROFILE	1. Goal of the incentive strategy?	Improve the state of the R&D pipeline	Reduce the burden of disease in area	Enable pharma to innovate easier	Gain market exclusivity over an innovation	Advance the R&D field	Political obligations	2. Which innovators are targeted?	Big pharmaceutical companies (private)	SMEs (private)	Governmental institutions	Independent scientists	Academic institutions	NGO organizations	Everyone
Push interventions															
Grant		1	1	0	0	0	1		0	1	0	1	1	1	0
Open-source initiative		1	1	1	0	1	1		0	1	0	1	1	1	0
Patent Pool		1	1	0	1	0	0		1	1	0	0	0	1	0
PPP		1	1	0	0	1	1		1	1	1	1	1	1	1
Tax credits		1	1	0	0	0	1		1	1	0	0	0	0	0
Outcome-based pull strategies															
Advanced market commitments (AMC)		1	1	0	0	0	1		1	1	1	0	0	1	1
Differential pricing		1	1	0	0	0	1		1	1	1	1	1	1	1
Patent buy-outs		1	1	0	1	0	0		0	1	0	0	0	1	1
Pooled fund		1	1	1	0	0	0		0	1	1	0	0	1	1
Prize fund		1	1	1	0	0	1		0	1	0	1	0	1	1
Rating system		0	1	0	0	0	0		1	1	0	0	1	1	1
Lego-regulatory pull strategies															
Intellectual property		1	1	0	1	0	1		1	1	1	1	1	1	1
Market exclusivity		1	1	0	1	0	1		1	1	1	1	1	1	1
Policy instrument		0	0	0	0	1	1		1	1	1	1	1	1	1
PRV		1	1	0	0	1	1		1	1	1	1	1	1	1
Trade, tariff adjustments		1	1	0	0	1	1		1	1	1	1	1	1	1
Hybrid strategies															
Collaboration network and consortiums		1	1	1	0	1	0		1	1	1	1	1	1	1
Colloquium and symposium		0	1	1	0	1	0		1	1	1	1	1	1	1
Policy and legislation		0	0	0	0	1	1		1	1	1	1	1	1	1
Drug status designation		1	1	0	1	1	0		1	1	1	1	1	1	1
Joint venture		1	1	1	0	1	0		1	1	1	0	0	1	0
Independent organization		0	1	0	0	1	0		1	1	0	1	0	1	0
Hybrid between PPP and other interventions		1	1	1	0	1	1		1	1	1	0	1	1	0
Research laboratories		1	1	1	0	1	1		0	1	1	1	1	1	0
Treaty		1	1	1	0	0	1		0	0	1	0	0	1	0
Working Group		1	1	1	0	1	0		0	1	0	1	1	1	0
Interventions to fund incentives															
Financing Intervention		1	1	1	0	0	1		0	1	0	1	1	1	0

ENABLER PROFILE	3. Intention for the consumers?	Provide vaccine	Provide drug	Provide novel drug/vaccine	Multi-purpose drug/vaccine	Play a role in improved access	Improve body of knowledge for consumer	Implement mass drug administrations	4. Desired relationship with innovators?	Once-off occasion	Limited to a number of years	Milestone related	Engage at given time instances	Collaborate and build a partnership	Alter or change regulation/policy
Push interventions															
Grant		1	1	1	1	0	1	1		1	1	1	0	0	0
Open-source initiative		0	0	0	0	1	1	0		0	0	0	0	1	0
Patent Pool		1	1	1	1	1	0	1		0	1	1	0	1	0
PPP		1	1	1	1	1	1	1		0	1	0	0	1	0
Tax credits		0	0	0	0	1	0	1		0	0	0	1	0	1
Outcome-based pull strategies															
Advanced market commitments (AMC)		1	1	1	1	1	0	1		1	1	0	0	1	0
Differential pricing		1	1	1	1	1	0	1		0	1	0	0	0	0
Patent buy-outs		1	1	1	1	1	0	1		1	1	0	0	0	0
Pooled fund		1	1	1	1	1	1	1		0	1	1	1	1	0
Prize fund		1	1	1	1	1	1	0		1	0	1	0	0	0
Rating system		0	0	0	0	1	1	0		1	1	0	1	0	0
Lego-regulatory pull strategies															
Intellectual property		1	1	1	1	0	0	0		0	1	1	0	0	0
Market exclusivity		1	1	1	1	0	0	0		0	1	1	0	0	1
Policy instrument		0	0	0	0	1	0	1		0	0	0	1	1	1
PRV		1	1	1	1	0	1	0		1	1	1	1	0	1
Trade, tariff adjustments		0	0	0	0	1	0	1		0	0	0	1	0	1
Hybrid strategies															
Collaboration network and consortiums		0	0	0	0	1	1	0		1	1	0	1	1	0
Colloquium and symposium		0	0	0	0	1	1	0		1	0	0	1	1	0
Policy and legislation		0	0	0	0	1	0	1		0	0	0	1	1	1
Drug status designation		0	0	0	0	1	1	1		0	0	0	0	0	1
Joint venture		1	1	1	1	1	1	1		1	1	1	1	1	0
Independent organization		0	0	0	0	1	1	0		1	1	1	0	1	0
Hybrid between PPP and other interventions		1	1	1	1	1	1	1		1	1	1	1	1	0
Research laboratories		1	1	1	1	0	1	0		0	1	0	1	1	0
Treaty		1	1	1	1	1	1	1		1	1	1	1	1	1
Working Group		1	1	1	1	1	1	1		0	1	0	1	1	0
Interventions to fund incentives															
Financing Intervention		1	1	1	1	0	1	1		1	1	1	0	0	0

ENABLER PROFILE	5. Role and Responsibility willing to play?	Fund R&D	Partially fund R&D	Facilitate collaboration between innovators	Collaborate with innovator	Facilitate in regulatory process	Provide market exclusivity	Adjust policies and regulations	Provide market certainty	1. Available funding?	Limited to ____________(amount)	Amount dependent on output of innovator	Do not offer any financial assistance
Push interventions													
Grant		1	1	0	0	0	0	0	0		1	0	0
Open-source initiative		0	0	1	0	0	0	0	0		0	0	1
Patent Pool		0	0	1	0	1	1	0	0		0	0	1
PPP		1	1	1	1	0	0	0	1		1	0	1
Tax credits		0	1	0	0	0	1	1	0		0	0	0
Outcome-based pull strategies													
Advanced market commitments (AMC)		0	0	0	0	0	0	0	1		0	0	1
Differential pricing		0	1	0	0	0	1	1	0		0	0	1
Patent buy-outs		0	1	0	0	0	1	0	1		1	1	1
Pooled fund		1	1	0	0	0	0	0	1		1	0	0
Prize fund		1	1	0	0	0	0	0	0		1	0	0
Rating system		0	0	0	0	0	0	0	0		0	0	1
Lego-regulatory pull strategies													
Intellectual property		0	1	0	0	0	1	0	0		0	0	1
Market exclusivity		0	1	0	0	0	1	0	0		0	0	1
Policy instrument		0	0	0	0	1	0	1	0		0	0	1
PRV		0	0	0	0	1	0	1	0		0	0	1
Trade, tariff adjustments		0	0	0	0	0	1	1	1		0	0	1
Hybrid strategies													
Collaboration network and consortiums		0	1	1	1	1	0	0	0		0	0	1
Colloquium and symposium		0	1	1	1	1	0	0	0		0	0	1
Policy and legislation		0	0	0	0	1	0	1	0		0	0	1
Drug status designation		0	0	0	0	1	1	1	1		0	0	1
Joint venture		1	1	1	1	0	0	0	1		1	1	0
Independent organization		1	1	0	0	1	0	0	1		1	0	1
Hybrid between PPP and other interventions		1	1	1	1	1	1	1	1		1	0	0
Research laboratories		0	0	1	1	1	0	0	0		0	0	1
Treaty		1	1	1	1	1	0	0	1		1	0	1
Working Group		1	1	1	1	0	0	0	1		0	0	1
Interventions to fund incentives													
Financing Intervention		1	1	0	0	1	0	0	0		1	0	0

ENABLER PROFILE	2. Funding timing?	Beginning once-off	End once-off	Incrementally based on output	Incrementally based on timing	Incrementally as innovator requires	Once output is received	3. Ability to influence policy?	Clinical trial regulation policies	Market authorization policy	Market exclusivity policies	Pricing policies	Tax credit policies	National policies and legislations	National Intellectual property policies	International Intellectual property policies	International trade law
Push interventions																	
Grant		1	0	1	1	0	0		0	0	0	0	0	0	0	0	0
Open-source initiative		0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
Patent Pool		0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
PPP		0	0	1	1	1	0		1	1	1	1	1	1	1	1	1
Tax credits		0	0	0	1	0	1		1	0	1	0	1	0	0	0	0
Outcome-based pull strategies																	
Advanced market commitments (AMC)		0	1	0	0	0	1		0	0	0	1	0	0	0	0	1
Differential pricing		0	0	0	0	0	1		0	0	1	1	0	0	0	0	1
Patent buy-outs		0	1	0	0	0	1		0	1	1	0	0	0	0	0	0
Pooled fund		1	1	1	1	1	1		0	0	0	0	0	0	0	0	0
Prize fund		0	1	1	0	0	1		0	0	0	0	0	0	0	0	0
Rating system		0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
Lego-regulatory pull strategies																	
Intellectual property		0	0	0	0	0	1		0	0	1	0	0	0	1	1	1
Market exclusivity		0	0	0	0	0	1		0	0	1	0	0	0	1	1	1
Policy instrument		0	0	0	0	0	0		1	1	1	1	1	1	1	1	1
PRV		0	0	0	0	0	0		1	1	0	0	0	1	0	0	0
Trade, tariff adjustments		0	0	0	0	0	0		0	1	1	1	0	1	1	1	1
Hybrid strategies																	
Collaboration network and consortiums		0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
Colloquium and symposium		0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
Policy and legislation		0	0	0	0	0	0		1	1	1	1	1	1	1	1	1
Drug status designation		0	0	0	0	0	0		1	1	1	1	1	1	0	0	1
Joint venture		1	1	0	1	0	1		0	0	0	0	0	0	0	0	0
Independent organization		1	1	1	1	1	1		0	0	0	0	0	0	0	0	0
Hybrid between PPP and other interventions		1	1	1	1	1	1		1	1	1	1	1	1	1	1	1
Research laboratories		0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
Treaty		0	1	0	1	0	1		1	1	1	1	1	1	1	1	1
Working Group		0	0	1	1	1	0		0	0	0	0	0	0	0	0	0
Interventions to fund incentives																	
Financing Intervention		1	1	1	1	1	1		0	0	0	0	0	0	0	0	0

Appendix J: SME pre-read document phase 2

INFORMATION DOCUMENT

DECISION-SUPPORT FRAMEWORK: SELECTING INCENTIVE INTERVENTIONS TO ENCOURAGE DRUG R&D FOR NEGLECTED DISEASES

Ms N Hanekom, Dr L Bam, Ms IH de Kock
September 2020

1. Introduction

1.1 Overview of the decision-support framework

The decision-support framework (Figure 1) aims to assist in the selection of an appropriate incentive intervention to encourage R&D for diseases that do not have adequate drugs available. The framework analyses the current pharmaceutical R&D environment, receives input from the enabling, innovating and consumer stakeholders, as well as uses what literature suggests, to provide a means of enabling or simplifying the decision-making process involved in choosing an incentive intervention for encouraging

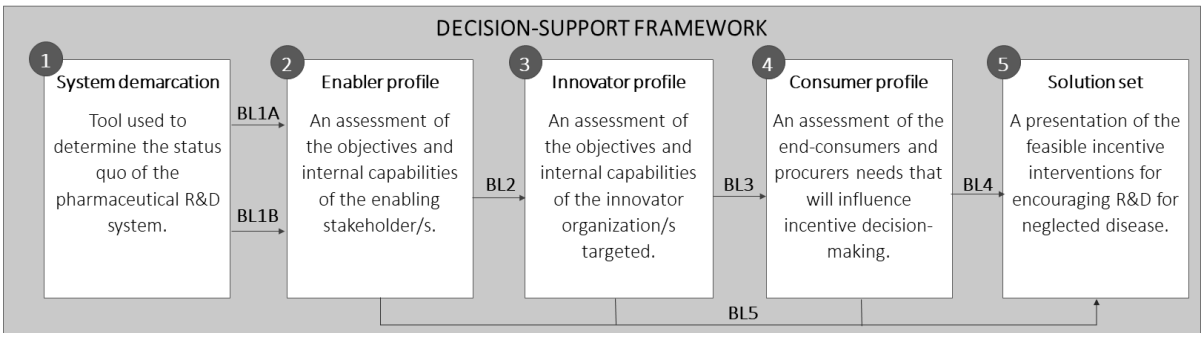


Figure 0.7 Decision-support framework overview.

R&D in drugs for neglected diseases.

The output of this framework is a proposed set of feasible incentive interventions that have been identified as being suitable to the requirements of the specific scenario. The presentation of the proposed set of feasible incentives highlights the ability of each incentive to address the multiple-decision criteria. The set of suggested interventions will each satisfy a different criteria cluster (focus area), or set of criteria clusters, consequently no one optimal solution exists. In addition, a set of non-incentive-based interventions that are likely to contribute to the scenario under consideration are also proposed.

1.2 Using this framework

The framework comprises of five domains and five background logic processes. The stakeholders and decision-makers involved are required to provide input in Domains 1 to 4. Domain 5 provides the feasible solution set, with supplementary results pages 1 to 4 providing more detailed insights. The background logic functions are included for the user to see, however, does not require any input or interaction from the stakeholders. The background logic functions are hardcoded and intended to run in the background, without the knowledge of the user (excluded from this document).

2. Overview and primary components description

Domain 1: System Demarcation

The system demarcation domain is developed to draft a holistic understanding of the pharmaceutical R&D system based on the scenario that will be investigated and consists out of 67 system elements. Each of the system elements should be ranked by the enabler stakeholder / decision-maker on a scale of [0, 1 or 2] – based on the state of the R&D system under investigation. Where 0 refer to the least ideal; and 2 refer to the ideal 'typical' state.

Domain 2: Enabler profile

The enabler is required to complete the inquiry form, that is predefined with a short list of objectives and internal capabilities. The enabler will give each of the objectives and internal capabilities a priority rating of 0 (lowest priority), 1 or 2 (highest priority). These provide an overview of the enabler profile and give an indication of what their objectives and capacity restrictions are, this set of criteria is called the enabler criteria, being the decision criteria that is relevant to this specific enabler. It is important to note the exclusion criteria of this stakeholder, which will affect the overall feasibility of the incentive interventions.

Domain 3: Innovator profile

The innovator is required to complete the inquiry form, that is predefined with a short list of objectives and internal capabilities. The innovator will give each of the objectives and internal capabilities a priority rating of 0 (lowest priority), 1 or 2 (highest priority). These provide an overview of the innovator profile and give an indication of what their objectives and capacity restrictions are, this set of criteria is called the innovator criteria, being the decision criteria that is relevant to this specific innovator.

Domain 4: Consumer profile

The consumer profile refers to the end-user or the procurer of the drug that is intended to be researched and developed. The end-consumers are for the purpose of this study divided into two groups, namely patients and procurers. The consumer profile exists of merely the most important requirements and needs that will assist the enabler stakeholder to decide on a feasible incentive intervention type. Similar to the other two stakeholder profiles, the consumer profile consists of an 'inquiry form' with consumer requirements and will be given a priority rating of 0 (lowest priority),1 or 2 (highest priority), by the enabler stakeholder, this set of criteria is called consumer criteria.

Domain 5: Solution set

The incentive-based solutions are presented by means of a heatmap indicating the 26 incentives and their corresponding cluster-scores (color scale) per criteria cluster, ranked from the incentive with the highest to the lowest number of cluster-scores that performed within the upper quartile (top 25%) range for the specific criteria cluster. In addition, a spider-diagram displays the top five incentives' cluster-scores for easy comparison, with the top five incentives being the incentives with the highest average number of criteria clusters addressed within the upper quartile. It should also be noted that the feasible incentive-based solutions exclude the incentives that did not address any of the exclusion criteria of the enabler stakeholder. The non-incentive-based solutions are included as reference for alternative interventions to consider for addressing the system elements that can't be addressed by the set of 26 incentive-based interventions.

3. Primary stakeholders involved

Enabler stakeholder: This stakeholder represents the initiator of the incentive intervention, therefore enabling the R&D of drugs for a specific neglected disease. The enabler stakeholder is required to provide input for three domains namely: (i) Domain 1 (system demarcation), (ii) Domain 2 (enabler profile); and (iii) Domain 4 (consumer profile). The enabler is the only stakeholder whose limitations will determine the feasibility of the incentive interventions, with enabler exclusion criteria not met leading to the incentive classified as infeasible, though still provided in the solution set for reference purposes.

Innovator stakeholder: This stakeholder is defined as the innovator that performs R&D to be delivered to the neglected disease market. The innovator stakeholder will be either (i) empowered, or (ii) encouraged to perform R&D by being provided or offered some kind of benefit from the enabler stakeholder. The innovator is required to complete Domain 3 (innovator profile), by providing a priority rating for the innovator decision criteria.

Consumer stakeholder: This stakeholder refers to the end-user or the procurer of the drug that is intended to be researched and developed. Only the most evident requirements / needs of the consumer stakeholder influencing the decision of an appropriate incentive intervention, are included in this profile. In contrast to the other two stakeholders, this profile is completed by the enabler stakeholder, and not the consumers themselves.

4. Framework components

The following five framework domains are depicted in the section that follows:

(i) Domain 1: System demarcation
(ii) Domain 2: Enabler profile
(iii) Domain 3: Innovator profile
(iv) Domain 4: Consumer profile
(v) Domain 5: Solution set

5. Conclusion

This document highlights the primary aim, intent and design of the decision-support framework, developed as a research output as part of the PhD research study, titled: "Selecting incentive interventions to encourage drug R&D of neglected diseases". An overview of the decision-support framework components can also be seen with all background logic functions not explained in the context of this document.

Domain 1: System demarcation

DOMAIN 1: SYSTEM DEMARCATION					System evaluation	
System elements	2	1	0	Aspect to address	Measure [0/1/2]	Sourced from section
Disease setting and affected population						
1 Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)		Section 2.2
2 Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact		Section 3.1.5, Section 4.4.1
3 Burden fully characterized	< 40% of population within 5km of health facility	40% - 60% of population within 5km of health facility	> 60% of population within 5km of health facility	Non-incentive-based solutions (I)		Section 4.4.1, Table 4.11
4 Physicians per 1000 population	< 1 per 1 000	1 - 2 physicians per 1 000 population	> 2 physicians per 1 000 population	Non-incentive-based solutions (I)		SME 4
Existing drug characteristics						
5 The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact		Section 4.3.1
6 Quality and efficacy of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)		Section 2.4.3
7 Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact		Section 1.4.1
8 Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)		Section 2.4.1, Figure 2.3
9 Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access		Section 2.4.1, Figure 2.3
10 Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)		Section 2.4.1, Figure 2.3
11 Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)		Section 2.4.1, Figure 2.3
12 Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)		Section 2.4.1, Figure 2.3
13 Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access		Section 4.4.1, Table 4.11
Service delivery						
14 Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)		Section 2.1.3
15 Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)		Section 2.1.3
16 Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)		Section 2.1.3
17 Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)		Section 2.1.3
Consumers, competitors, and suppliers						
18 Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)		Section 4.5.3
19 The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)		Section 4.5.3, Table 4.12
20 Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)		Section 4.4.3
21 Existence of competitors	No competitors	Some competitors	Significant competition	Non-incentive-based solutions (V)		Section 4.4.3
22 Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility		Section 4.4.3
23 Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation		Section 4.4.3
24 Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation		Section 4.4.3
Governance and leadership						
25 Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)		Section 4.4.1, Table 4.11
26 Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership		Section 4.4.1, Table 4.11
27 Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership		Section 4.4.1, Table 4.11
28 Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership		Section 4.4.1, Table 4.11
29 Effective national budget allocation (Country ownership)	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)		Section 2.1.2
30 Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)		Section 2.1.2
31 Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership		Section 2.1.3
32 Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)		Section 2.2.5
33 Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)		Section 2.1.3
Profitability and market forces						
34 Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces		Sections & 4.4.1 & 4.5.3
35 Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)		Section 4.4.1, Table 4.11
36 Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)		Section 2.1.2
37 Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)		Section 4.4.3
38 Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces		Section 4.5.3, Table 4.12
39 Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership		Section 4.4.1, Table 4.11
Research and development process						
40 Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials		Section 3.1.2
41 Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)		Section 3.1.2
42 Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)		Section 3.1.2
43 Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)		Section 3.1.2
44 Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)		Section 3.1.2
45 Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials		Section 3.1.2
46 Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials		Section 3.1.2
47 Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials		Section 3.1.2
48 Quality assurance of clinical trials (WHOPQ)	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable (National)	Good clinical trial quality (WHOPQ)	9. R&D and clinical trials		Section 3.1.2
49 Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials		Section 4.4.1, Table 4.11
50 The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)		Section 3.1.2
51 Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)		Section 3.1.2
52 Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)		Section 3.1.2
53 Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)		Section 3.1.2
54 Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)		Section 3.1.2
55 Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)		Section 3.1.2
56 Diversity in clinical trial	No diversity in clinical trials	Some diversity in clinical trials	Clinical trials incorporate diversity adequately	Non-incentive-based solutions (VIII)		Section 3.1.2
57 Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)		Section 3.1.2
58 Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)		Section 3.1.2
59 Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)		Section 4.4.3
60 R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials		Section 2.1.3
61 Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials		Section 2.1.2 & 2.1.3
Manufacturing systems						
62 Existence of qualified manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)		Section 2.1.2
63 Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)		Section 2.1.2
64 Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)		Section 4.4.3
Sustainability						
65 Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs		Section 4.4.3
Health information systems						
66 Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)		Section 2.1.3
67 Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)		Section 2.1.3

Domain 2: Enabler profile

DOMAIN 2: ENABLER INQUIRY FORM	
OBJECTIVES	INTERNAL CAPABILITIES
1 **Goal of the incentive strategy? (Inclusion)** Improve the state of the R&D pipeline Enable organizations to innovate easier Gain market exclusivity over an innovation Advance the R&D field Deliver affordable and accessible treatment Convey an important message Fulfil corporate social responsibility Increase bandwidth and network De-risk R&D process Political obligations 2 **Which innovators are targeted? (Inclusion)** Large pharmaceutical organizations (private) SMEs (private) Governmental institutions Independent scientists Academic institutions NGO organizations Everyone 3 **Intention for the consumers? (Exclusion)** Provide drug Multi-purpose drug Play a role in improved access Implement mass drug administrations Deliver regime treatment 4 **Desired relationship with innovators? (Inclusion)** Once-off occasion Limited to a number of years Milestone related Engage at given time instances Collaborate and build a partnership 5 **Role and Responsibility willing to play? (Exclusion)** Fund R&D Partially fund R&D Facilitate collaboration between innovators Collaborate with innovator Facilitate in regulatory process Provide market exclusivity Adjust policies and regulations Provide market certainty	1 **Available funding. (Exclusion)** Limited to an amount Full capacity No capacity 2 **Payoff to innovators. (Inclusion)** Beginning once-off End once-off Incrementally, based on output Incrementally, based on timing Incrementally, as innovator requires 3 **Ability to influence policy. (Inclusion)** Clinical trial regulation policies Market authorization policies Market exclusivity policies Pricing policies Tax credit policies National policies and legislations National/international intellectual property policies International trade law 4 **Access and expertise. (Inclusion)** Access to key data Access to compounds Access to intellectual property Technology expertise and access R&D expertise

Domain 3: Innovator profile

DOMAIN 3: INNOVATOR INQUIRY FORM	
OBJECTIVES	INTERNAL CAPABILITIES
1 Reason for performing R&D for the disease?	**1 Nature of innovator stakeholder?**
Profit maximization	Small to medium organization (includes start-up)
Corporate social responsibility	Large pharmaceutical organization
Not for profit	Not-for-profit organization
Profit improvement	Governmental institution
Political obligations	Academic institution
2 Focus area of R&D and intention for patients?	Independent scientist (no organization linked)
R&D of drug	**2 Capacity to provide own funding?**
R&D of multi-purpose drug	No capacity
Play a role in improved access	Limited to an amount
Drug repurposing	Full capacity
Deliver regime treatment	**3 R&D limitations?**
3 Require from the enabler?	Do not have research laboratory
Fund all R&D costs	Do not have adequate equipment
Partially fund R&D	Lack of information (knowledge) on disease
Collaboration with enabler	Cumbersome nature of clinical trial regulations
Adjust policies and regulations	Shortage of finances
Facilitate regulatory process	Policies or regulatory limitations
Provide market exclusivity	No market certainty
Provide market certainty	**4 Authorization standards adhered to?**
Provide a collaboration platform	None
Provide risk insurance or security	Accredited authorisation organization
Improve export potential	
4 Preference or required funding timing?	
Beginning once-off	
End once-off	
Incrementally based on output	
Incrementally based on timing	
Incrementally as required	
Once output provided	
Do not require any funding	

Domain 4: Consumer profile

DOMAIN 4: CONSUMER INQUIRY FORM	
END CONSUMER (patient)	
1	**Socio-economic inequalities**
	Require differential pricing
	Must eliminate all financial risk
2	**Contextual treatment criteria**
	Accommodate contextual treatment criteria
PROCUREMENT: PUBLIC /PRIVATE (for-/ not forprofit)	
3	**Affordability**
	Require differential pricing
4	**End-price profit margins**
	Any profit margins allowed
	Restricted profit margins
	No profit
5	**Availability and accessibility**
	IP regulation allows procurement of drugs to target area
	Existing drugs not allowed in target area
	Drug status designation required

Domain 5: Solution set

The solution set consists of both incentive-based interventions, and non-incentive-based interventions. The incentive-based interventions solution layout is, as mentioned, depicted by means of a heatmap, and with the top five incentives and cluster-scores depicted by means of a spider diagram. Figure 2 depicts the layout of the proposed set of feasible incentive interventions.

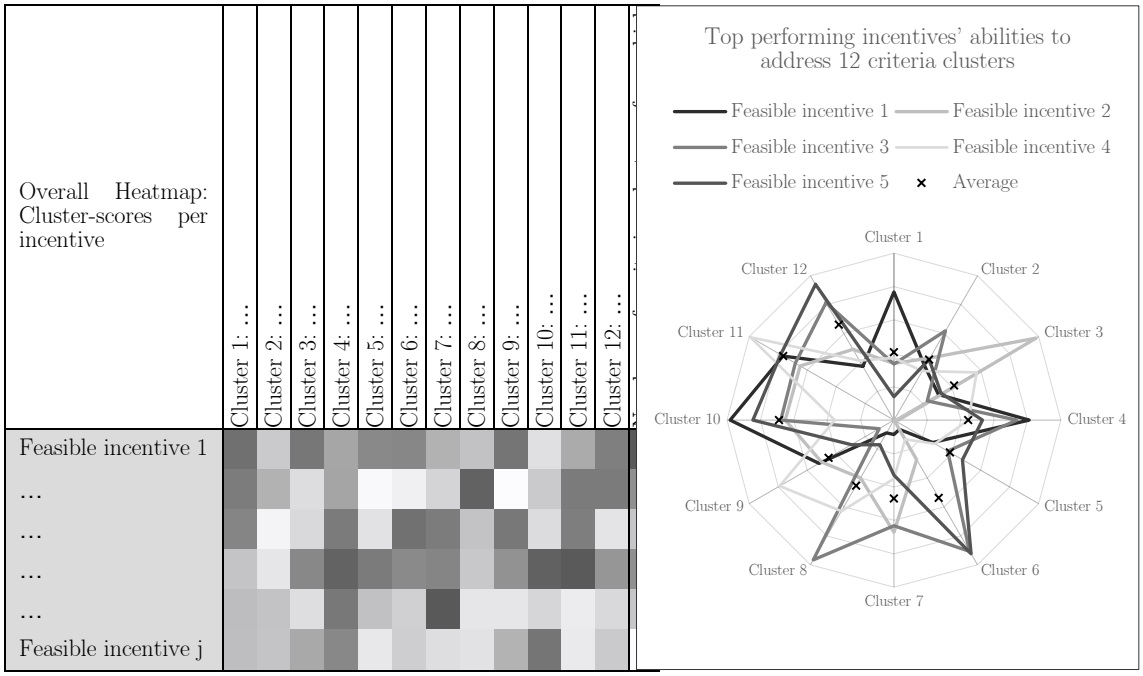


Figure 0.8: Incentive based solutions, Domain 5, overview.

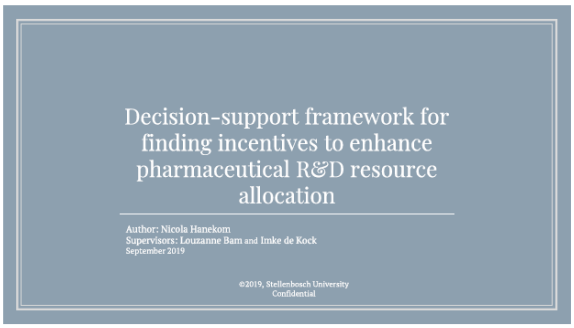
The non-incentive-based interventions are depicted in Table 1. Table 1 is merely a preview of the complete list of the non-incentive-based intervention solutions. The non-incentive-based interventions are not ranked, but indicates the priory assigned in Domain 1, therefore 2 (highest), 1, or (0) lowest priority.

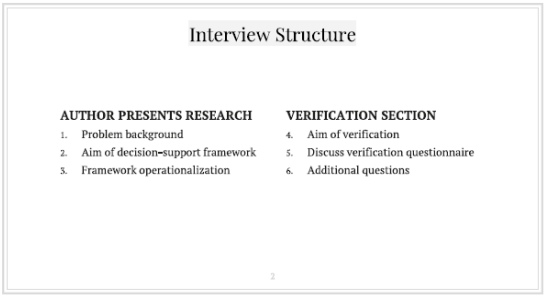
Table 0.2: Non-incentive-based solutions (1 of 43).

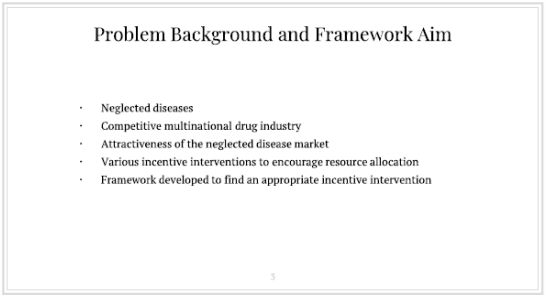
DOMAIN 4: NON-INCENTIVE-BASED SOLUTIONS			
1. Country economic status		For further reference	Priority rating
Meaning	Countries are categorized based on a national income per capita.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)	
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention	The classification measures are described in Table 2.3		
considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

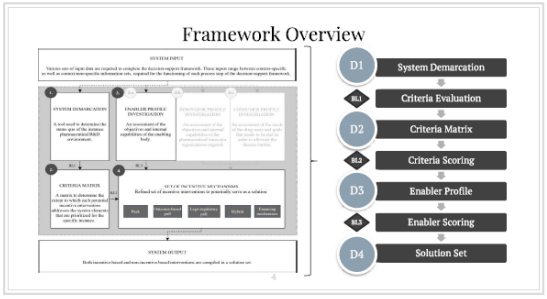
Appendix K: SME presentation phase 1

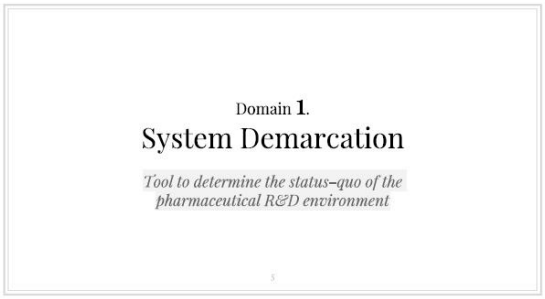
As described in Section 7.1.3.3, the interview protocol included an overview presentation of the developed decision-support framework. The presentation, created in MS PowerPoint, was displayed to the SME while discussing each of the decision-support domains, and functions.

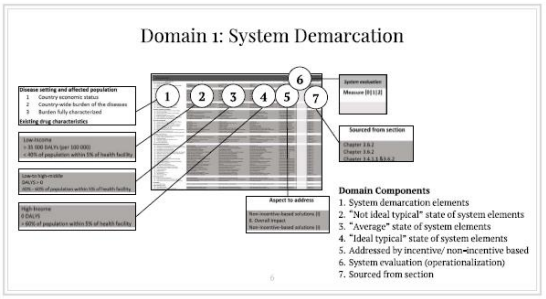


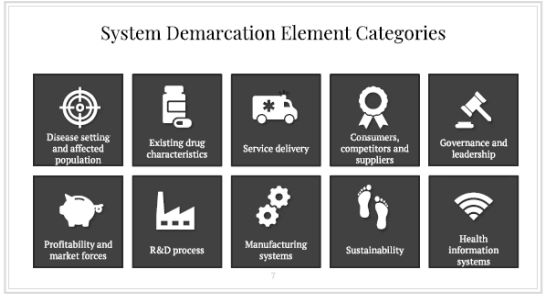


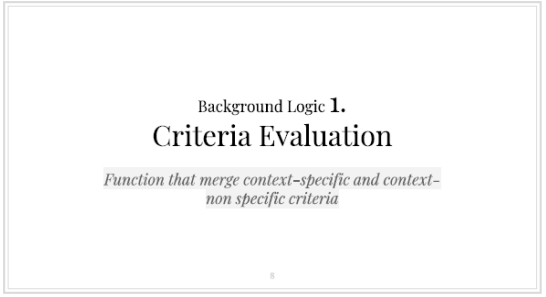




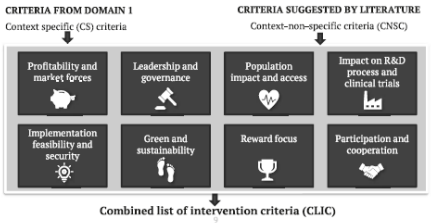








Background Logic 1: Criteria Evaluation

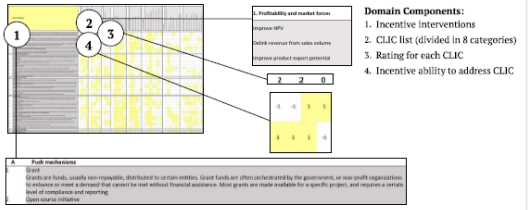


Domain 2.

Criteria Matrix

Matrix to determine the extent to which each potential incentive intervention addresses the prioritized system elements

Domain 2: Criteria Matrix



Background Logic 2.

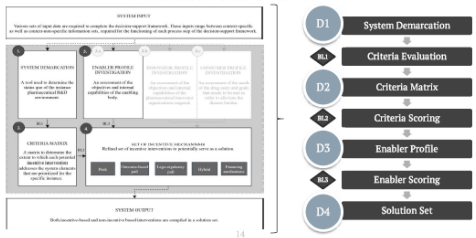
Criteria Scoring

Function that calculates a score metric for each incentive intervention measuring the extent to which it can adhere the CLIC list.

Background Logic 2: Criteria scoring

All incentive interventions	CSNS- SCORE
Grant	37/60 = 0.62
Open source initiative	48/60 = 0.80
Patent pool	26/60 = 0.43
PPP	52/60 = 0.87

Framework Overview

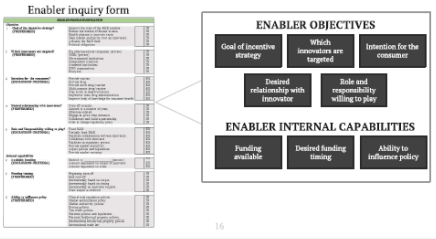


Domain 3.

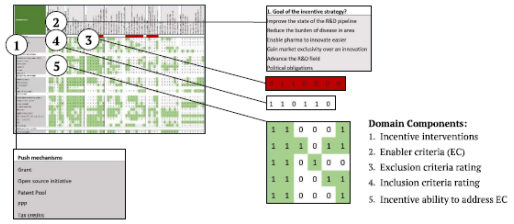
Enabler Profile

Tool to determine the objectives and capabilities of the enabler stakeholder

Domain 3: Enabler Profile



Domain 3: Enabler Profile



Domain Components:

1. Incentive interventions
2. Enabler criteria (EC)
3. Exclusion criteria rating
4. Inclusion criteria rating
5. Incentive ability to address EC

17

Background Logic 3.

Enabler Scoring

Function that calculates to what extent each incentive intervention satisfies the enabler profile criteria

18

Background Logic 3: Enabler scoring

All incentive interventions	**EP- SCORE**
Grant	22/45 = 0.48
Open source initiative	10/45 = 0.22
Patent pool	31/45 = 0.68
PPP	36/45 = 0.80

19

Domain 4.

Solution Set

A refined set of incentive and non-incentive-based interventions are suggested as possible solutions

20

Domain 4: Solution set

Incentive interventions	**OF- SCORE (CSNS x EP SCORE)**
Grant	0.62 x 0.48 = 0.298
Open source initiative	0.80 x 0.22 = 0.176
Patent pool	0.43 x 0.68 = 0.292
PPP	0.87 x 0.80 = 0.696

21

Domain 4: Solution Set

Incentive-based interventions
(ranked most to least feasible)

(1) Push interventions
(2) Lego-regulatory pull interventions
(3) Outcome-based pull interventions
(4) Hybrid interventions
(5) Financing interventions

Feasibility score is a combined measure of the CNSC and Enabler Profile scores, per intervention

Non-incentive-based interventions

List of 40 interventions that cannot be addressed by incentive interventions

22

Verification

The process of establishing the accuracy of the proposed solution

23

Part 1: System Demarcation

Question 1.1 : To what extent is the system demarcation effective to determine the status quo of a R&D environment?

Refer to page 19 (Appendix B.1) of pre-read document (pdf page 22)

24

Part 3: Enabler profile and framework focus area

Question 3.2: Do you think all the focus areas that play a role on decision-making of an appropriate incentive intervention are included in the framework? If not, could you provide any guidance on additional focus areas that should be considered for inclusion?

Refer to page 13 (Appendix A.7) of pre-read document (pdf page 16)

33

Part 4: Overall framework verification

Question 4.1: To what extent do you agree that the framework is a logical and holistic approach to find an applicable set of incentive interventions for encouraging R&D?

1 Strongly disagree | 2 Disagree | 3 Neutral | 4 Agree | 5 Strongly agree

34

Part 4: Overall framework verification

Question 4.2: Does this framework exclude any major components that you believe should be included?

35

Part 5: Framework reflection

Question 5.1: What do you view as the key strengths of the decision-support framework?

36

Part 1: System Demarcation

Question 1.2: Does the system demarcation contain all the applicable context-specific element categories and system elements (frequently experienced challenges) to assist in understanding the need that the pharmaceutical R&D environment might have for an incentive intervention? If not, could you provide any guidance on additional elements that should be considered for inclusion?

Refer to page 19 (Appendix B.1) of pre-read document (pdf page 22)
Column 1 contains all the system elements

25

Part 1: System Demarcation

Question 1.3: To what extent do you agree that incentive-based interventions cannot address all the pharmaceutical R&D system demarcation elements?

Refer to page 19 (Appendix B.1) of pre-read document (pdf page 22)
The aspect to address column indicates whether system elements can be addressed by an incentive intervention or not

1 Strongly disagree | 2 Disagree | 3 Neutral | 4 Agree | 5 Strongly agree

26

Part 2: Incentive-based interventions and incentive-based-intervention criteria

Question 2.1 : Can you think of any incentive-based intervention category not included in the list of 27 incentive intervention categories?

Refer to page 20 (Appendix B.2) of pre-read document (pdf page 23)

27

Part 2: Incentive-based interventions and incentive-based-intervention criteria

Question 2.2: Are the definitions of the incentive interventions adequate in providing a brief introduction to the meaning of the interventions?

Refer to page 20 (Appendix B.2) of pre-read document (pdf page 23)

1 Strongly disagree | 2 Disagree | 3 Neutral | 4 Agree | 5 Strongly agree

28

Part 2: Incentive-based interventions and incentive-based-intervention criteria

Question 2.3: Do you think the CLIC is sufficient in depicting the most critical requirements that an incentive-based intervention must adhere to (criteria matrix columns)? If these are not sufficient, could you provide any guidance on additional elements that should be considered for inclusion?

Refer to the next slide (slide 27) OR

Refer to page 20 (Appendix B.2) of pre-read document (pdf page 23)

1	2	3	4	5
Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Complete list of intervention criteria (CLIC)

1. Profitability and market forces
1. Improve NPV
2. Delink revenue from sales volume
3. Improve product export potential

2. Implementation feasibility and security
4. Minimizes barriers to implementation
5. Minimize disruptive effects to population
6. Affordable to implement the incentive
7. Provide R&D project insurance

3. Green and sustainability
8. Ensure conservation of resources in R&D process
9. Encourage efficient innovation
10. Green R&D of drugs

4. Population impact and Access
11. Potential to reduce burden of disease
12. Encourage R&D of a drug or intervention
13. Encourage novel drug R&D
14. Improve consumer access
15. Enable mass drug administration

5. Participation and cooperation
16. Enables participation of SMEs
17. Encourage large firm participation
18. Facilitates cooperation and synergy
19. Platform for coordinating innovators
20. Allow for great competition among parallel experiments

6. Governance and leadership
21. Promote equitable health-focused governance
22. Promote transparency and accountability
23. Advances the priority of disease on health agenda
24. Advance proper functioning of domestic policy structures
25. Regulatory oversight to promote R&D for the disease
26. Regulatory exclusivity provisions for R&D of the disease
27. Resources to deliver health service are financed by government

7. Rewards focus
28. Payoff to innovators based on drug cost-effectiveness
29. Reward innovation
30. Financing timed across drug lifecycle
31. Provide long term R&D financing
32. Provide sustainable financing
33. Provide public subsidies for clinical trials

8. Impact on R&D process and clinical trials
34. Reduce clinical trial risk involved
35. Assist in registration and monitor of trials
36. Globalize clinical trial methods
37. Reduce clinical trials activation difficulty
38. Enhance or prompt the quality of clinical trials
39. Assist in expensive clinical trial regulation
40. Improve R&D productivity
41. Enlarge the number of clinical trials registered

30

Part 2: Incentive-based interventions and incentive-based-intervention criteria

Question 2.4: Do all the CLIC and CLIC categories included, affect the consideration of incentive interventions?

Refer to the previous slide (slide 27) OR

Refer to page 20 (Appendix B.2) of pre-read document (pdf page 23)

31

Part 3: Enabler profile and framework focus area

Question 3.1: Can you think of any objective or internal capability, in the enabler inquiry form, that is absent and might play a crucial role in the solution decision?

Refer to page 11 (Appendix A.5) of pre-read document (pdf page 14)

32

Part 5: Framework reflection

Question 5.2: What do you view as the key weaknesses of the decision-support framework?

37

Part 5: Framework reflection

Question 5.3: Based on your experience, and what you perceive from the framework, if the framework were to fail, what do you think would be the most likely cause of this failure?

38

Part 5: Framework reflection

Question 5.4: Are you aware of any other approach that will lead to a similar or superior solution to the one delivered by the decision-support framework that has been presented in this document?

39

Part 5: Framework reflection

Question 5.5: Do you have any additional comments or critique?

40

Appendix L: SME presentation phase 2

Selecting incentive interventions to encourage pharmaceutical research and development for neglected diseases: A decision-support framework

Nicola Hanekom
Supervisors: Dr Louzanne Bam and Ms Imke de Kock
July 2020

UNIVERSITEIT IYUNIVESITHI STELLENBOSCH UNIVERSITY

Problem background

AUTHOR PRESENTS RESEARCH

1. Problem background
2. Aim of decision-support framework
3. Framework operationalization

VERIFICATION & VALIDATION

4. Aim of verification & validation
5. Discuss questionnaire
6. Additional questions

2

Problem background

Consumer

Neglected diseases
- Inadequate treatment options
- Developing countries
- Low purchasing power

Attractive diseases
- High purchasing power
- Stronger political voice

Innovator

Pharmaceutical research and development (R&D)
- Highly competitive multi-national industry
- Research agendas based on market attractiveness

Enabler

Incentivizing R&D for neglected diseases
- Various incentive interventions

3

Existing incentive interventions

- Incentive interventions promote a desired activity
- Incentive strategies
  - Push strategy
  - Pull (outcome-based pull and lego-regulatory pull)
  - Hybrid strategy
- Systematic literature review: Existing incentives
  - 96 Incentive intervention instances
  - 26 Incentive types *
- Literature-based criteria that incentives should adhere to *
  (Context-non-specific criteria)

4

Fundamental framework concepts

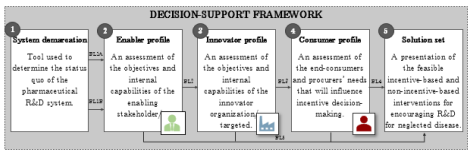
- Multi-objective decision
  - Overall feasibility score vs cluster score
  - Qualitative score not presented
- Enabler exclusion criteria

5

Develop a decision-support framework to assist in establishing an incentive intervention that will increase the interest of pharmaceutical R&D organizations to develop drugs for a specific disease or set of neglected diseases

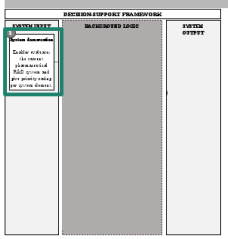
6

Framework overview

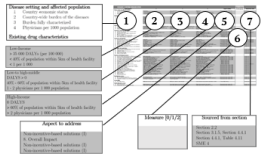


7

Domain 1: System demarcation



Tool to determine the status-quo of the pharmaceutical R&D environment



8

Background logic 1A: Criteria evaluation

Function that merge context-specific and context-non specific criteria

Domain 1 (context-specific)

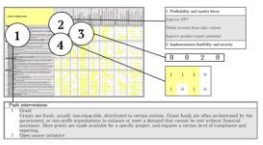
Literature* (context-non-specific)

Decision criteria (CLIC)

9

Background Logic 1B: Criteria matrix

Matrix to determine the extent to which each incentive type addresses the decision criteria (CLIC)*



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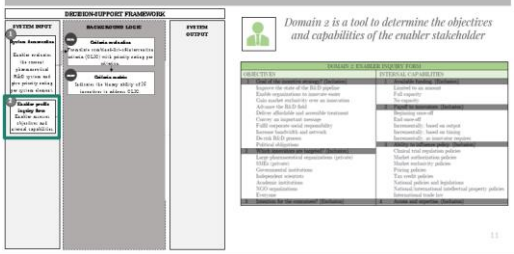
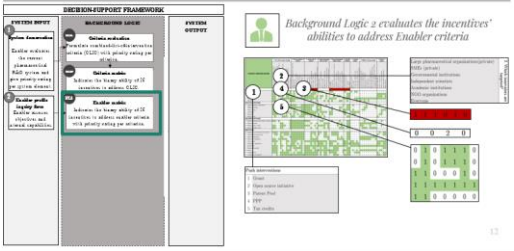
Domain 2: Enabler profile



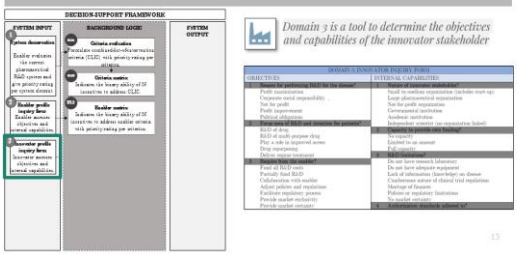
Domain 2 is a tool to determine the objectives and capabilities of the enabler stakeholder

4. | Background Logic 2: Enabler matrix



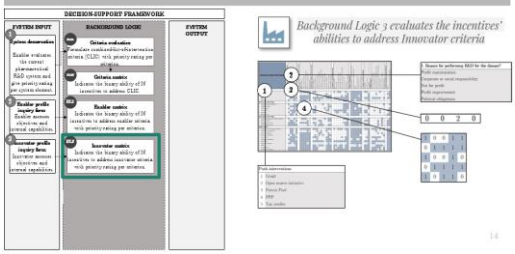
Background Logic 2 evaluates the incentives' abilities to address Enabler criteria

Domain 3: Innovator profile



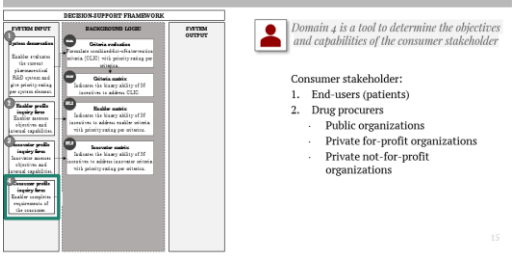
Domain 3 is a tool to determine the objectives and capabilities of the innovator stakeholder

Background Logic 3: Innovator matrix



Background Logic 3 evaluates the incentives' abilities to address Innovator criteria

Domain 4: Consumer profile

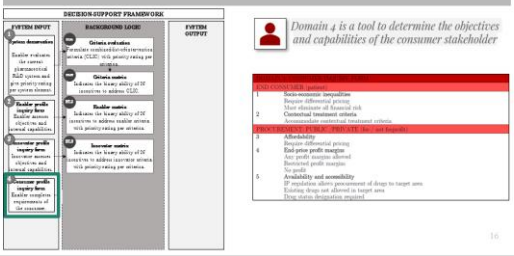


Domain 4 is a tool to determine the objectives and capabilities of the consumer stakeholder

Consumer stakeholder:

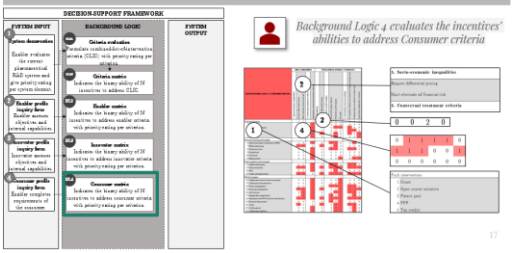
1. End-users (patients)
2. Drug procurers
   - Public organizations
   - Private for-profit organizations
   - Private not-for-profit organizations

Domain 4: Consumer profile



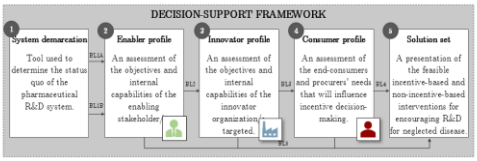
Domain 4 is a tool to determine the objectives and capabilities of the consumer stakeholder

Background Logic 4: Consumer matrix



Background Logic 4 evaluates the incentives' abilities to address Consumer criteria

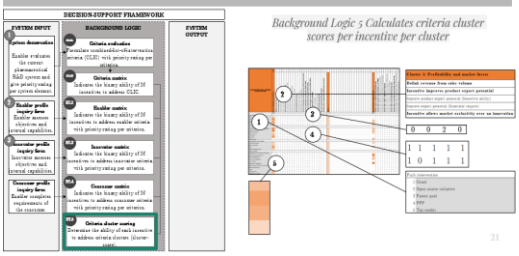
Framework overview



Background Logic 5: Criteria cluster scoring

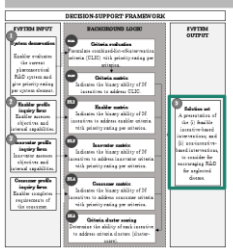
1. Profitability and market forces	2. Facilitate registration of drug / approval for use	3. Ability to influence nature of drug that is developed	4. Improved governance	5. Population impact and access	6. Limited enabler resource investment
7. Encourage competition in the innovation process	8. Overcome barriers to innovator participation in R&D process	9. Facilitate clinical trials	10. Facilitate / improve R&D process and R&D body of knowledge	11. Facilitate collaboration during R&D	12. Altruistic / political motivations

Background Logic 5: Criteria cluster scoring



Background Logic 5 Calculates criteria cluster scores per incentive per cluster

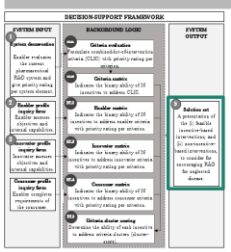
Domain 5: Solution set



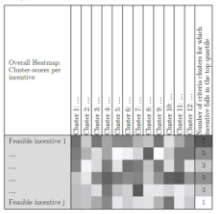
Solution set domain

1. Feasible incentive-based interventions
2. Set of 43 non-incentive-based interventions with priority rating

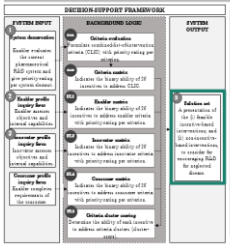
Domain 5: Solution set

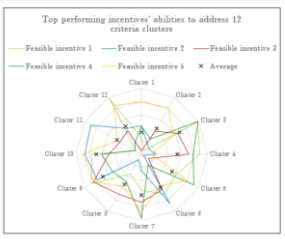


(i) Feasible incentive-based interventions

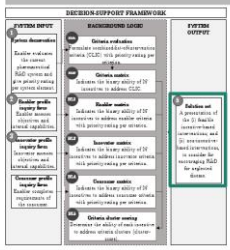


Domain 5: Solution set





Domain 5: Solution set



(ii) Set of 43 non-incentive-based interventions with priority rating

Major changes from previous version

1. Innovator and consumer stakeholders
2. Vaccine R&D incentives are omitted
3. Presentation of the feasible incentives (clusters and scoring)

SME Interviews: Verification and validation

Verification (10 questions):

- Process of establishing the accuracy of the proposed solution

Validation (6 questions):

- Establish value and novelty

Question 1:

To what extent do you agree that the system demarcation is effective to determine the status quo of the R&D environment?

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1	2	3	4	5
Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Question 2:

Does the system demarcation contain all the applicable context-specific element categories and system elements (frequently experienced challenges) to assist in understanding the need that the pharmaceutical R&D environment might have for an incentive intervention? If not, could you provide any guidance on additional elements that should be considered for inclusion?

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Question 3:

To what extent do you agree that incentive-based interventions cannot address all the pharmaceutical R&D system demarcation elements?

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1	2	3	4	5
Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Question 4:

Can you think of any incentive intervention types not included in the list of 26 incentive types?

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Question 5:

Do you think the CLIC is sufficient in depicting the most critical requirements that an incentive-based intervention must adhere to (criteria matrix columns)? If these are not sufficient, could you provide any guidance on additional elements that should be considered for inclusion, or should be excluded?

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32

Combined list of intervention criteria (CLIC)

1. Profitability and market forces
1. Improve NPV
2. Delink revenue from sales volume
3. Improve product export potential

2. Implementation feasibility and security
4. Minimizes barriers to implementation
5. Minimize disruptive effects to population
6. Affordable to implement the incentive
7. Provide R&D project insurance

3. Green and sustainability
8. Ensure conservation of resources in R&D process
9. Encourage efficient innovation
10. Green R&D of drugs

4. Population Impact and Access
11. Potential to reduce burden of disease
12. Encourage R&D of a drug or intervention
13. Improve consumer access
14. Enable mass drug administration

5. Participation and cooperation
15. Enables participation of SMEs
16. Encourage large firm participation
17. Facilitates cooperation and synergy
18. Platform for coordinating innovators
19. Allow for competition among parallel experiments

6. Governance and leadership
20. Promote equitable health-focused governance
21. Promote transparency and accountability
22. Advances the priority of disease on health agenda
23. Advance proper functioning of domestic policy structures
24. Regulatory oversight to promote R&D for the disease
25. Regulatory exclusivity provisions for R&D of the disease
26. Resources to deliver health service are financed by government

7. Rewards focus
27. Payoff to innovators based on drug cost-effectiveness
28. Reward innovation
29. Financing timed across drug lifecycle
30. Provide long term R&D financing
31. Provide sustainable financing
32. Provide public subsidies for clinical trials

8. Impact on R&D process and clinical trials
33. Reduce clinical trial risk involved
34. Assist in registration and monitor of trials
35. Globalize clinical trial methods
36. Reduce clinical trials activation difficulty
37. Enhance or prompt the quality of clinical trials
38. Assist in expensive clinical trial regulation
39. Improve R&D productivity
40. Enlarge the number of clinical trials registered

33

Question 6:

Can you think of any objective or internal capability, in the enabler inquiry form, that is absent and might play a crucial role in the solution decision?

Page 28 of 37 (Appendix B.3)

34

Question 7:

Can you think of any objective or internal capability, in the innovator inquiry form, that is absent and might play a crucial role in the solution decision?

Page 30 of 37 (Appendix B.5)

35

Question 8:

Do you think the consumer requirements and objectives is sufficient to depict the most salient requirements of the consumers that should be considered when selecting an incentive intervention?

Page 32 of 37 (Appendix B.7)

36

Question 9:

Do you think the criteria clusters of the solution set are effective and comprehensive in depicting the different incentives' abilities?

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37

Question 10:

To what extent do you agree that the decision-support framework output is presented in a manner that provides insight into the relative strengths of incentives per criteria clusters? Thus, providing the decision-maker with and objective overview of the multi-criteria decision.

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1	2	3	4	5
Strongly disagree	Disagree	Neutral	Agree	Strongly agree

38

Question 11:

To what extent do you agree that the framework is a logical and holistic approach to identify an applicable set of incentive interventions for encouraging R&D?

39

Question 12:

Does this framework exclude any major components that you believe should be included?

40

Question 13:

What do you view as the key strengths of the decision-support framework?

41

Question 14:

What do you view as the key weaknesses of the decision-support framework?

42

Question 15:

Based on your experience, and what you perceive from the framework, if the framework were to fail, what do you think would be the most likely cause of this failure?

43

Question 16:

Are you aware of any other approach that will lead to a similar or superior solution to the one delivered by the decision-support framework that has been presented in this document?

44

Question 17:

Do you have any additional questions, comments or critique?

45

Appendix M: Prize fund case study results

This appendix includes:

(i) Domain 1: Prize fund results (SME 10)
(ii) Background logic 1AB: Prize fund results (SME 10)
(iii) Domain 2: Prize fund results (SME 10)
(iv) Background logic 2: Prize fund results (SME 10)
(v) Domain 3: Prize fund results (SME 10)
(vi) Background logic 3: Prize fund results (SME 10)
(vii) Domain 4: Prize fund results (SME 10)
(viii) Domain 5: Prize fund results (SME 10)
(ix) Domain 1: Prize fund results (SME 11)
(x) Background logic 1AB: Prize fund results (SME 11)
(xi) Domain 2: Prize fund results (SME 11)
(xii) Background logic 2: Prize fund results (SME 11)
(xiii) Domain 3: Prize fund results (SME 11)
(xiv) Background logic 3: Prize fund results (SME 11)
(xv) Domain 5: Prize fund results (SME 11)
(xvi) Background logic 4: Prize fund results (Combined)
(xvii) Background logic 5: Prize fund results (Combined)
(xviii) Domain 5: Prize fund results (Combined)
(xix) Supplementary page 1: Prize fund results (Combined)
(xx) Supplementary page 2: Prize fund results (Combined)
(xxi) Supplementary page 3: Prize fund results (Combined)
(xxii) Supplementary page 4: Prize fund results (Combined)

Domain 1 system demarcation: Prize fund results SME 10

DOMAIN 1: SYSTEM DEMARCATION						*System evaluation*	
	System elements	**2**	**1**	**0**	**Aspect to address**	**Measure [0|1|2]**	**Sourced from section**
Disease setting and affected population							
1	Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)	1	Chapter 3.6.2
2	Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact	2	Chapter 3.6.2
3	Burden fully characterized	< 40% of population within 5% of health facility	40% - 60% of population within 5% of health facility	> 60% of population within 5% of health facility	Non-incentive-based solutions (I)	1	Chapter 3.4.1.1 &3.6.2
4	Physicians per 1000 population	¡ 1 per 1 000	1 - 2 physicians per 1 000 population	¿ 2 physicians per 1 000 population	Non-incentive-based solutions (I)	1	SME 4
Existing drug characteristics							
5	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact	1	Chapter 3.6
6	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)	1	Chapter 3.6
7	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact	1	Chapter 2.1.2
8	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)	1	Chapter 2.2.5
9	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access	1	Chapter 2.2.5
10	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)	2	Chapter 2.2.5
11	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)	1	Chapter 2.2.5
12	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (Respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)	1	Chapter 2.2.5
13	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access	1	Chapter 3.6.2
Service delivery							
14	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)	1	Chapter 2.2.3
15	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)	1	Chapter 2.2.3
16	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)	1	Chapter 2.2.3
17	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)	2	Chapter 2.2.3
Consumers, Competitors, and suppliers							
18	Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)	0	Chapter 3.4.3 & 3.7.3
19	The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)	1	Chapter 3.7.3
20	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)	1	Chapter 3.4.3
21	Existence of competitors	No competitors	Some competitors	A lot of competition	Non-incentive-based solutions (V)	1	Chapter 3.4.3
22	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility	2	Chapter 3.4.3
23	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation	2	Chapter 3.4.3
24	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation	2	Chapter 3.4.3
Governance and leadership							
25	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)	1	Chapter 3.6.2
26	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership	1	Chapter 3.6.2
27	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership	2	Chapter 3.6.2
28	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership	2	Chapter 3.6.2
29	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
30	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
31	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership	0	Chapter 2.2.3
32	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)	2	Chapter 2.2.5
33	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)	1	Chapter 2.2.3
Profitability and market forces							
34	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces	1	Chapter 2.1 & 3.6.2
35	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)	2	Chapter 3.6.2
36	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)	1	Chapter 2.1.2
37	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)	1	Chapter 3.4.3
38	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces	1	Chapter 3.4.3 & 3.6.2
39	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership	1	Chapter 3.6.2
Research and development process							
40	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials	2	Chapter 2.1.2
41	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
42	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
43	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
44	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
45	Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials	1	Chapter 2.1.2
46	Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials	0	Chapter 2.1.2
47	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials	1	Chapter 2.1.2
48	Quality of clinical trials	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable	Good clinical trial quality	9. R&D and clinical trials	2	Chapter 2.1.2
49	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials	1	Chapter 3.6.2
50	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
51	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
52	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
53	Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
54	Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
55	Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
56	Racial differences in participation in clinical trial	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
57	Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
58	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
59	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)	1	Chapter 3.4.3
60	R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials	0	Chapter 2.1.3
61	Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials	0	Chapter 2.1.2 & 2.1.3
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)	1	Chapter 2.1.2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)	0	Chapter 2.1.2
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)	1	Chapter 3.4.3
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs	2	Chapter 3.4.3
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)	0	Chapter 2.2.3
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)	1	Chapter 2.2.3

Background Logic 1AB: Prize fund results SME 10

	BACKGROUND LOGIC 1A&B: CRITERIA MATRIX	1. Profitability and market forces	Improve NPV	Delink revenue from sales volume	Improve product export potential	2. Implementation feasibility and security	Minimizes barriers to implementation	Minimize disruptive effects to population	Affordable to implement the incentive	Provide R&D project insurance	3. Green and sustainability	Ensure conservation of resources in R&D process	Encourage efficient innovation	Green R&D of drugs	4. Population impact and access	Potential to reduce burden of disease	Encourage R&D of a drug/novel drug	Improve consumer access	Enable mass drug administration	5. Participation and cooperation	Enables participation of small and medium organization	Encourage large firm participation	Facilitates cooperation and synergy	Platform for coordinating innovators	Allow competition among parallel experiments	6. Governance and leadership	Promote equitable health-focused governance	Promote transparency and accountability	Advances the priority of disease on health agenda	Advance proper functioning of domestic policy	Regulatory oversight to promote R&D	Regulatory exclusivity provisions for R&D	Resources to develop drug government financed	7. Rewards focus	Payoff to innovators based on cost-effectiveness	Reward innovation	Financing timed across drug lifecycle	Provide long term R&D financing	Provide sustainable financing	Provide public subsidies for clinical trials	8. Impact on R&D process and clinical trials	Reduce clinical trial risk involved	Assist in registration and monitor of trials	Globalize clinical trial methods	Reduce clinical trials activation difficulty	Enhance or prompt the quality of clinical trials	Assist in expensive clinical trial regulation	Improves R&D productivity	Enlarge number of clinical trials registered
			2	2	1		2	2	2	2		2	2	2		0	1	2	1		2	2	2	2	2		2	2	0	1	2	2	0		2	2	2	2	2	2		2	1	0	1	2	1	0	0
1	**Grants:** Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting		1	0	0		0	0	1	0		0	0	0		1	1	1	1		1	0	0	0	0		0	1	1	0	1	0	1		0	0	0	1	0	0		0	0	0	1	0	0	0	0
2	**Open-source initiative:** Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets have the ability to benefit all participants.		1	1	0		1	1	1	0		0	0	0		1	0	0	0		1	1	1	1	0		1	1	1	1	0	0	0		0	0	0	0	0	0		1	1	1	0	0	0	1	1
3	**Patent pool:** Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.		1	1	1		0	0	1	0		0	0	0		1	1	1	0		1	1	0	1	0		1	1	0	0	0	0	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
4	**Public-private partnership:** Public-private partnerships is any arrangement between one or more public and private entities. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.		1	0	1		1	1	1	1		0	0	0		1	1	1	1		1	1	1	1	0		1	1	1	1	0	0	1		0	0	1	1	1	1		0	1	1	1	0	1	0	1
5	**Tax credits:** Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.		1	0	0		1	0	0	0		0	0	0		1	1	0	1		1	1	0	0	0		0	1	1	0	1	1	1		0	1	1	0	0	1		0	0	0	0	0	0	0	0
6	**Advanced market commitments:** Advanced market commitments are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.		1	1	0		1	1	1	1		1	1	0		1	1	1	1		1	1	0	0	0		0	0	1	0	0	0	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
7	**Differential pricing:** Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.		1	1	1		1	0	0	0		0	0	0		1	1	1	1		1	1	0	0	0		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
8	**Patent buyouts:** IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.		1	0	0		0	0	0	1		0	0	0		1	1	0	0		1	1	0	0	0		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
9	**Pooled fund:** When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.		0	1	0		1	0	1	1		1	1	0		1	1	1	1		1	0	1	1	0		0	1	1	0	0	0	0		0	0	1	1	1	0		1	0	0	0	0	0	0	0
10	**Prize fund:** Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.		1	1	0		1	0	1	0		1	1	0		1	1	1	0		1	0	0	0	1		0	1	1	0	0	0	0		1	1	1	0	0	0		0	0	1	0	1	0	0	1
11	**Rating system:** Pharmaceutical organizations are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.		0	0	0		0	0	1	0		1	1	1		1	1	1	0		1	1	0	0	1		1	1	1	1	1	1	0		0	0	0	0	0	0		0	0	0	0	1	0	1	0
12	**Intellectual property and market exclusivity:** Intellectual property refers to the right that the innovator receives when a new innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.		1	0	1		0	0	1	1		0	0	0		1	1	0	0		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
13	**Policy instrument:** Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy. Instruments can also include altering and enforcing domestic policies.		0	0	1		1	1	1	0		1	1	1		1	0	1	1		1	1	0	0	0		1	1	0	1	1	0	0		0	0	0	0	0	0		0	1	1	0	1	1	0	1
14	**Priority review voucher:** Law under which companies that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.		1	1	0		1	0	1	0		0	0	0		1	1	0	0		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	1	0	1	0	0
15	**Trade, tariff adjustments:** Adjustments made to the trading or the taxes and required costs associated with trading of specified manufactured drugs.		1	0	1		0	1	0	1		0	0	0		1	1	1	1		1	1	0	0	0		1	0	1	1	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
16	**Collaboration and consortiums:** A collaboration network refer to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a goal.		0	0	1		0	0	1	1		1	1	0		1	1	1	1		1	1	1	1	0		1	1	1	0	0	0	0		0	1	0	1	1	0		1	1	1	0	1	1	1	0
17	**Colloquium and symposium:** An academic conference or seminar held, focussing on one topic.		0	0	0		0	0	1	0		0	1	0		1	0	0	0		1	1	1	1	0		0	1	1	1	1	0	0		0	0	0	0	0	0		0	0	1	0	1	0	1	0
18	**Policy and legislation:** Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.		0	0	1		1	1	0	0		0	1	1		1	0	1	1		1	1	0	0	0		1	1	0	1	1	0	1		0	0	0	0	0	1		0	1	1	1	1	0	0	1
19	**Drug status designation:** Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.		1	1	1		1	0	0	1		0	0	0		1	1	1	1		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
20	**Joint venture:** Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.		1	0	1		1	0	1	1		1	1	0		1	1	1	1		1	1	1	1	0		0	1	1	0	0	0	0		0	1	1	0	0	0		1	0	1	1	1	1	0	1
21	**Independent organization:** Independent organizations does not require the approval of a government agency for decision-making and financial planning.		1	1	0		1	0	0	0		0	0	0		1	1	1	0		1	1	1	1	0		1	1	1	0	0	0	0		0	1	1	1	1	0		0	0	0	0	1	0	0	0
22	**Hybrid public-private partnership:** This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention, the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.		1	0	1		1	1	1	1		0	0	0		1	1	1	1		1	1	1	1	0		1	1	1	1	1	0	1		0	0	1	1	1	1		1	1	1	1	0	1	0	1
23	**Research laboratories:** Research laboratories are scientifically orientated facilities equipped with equipment to complete experiments aimed at R&D of drugs.		1	0	0		1	1	0	0		1	1	1		1	1	0	0		1	0	1	0	0		0	1	1	0	0	0	0		0	0	0	1	1	0		0	1	1	1	1	1	0	1
24	**Treaty:** Formal agreement between two or more political authorities, subject to international law.		1	0	1		1	1	1	1		1	1	1		1	1	1	1		0	0	1	1	0		1	1	1	1	1	0	1		0	0	0	0	0	1		0	0	1	0	1	1	0	1
25	**Working Group:** Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.		1	0	1		1	0	1	1		0	0	0		1	1	1	1		1	0	1	1	0		0	0	1	0	0	0	0		0	0	1	0	1	0		0	0	1	1	0	0	0	0
26	**Coordination mechanism and platform:** Initiatives to coordinate R&D investments and activities. Operate to clarify priorities, increase transparency, and diversify stakeholders.		0	0	1		1	1	1	0		1	1	1		1	1	1	1		1	1	1	1	0		0	1	1	0	0	0	0		0	0	0	0	0	0		1	1	1	1	1	1	0	1

Domain 2 Enabler profile: Prize fund results SME 10

DOMAIN 2: ENABLER INQUIRY FORM					
OBJECTIVES			**INTERNAL CAPABILITIES**		
1	**Goal of the incentive strategy? (Inclusion)**		**1**	**Available funding. (Exclusion)**	
	Improve the state of the R&D pipeline	2		Limited to an amount	2
	Enable organizations to innovate easier	2		Full capacity	0
	Gain market exclusivity over an innovation	0		No capacity	0
	Advance the R&D field	2	**2**	**Payoff to innovators. (Inclusion)**	
	Deliver affordable and accessible treatment	1		Beginning once-off	0
	Convey an important message	2		End once-off	2
	Fulfil corporate social responsibility	0		Once output is provided	0
	Increase bandwidth and network	1		Incrementally, based on output	0
	De-risk R&D process	0		Incrementally, based on timing	0
	Political obligations	0		Incrementally, as innovator requires	0
2	**Which innovators are targeted? (Inclusion)**		**3**	**Ability to influence policy. (Inclusion)**	
	Large pharmaceutical organizations (private)	1		Clinical trial regulation policies	0
	SMEs (private)	1		Market authorization policies	0
	Governmental institutions	2		Market exclusivity policies	0
	Independent scientists	2		Pricing policies	0
	Academic institutions	2		Tax credit policies	0
	NGO organizations	2		National/international intellectual property policies	1
	Everyone	2		National policies and legislation	0
3	**Intention for the consumers? (Exclusion)**			International trade law	0
	Provide drug	1		**Access and expertise. (Inclusion)**	
	Multi-purpose drug	1	**4**	Access to key data	2
	Play a role in improved access	2		Access to compounds	0
	Implement mass drug administrations	1		Access to intellectual property	0
	Deliver regime treatment	1		Technology expertise and access	1
4	**Desired relationship with innovators? (Inclusion)**			R&D expertise	2
	Once-off occasion	2			
	Limited to a number of years	0			
	Milestone related	1			
	Engage at given time instances	0			
	Collaborate and build a partnership	1			
5	**Role and Responsibility willing to play? (Exclusion)**				
	Fund R&D	2			
	Partially fund R&D	2			
	Facilitate collaboration between innovators	2			
	Collaborate with innovator	1			
	Facilitate in regulatory process	0			
	Provide market exclusivity	0			
	Adjust policies and regulations	0			
	Provide market certainty	0			

Background Logic 1AB: Prize fund results SME 10

	Background Logic 2: Enabler Matrix	1. Goal of the incentive strategy										2. Which innovators are targeted?							3. Intention for the patients?					4. Desired relationship with innovator?					5. Role & responsibility willing to play?								1. Available funding?			2. Funding timing?			3. Ability to influence /provide guidance in policies?									4. Access to aspects?				
		Improve the state of the R&D pipeline	Enable organizations to innovate easier	Gain market exclusivity over an innovation	Advance the R&D field & body of knowledge	Deliver affordable and accessible treatment	Convey an important message	Fulfil corporate social responsibility	Increase bandwidth and network	De-risk R&D process	Political obligations	Large pharmaceutical organizations(private)	SMEs (private)	Governmental institutions	Independent scientists	Academic institutions	NGO organizations	Everyone	Provide drug/novel drug	Multi-purpose drug	Play a role in improved access	Deliver regime treatment	Implement mass drug administrations	Once-off occasion	Limited to a number of years	Milestone related	Engage at given time instances	Collaborate and build a partnership	Fund R&D	Partially fund	Facilitate collaboration between innovators	Collaborate with innovator	Facilitate in regulatory process	Provide market exclusivity	Adjust policies and regulations	Provide market certainty	Limited to an amount	Full capacity	No capacity	Beginning once-off	End once-off	Once output provided	Incrementally, based on output	Incrementally, based on timing	Incrementally, as innovator requires	Clinical trial regulation policies	Market authorization policy	Market exclusivity policies	Pricing policies	Tax credit policies	National policies and legislations	National/International intellectual property policies	International trade law	Access to key data	Access to compounds	Access to intellectual property	Technology expertise and access	R&D expertise
	Push interventions	2	2	0	2	1	2	0	1	0	0	1	1	2	2	2	2	2	1	1	2	1	1	2	0	1	0	1	2	2	2	1	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	2
1	Grant	1	0	0	1	0	0	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	Open-source initiative	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
3	Patent Pool	1	0	1	0	1	0	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	0	1	1	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0	0
4	PPP	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	Tax credits	1	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0
	Outcome-based pull strategies																																																									
6	Advanced market commitments	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
7	Differential pricing	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
8	Patent buyouts	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	1	0	1	1	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	1	1	0
9	Pooled fund	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0
10	Prize fund	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0
11	Rating system	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lego-regulatory pull strategies																																																								
12	Intellectual property and market exclusivity	1	0	1	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	1	0	0	1	0	0
13	Policy instrument	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0
14	Priority review voucher	1	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0	1	0	0
15	Trade, tariff adjustments	1	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0
	Hybrid strategies																																																								
16	Collaboration network and consortiums	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
17	Colloquium and symposium	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
18	Policy and legislation	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	1	0	1	1	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	1	1	0
19	Drug status designation	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0
20	Joint venture	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1
21	Independent organization	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	Hybrid PPP	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	0	0
23	Research laboratories	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
24	Treaty	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	1	0	1	1	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	1	1	0
25	Working Group	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0
26	Coordination mechanism*	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1

Domain 3 Innovator matrix: Prize fund results SME 10

DOMAIN 3: INNOVATOR INQUIRY FORM					
OBJECTIVES			INTERNAL CAPABILITIES		
1	**Reason for performing R&D for the disease?**		**1**	**Nature of innovator stakeholder?**	
	Profit maximization	0		Small to medium organization (includes start-up)	2
	Corporate social responsibility	0		Large pharmaceutical organization	2
	Not for profit	2		Not-for-profit organization	2
	Profit improvement	1		Governmental institution	2
	Political obligations	0		Academic institution	2
2	**Focus area of R&D and intention for patients?**			Independent scientist (no organization linked)	0
	R&D of drug	2	**2**	**Capacity to provide own funding?**	
	R&D of multi-purpose drug	1		No capacity	2
	Play a role in improved access	2		Limited to an amount	2
	Drug repurposing	0		Full capacity	1
	Deliver regime treatment	0	**3**	**R&D limitations?**	
3	**Require from the enabler?**			Don't have research laboratory	0
	Fund all R&D costs	0		Don't have adequate equipment	2
	Partially fund R&D	2		Lack of information (knowledge) on disease	0
	Collaboration with enabler	2		Cumbersome nature of clinical trial regulations	0
	Adjust policies and regulations	1		Shortage of finances	2
	Facilitate regulatory process	0		Policies or regulatory limitations	0
	Provide market exclusivity	0		No market certainty	0
	Provide market certainty	0	**4**	**Authorization standards adhered to?**	
	Provide a collaboration platform	2		None	0
	Provide risk insurance or security	0		Accredited authorisation organization	2
	Improve export potential	0			
4	**Preference or required funding timing?**				
	Beginning once-off	0			
	End once-off	2			
	Incrementally based on output	0			
	Incrementally based on timing	1			
	Incrementally as required	0			
	Once output provided	0			
	Don't require any funding	0			

Background Logic 3 Innovator matrix: Prize fund results SME 10

	1. Reason for performing R&D for the disease?	Profit maximization	Corporate or social responsibility	Not for profit	Profit improvement	Political obligations	2. Focus area of R&D and intention for patients?	R&D of drugs / novel drugs	Develop regime treatment	R&D a multi-purpose drug/vaccine	Play a role in improved access	Drug repurposing	3. Require from enabler / incentive intervention	Cover all R&D costs	Partly cover R&D costs	Collaboration with enabler	To adjust policies and regulations	To facilitate in the regulatory process	To provide market certainty	To provide market exclusivity	Collaboration platform	Risk insurance or security	Improve export potential	4. Preference or required funding timing?	Beginning once-off	End once-off	Incrementally based on output	Incrementally based on timing	Incrementally as required / incrementally	Once output provided	Do not require any funding	1. Nature of organization?	Large pharmaceutical organizations (private)	Small-and medium enterprise (private)	NGO	Governmental institution	Academic Institution	Scientist (no company)	2. Capacity to provide own funding?	No capacity	Limited to an amount	Full capacity	3. R&D limitations?	Don't have research laboratory	Don't have adequate equipment	Lack of information (knowledge) on disease	Cumbersome nature of clinical trial regulations	Shortage of finances	Policies or regulation limitations	No market certainty	4. Which Authorization standards adhered to?	None	Accredited authorisation organization
Push interventions		0	0	2	1	0	.	2	0	1	2	0	.	0	2	2	1	0	0	0	2	0	0	.	0	2	0	1	0	0	0	.	2	2	2	2	2	0	.	2	2	1	.	0	2	0	0	2	0	0	.	0	2
1 Grant		0	1	1	1	1		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		1	0	1	1	0	0	0		0	1	1	1	1	1		1	1	1		0	0	0	0	1	0	0		0	1
2 Open-source initiative		0	1	1	1	1		0	0	0	0	1		0	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	0		0	0	1	1	0	0	0		1	1
3 Patent Pool		0	1	1	1	0		1	1	1	1	1		0	0	0	0	0	0	1	1	0	1		0	0	0	0	1	0	1		1	1	1	1	0	0		0	0	0		0	0	0	0	0	0	0		0	1
4 PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
5 Tax credits		1	0	0	1	0		1	1	1	0	1		0	1	0	1	0	0	0	0	0	0		0	0	0	1	0	1	1		1	1	0	1	1	0		0	0	0		0	0	0	0	0	0	0		0	0
Outcome-based pull incentives																																																							
6 Advanced market commitments		1	1	0	1	1		1	1	1	1	1		0	0	0	0	0	1	0	0	1	0		0	1	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		0	1
7 Differential pricing		0	1	1	1	1		1	1	1	1	1		0	1	0	1	0	0	0	0	0	1		0	0	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	0		0	0
8 Patent buyouts		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	1	1	0	1	0		0	1	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	0	0		0	1
9 Pooled fund		0	1	1	0	1		1	1	1	1	1		1	1	0	0	0	0	0	1	1	0		1	1	1	1	1	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		1	1
10 Prize fund		1	1	1	1	0		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		0	1	1	0	0	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		0	1
11 Rating system		0	1	1	0	1		1	1	1	1	0		0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	1		1	1	1	1	1	0		0	0	1		0	0	0	0	0	0	0		1	1
Lego-regulatory pull strategies																																																						
12 Intellectual property and market exclusivity		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	0	1	0	1	1		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		0	1
13 Policy instrument		0	1	1	0	1		0	0	0	1	0		0	0	0	1	1	0	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	0	1		0	0	0	0	0	1	0		1	1
14 Priority review voucher		1	0	1	1	0		1	1	1	0	0		0	1	0	0	1	0	0	0	0	0		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	1	0	1	0		1	1
15 Trade, tariff adjustments		1	1	1	1	1		1	1	1	1	0		0	1	0	1	0	1	1	0	1	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		0	0	0	0	1	1	0		1	1
Hybrid strategies																																																						
16 Collaboration network and consortiums		0	1	1	0	1		1	1	1	1	1		1	1	1	0	0	0	0	1	1	1		0	0	1	1	1	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
17 Colloquium and symposium		0	1	1	0	0		0	0	0	0	0		0	0	1	0	1	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	1	1	0	0	0		1	1
18 Policy and legislation		0	1	1	0	1		0	1	0	1	1		0	0	0	1	1	1	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		1	1
19 Drug status designation		1	1	1	1	0		1	1	1	1	1		0	1	0	1	0	1	0	0	1	1		0	0	0	0	0	0	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		1	1
20 Joint venture		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	1	1	1	1	0	1		1	1	1	1	1	1		0	1	1		1	1	1	1	1	0	0		1	1
21 Independent organization		1	1	1	1	0		1	1	1	1	1		1	0	1	0	1	1	0	1	0	0		1	1	1	1	1	0	1		1	1	1	0	0	1		0	0	1		1	1	1	1	0	0	0		1	1
22 Hybrid PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	1	1		1	1
23 Research laboratories		1	1	0	1	1		1	1	1	0	1		0	0	1	0	0	0	0	0	0	0		0	0	0	0	0	0	1		0	1	1	1	1	1		0	0	1		1	1	0	0	0	0	0		1	1
24 Treaty		0	0	0	1	1		1	1	1	1	1		1	1	0	1	1	1	1	1	1	1		1	1	0	1	0	0	1		0	0	0	1	0	0		1	1	1		0	0	1	1	1	1	0		1	1
25 Working Group		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	0	1	1	1	0	1		0	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
26 Coordination mechanism		1	1	1	0	1		1	1	1	1	1		0	1	1	0	0	0	0	1	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	0		1	1

Domain 4 Consumer profile: Prize fund results SME 10

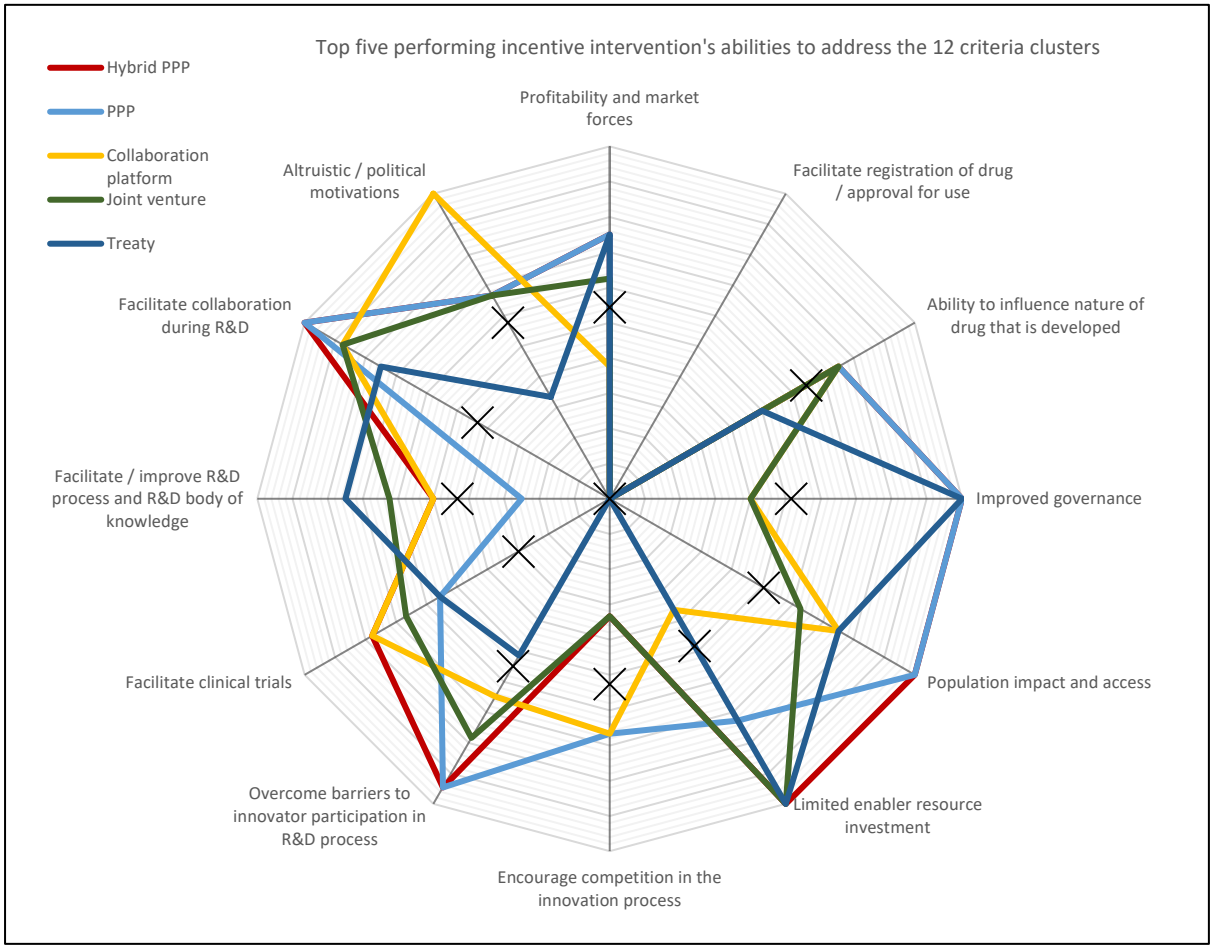
DOMAIN 4: CONSUMER REQUIREMENTS		
END CONSUMER (patient)		
1	**Socio-economic inequalities**	
	Require differential pricing	0
	Must eliminate all financial risk	2
2	**Contextual treatment criteria**	
	Accommodates contextual treatment criteria	2
PROCUREMENT: PUBLIC / PRIVATE (FOR-/ NOT FOR PROFIT)		
3	**Affordability**	
	Require differential pricing	0
4	**End-price profit margins**	
	Any profit margins allowed	0
	Restricted profit margins	0
	No profit	2
5	**Availability and accessibility**	
	IP regulation allows procurement of drugs to target area	-
	Existing drugs not allowed in target area	-
	Drug status designation required	-

BACKGROUND LOGIC 4: CONSUMER MATRIX	END-CONSUMER				PROCURERS (PUBLIC / PRIVATE)								
	1. Socio-economic inequalities	Require differential pricing	Must eliminate all financial risk	**2. Contextual treatment criteria**	Addresses contextual treatment criteria	**3. Affordability**	Require differential pricing	**4. End-price profit margins**	Any profit margins allowed	Restricted profit margins	No profit	**5. Availability and accessibility**	IP regulation allows procurement of drugs to target area	Existing drugs not allowed in target area	Drug status designation required
Push intervention		0	2	.	2	.	0	.	0	0	2	.	0	0	0
1 Grant		0	0		1		0		0	0	0		0	0	0
2 Open-source initiative		0	0		1		0		0	1	1		1	0	0
3 Patent pool		0	0		1		0		0	0	0		1	1	0
4 PPP		1	1		1		1		0	1	0		1	0	1
5 Tax credits		0	0		1		0		0	1	0		0	0	1
Outcome-based pull strategies															
6 Advanced market commitments		0	0		1		0		1	1	0		0	1	0
7 Differential pricing		1	1		0		1		0	1	0		0	0	0
8 Patent buy-outs		0	0		1		0		1	1	0		1	1	0
9 Pooled fund		0	0		1		0		0	0	0		0	0	0
10 Prize fund		0	0		1		0		0	0	0		0	0	0
11 Rating system		0	0		1		0		0	0	1		0	1	1
Lego-regulatory pull strategies															
12 Intellectual property		0	0		1		0		1	1	0		1	1	0
13 Policy instrument		1	1		1		1		1	1	1		1	1	1
14 PRV		0	0		1		0		0	1	0		0	0	0
15 Trade, tariff adjustments		1	1		0		1		1	1	1		1	1	1
Hybrid strategies															
16 Collaboration network and consortiums		0	0		1		0		0	0	1		0	0	0
17 Colloquium and symposium		0	0		1		0		0	0	1		0	0	0
18 Policy and legislation		0	0		1		0		1	1	1		1	1	0
19 Drug status designation		1	1		1		1		0	0	1		1	1	1
20 Joint venture		0	1		1		0		0	1	1		1	1	0
21 Independent organization		0	1		1		0		1	0	1		0	1	0
22 Hybrid between PPP and other mechanisms		1	1		1		1		1	1	1		1	1	1
23 Research laboratories		0	0		0		0		1	0	1		0	0	0
24 Treaty		1	0		0		1		0	1	1		1	1	0
25 Working group		0	0		1		0		0	1	1		0	1	0
26 Coordination mechanism		0	0		1		0		0	1	1		0	1	0

Domain 5 Solution set (1 of 2): Prize fund results SME 10

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													9	Feasible
22	Hybrid PPP													9	Feasible
26	Coordination mechanism													8	Feasible
20	Joint venture													7	Feasible
24	Treaty													7	Feasible
21	Independent organization													6	Feasible
10	Prize fund													6	Feasible
9	Pooled fund													4	Feasible
1	Grant													3	Feasible
8	Patent buy-outs													3	Feasible
16	Collaboration network													8	Infeasible
11	Rating system													6	Infeasible
19	Drug status designation													6	Infeasible
13	Policy instrument													5	Infeasible
25	Working group													5	Infeasible
18	Policy and legislation													5	Infeasible
6	Advanced market commitments													4	Infeasible
2	Open source initiative													4	Infeasible
17	Colloquium and symposium													4	Infeasible
14	PRV													4	Infeasible
7	Differential pricing													4	Infeasible
12	Intellectual property													3	Infeasible
15	Trade, tariff adjustments													3	Infeasible
23	Research laboratories													3	Infeasible
3	Patent pool													2	Infeasible
5	Tax credits													2	Infeasible

Domain 5 solution set (2 of 2): Prize fund results SME 10



Domain 1 system demarcation: Prize fund results SME 11

DOMAIN 1: SYSTEM DEMARCATION						System evaluation	
	System elements	2	1	0	Aspect to address	Measure [0|1|2]	Sourced from section
Disease setting and affected population							
1	Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)	1	Chapter 3.6.2
2	Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact	2	Chapter 3.6.2
3	Burden fully characterized	< 40% of population within 5% of health facility	40% - 60% of population within 5% of health facility	> 60% of population within 5% of health facility	Non-incentive-based solutions (I)	1	Chapter 3.4.1.1 &3.6.2
4	Physicians per 1000 population	¡ 1 per 1 000	1 - 2 physicians per 1 000 population	¿ 2 physicians per 1 000 population	Non-incentive-based solutions (I)	1	SME 4
Existing drug characteristics							
5	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact	1	Chapter 3.6
6	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)	1	Chapter 3.6
7	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact	2	Chapter 2.1.2
8	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)	1	Chapter 2.2.5
9	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access	1	Chapter 2.2.5
10	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)	2	Chapter 2.2.5
11	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)	1	Chapter 2.2.5
12	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (Respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)	1	Chapter 2.2.5
13	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access	1	Chapter 3.6.2
Service delivery							
14	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)	1	Chapter 2.2.3
15	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)	1	Chapter 2.2.3
16	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)	1	Chapter 2.2.3
17	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)	2	Chapter 2.2.3
Consumers, Competitors, and suppliers							
18	Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)	0	Chapter 3.4.3 & 3.7.3
19	The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)	1	Chapter 3.7.3
20	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)	1	Chapter 3.4.3
21	Existence of competitors	No competitors	Some competitors	A lot of competition	Non-incentive-based solutions (V)	1	Chapter 3.4.3
22	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility	2	Chapter 3.4.3
23	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation	0	Chapter 3.4.3
24	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation	1	Chapter 3.4.3
Governance and leadership							
25	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)	1	Chapter 3.6.2
26	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership	1	Chapter 3.6.2
27	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership	0	Chapter 3.6.2
28	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership	0	Chapter 3.6.2
29	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
30	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
31	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership	1	Chapter 2.2.3
32	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)	2	Chapter 2.2.5
33	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)	1	Chapter 2.2.3
Profitability and market forces							
34	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces	1	Chapter 2.1 & 3.6.2
35	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)	2	Chapter 3.6.2
36	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)	1	Chapter 2.1.2
37	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)	1	Chapter 3.4.3
38	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces	1	Chapter 3.4.3 & 3.6.2
39	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership	1	Chapter 3.6.2
Research and development process							
40	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials	1	Chapter 2.1.2
41	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
42	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
43	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
44	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
45	Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials	1	Chapter 2.1.2
46	Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials	0	Chapter 2.1.2
47	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials	2	Chapter 2.1.2
48	Quality of clinical trials	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable	Good clinical trial quality	9. R&D and clinical trials	1	Chapter 2.1.2
49	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials	2	Chapter 3.6.2
50	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
51	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
52	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
53	Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
54	Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
55	Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
56	Racial differences in participation in clinical trial	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
57	Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
58	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
59	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)	1	Chapter 3.4.3
60	R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials	2	Chapter 2.1.3
61	Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials	1	Chapter 2.1.2 & 2.1.3
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)	1	Chapter 2.1.2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)	0	Chapter 2.1.2
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)	1	Chapter 3.4.3
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs	2	Chapter 3.4.3
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)	0	Chapter 2.2.3
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)	1	Chapter 2.2.3

Background Logic 1AB: Prize fund results SME 11

	BACKGROUND LOGIC 1A&B: CRITERIA MATRIX	**1. Profitability and market forces**	Improve NPV	Delink revenue from sales volume	Improve product export potential	**2. Implementation feasibility and security**	Minimizes barriers to implementation	Minimize disruptive effects to population	Affordable to implement the incentive	Provide R&D project insurance	**3. Green and sustainability**	Ensure conservation of resources in R&D process	Encourage efficient innovation	Green R&D of drugs	**4. Population impact and access**	Potential to reduce burden of disease	Encourage R&D of a drug/novel drug	Improve consumer access	Enable mass drug administration	**5. Participation and cooperation**	Enables participation of small and medium organization	Encourage large firm participation	Facilitates cooperation and synergy	Platform for coordinating innovators	Allow competition among parallel experiments	**6. Governance and leadership**	Promote equitable health-focused governance	Promote transparency and accountability	Advances the priority of disease on health agenda	Advance proper functioning of domestic policy	Regulatory oversight to promote R&D	Regulatory exclusivity provisions for R&D	Resources to develop drug government financed	**7. Rewards focus**	Payoff to innovators based on cost-effectiveness	Reward innovation	Financing timed across drug lifecycle	Provide long term R&D financing	Provide sustainable financing	Provide public subsidies for clinical trials	**8. Impact on R&D process and clinical trials**	Reduce clinical trial risk involved	Assist in registration and monitor of trials	Globalize clinical trial methods	Reduce clinical trials activation difficulty	Enhance or prompt the quality of clinical trials	Assist in expensive clinical trial regulation	Improves R&D productivity	Enlarge number of clinical trials registered
			2	2	0		2	2	2	2		2	2	2		0	1	2	1		2	2	2	2	2		2	2	0	1	0	0	1		2	2	2	2	2	2		2	1	0	2	1	2	2	1
1	**Grants:** Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting		1	0	0		0	0	1	0		0	0	0		1	1	1	1		1	0	0	0	0		0	1	1	0	1	0	1		0	0	0	1	0	0		0	0	0	1	0	0	0	0
2	**Open-source initiative:** Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets have the ability to benefit all participants.		1	1	0		1	1	1	0		0	0	0		1	0	0	0		1	1	1	1	0		1	1	1	1	0	0	0		0	0	0	0	0	0		1	1	1	0	0	0	1	1
3	**Patent pool:** Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.		1	1	1		0	0	1	0		0	0	0		1	1	1	0		1	1	0	1	0		1	1	0	0	0	0	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
4	**Public-private partnership:** Public-private partnerships is any arrangement between one or more public and private entities. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.		1	0	1		1	1	1	1		0	0	0		1	1	1	1		1	1	1	1	0		1	1	1	1	0	0	1		0	0	1	1	1	1		0	1	1	1	0	1	0	1
5	**Tax credits:** Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.		1	0	0		1	0	0	0		0	0	0		1	1	0	1		1	1	0	0	0		0	1	1	0	1	1	1		0	1	1	0	0	1		0	0	0	0	0	0	0	0
6	**Advanced market commitments:** Advanced market commitments are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.		1	1	0		1	1	1	1		1	1	0		1	1	1	1		1	1	0	0	0		0	0	1	0	0	0	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
7	**Differential pricing:** Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.		1	1	1		1	0	0	0		0	0	0		1	1	1	1		1	1	0	0	0		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
8	**Patent buyouts:** IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.		1	0	0		0	0	0	1		0	0	0		1	1	0	0		1	1	0	0	0		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
9	**Pooled fund:** When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.		0	1	0		1	0	1	1		1	1	0		1	1	1	1		1	0	1	1	0		0	1	1	0	0	0	0		0	0	1	1	1	0		1	0	0	0	0	0	0	0
10	**Prize fund:** Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.		1	1	0		1	0	1	0		1	1	0		1	1	1	0		1	0	0	0	1		0	1	1	0	0	0	0		1	1	1	0	0	0		0	0	1	0	1	0	0	1
11	**Rating system:** Pharmaceutical organizations are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.		0	0	0		0	0	1	0		1	1	1		1	1	1	0		1	1	0	0	1		1	1	1	1	1	1	0		0	0	0	0	0	0		0	0	0	1	0	1	0	
12	**Intellectual property and market exclusivity:** Intellectual property refers to the right that the innovator receives when a new innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.		1	0	1		0	0	1	1		0	0	0		1	1	0	0		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
13	**Policy instrument:** Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy. Instruments can also include altering and enforcing domestic policies.		0	0	1		1	1	1	0		1	1	1		1	0	1	1		1	1	0	0	0		1	1	0	1	1	0	0		0	0	0	0	0	0		0	1	1	0	1	1	0	1
14	**Priority review voucher:** Law under which companies that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.		1	1	0		1	0	1	0		0	0	0		1	1	0	0		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	1	0	1	0	0
15	**Trade, tariff adjustments:** Adjustments made to the trading or the taxes and required costs associated with trading of specified manufactured drugs.		1	0	1		0	1	0	1		0	0	0		1	1	1	1		1	1	0	0	0		1	0	1	1	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
16	**Collaboration and consortiums:** A collaboration network refer to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a goal.		0	0	1		0	0	1	1		1	1	0		1	1	1	1		1	1	1	1	0		1	1	1	0	0	0	0		0	1	0	1	1	0		1	1	1	0	1	1	1	0
17	**Colloquium and symposium:** An academic conference or seminar held, focussing on one topic.		0	0	0		0	0	1	0		0	1	0		1	0	0	0		1	1	1	1	0		0	1	1	1	1	0	0		0	0	0	0	0	0		0	0	1	0	1	0	1	0
18	**Policy and legislation:** Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.		0	0	1		1	1	0	0		0	1	1		1	0	1	1		1	1	0	0	0		1	1	0	1	1	0	1		0	0	0	0	0	1		0	1	1	1	1	0	0	1
19	**Drug status designation:** Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.		1	1	1		1	0	0	1		0	0	0		1	1	1	1		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
20	**Joint venture:** Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.		1	0	1		1	0	1	1		1	1	0		1	1	1	1		1	1	1	1	0		0	1	1	0	0	0	0		0	1	1	0	0	0		1	0	1	1	1	1	0	1
21	**Independent organization:** Independent organizations does not require the approval of a government agency for decision-making and financial planning.		1	1	0		1	0	0	0		0	0	0		1	1	1	0		1	1	1	1	0		1	1	1	0	0	0	0		0	1	1	1	1	0		0	0	0	0	1	0	0	0
22	**Hybrid public-private partnership:** This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention, the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.		1	0	1		1	1	1	1		0	0	0		1	1	1	1		1	1	1	1	0		1	1	1	1	0	1	0		0	0	1	1	1	1		1	1	1	1	0	1	0	1
23	**Research laboratories:** Research laboratories are scientifically orientated facilities equipped with equipment to complete experiments aimed at R&D of drugs.		1	0	0		1	1	0	0		1	1	1		1	1	0	0		1	0	1	0	0		0	1	1	0	0	0	0		0	0	0	1	1	0		0	1	1	1	1	1	0	1
24	**Treaty:** Formal agreement between two or more political authorities, subject to international law.		1	0	1		1	1	1	1		1	1	1		1	1	1	1		0	0	1	1	0		1	1	1	1	1	0	1		0	0	0	0	0	1		0	0	1	0	1	1	0	1
25	**Working Group:** Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.		1	0	1		1	0	1	1		0	0	0		1	1	1	1		1	0	1	1	0		0	0	1	0	0	0	0		0	0	1	0	1	0		0	0	1	1	0	0	0	0
26	**Coordination mechanism and platform:** Initiatives to coordinate R&D investments and activities. Operate to clarify priorities, increase transparency, and diversify stakeholders.		0	0	1		1	1	1	0		1	1	1		1	1	1	1		1	1	1	1	0		0	1	1	0	0	0	0		0	0	0	0	0	0		1	1	1	1	1	1	0	1

Domain 2 Enabler profile: Prize fund results SME 11

DOMAIN 2: ENABLER INQUIRY FORM					
OBJECTIVES			**INTERNAL CAPABILITIES**		
1	**Goal of the incentive strategy? (Inclusion)**		1	**Available funding. (Exclusion)**	
	Improve the state of the R&D pipeline	1		Limited to an amount	2
	Enable organizations to innovate easier	1		Full capacity	0
	Gain market exclusivity over an innovation	0		No capacity	0
	Advance the R&D field	2	2	**Tranches to innovators. (Inclusion)**	
	Deliver affordable and accessible treatment	1		Beginning once-off	0
	Convey an important message	2		End once-off	2
	Fulfil corporate social responsibility	1		Once output is provided	0
	Increase bandwidth and network	2		Incrementally, based on output	0
	De-risk R&D process	1		Incrementally, based on timing	0
	Political obligations	0		Incrementally, as innovator requires	0
2	**Which innovators are targeted? (Inclusion)**		3	**Ability to influence policy. (Inclusion)**	
	Large pharmaceutical organizations (private)	0		Clinical trial regulation policies	0
	SMEs (private)	2		Market authorization policies	0
	Governmental institutions	2		Market exclusivity policies	0
	Independent scientists	2		Pricing policies	0
	Academic institutions	2		Tax credit policies	0
	NGO organizations	2		National/international IP policies	0
	Everyone	1		National policies and legislation	0
3	**Intention for the consumers? (Exclusion)**			International trade law	0
	Provide drug	1	4	**Access and expertise. (Inclusion)**	
	Multi-purpose drug	0		Access to key data	0
	Play a role in improved access	1		Access to compounds	0
	Implement mass drug administrations	0		Access to intellectual property	0
	Deliver regime treatment	0		Technology expertise and access	1
4	**Desired relationship with innovators? (Inclusion)**			R&D expertise	1
	Once-off occasion	2			
	Limited to a number of years	0			
	Milestone related	0			
	Engage at given time instances	0			
	Collaborate and build a partnership	0			
5	**Role and Responsibility willing to play? (Exclusion)**				
	Fund R&D	2			
	Partially fund R&D	1			
	Facilitate collaboration between innovators	2			
	Collaborate with innovator	1			
	Facilitate in regulatory process	0			
	Provide market exclusivity	0			
	Adjust policies and regulations	0			
	Provide market certainty	0			

Background Logic 1AB: Prize fund results SME 11

Background Logic 2: Enabler Matrix	1. Goal of the incentive strategy										2. Which innovators are targeted?							3. Intention for the patients?					4. Desired relationship with innovator?					5. Role & responsibility willing to play?								1. Available funding?			2. Funding timing?			3. Ability to influence /provide guidance in policies?								4. Access to aspects?				
	Improve the state of the R&D pipeline	Enable organizations to innovate easier	Gain market exclusivity over an innovation	Advance the R&D field & body of knowledge	Deliver affordable and accessible treatment	Convey an important message	Fulfil corporate social responsibility	Increase bandwidth and network	De-risk R&D process	Political obligations	Large pharmaceutical organizations(private)	SMEs (private)	Governmental institutions	Independent scientists	Academic institutions	NGO organizations	Everyone	Provide drug/novel drug	Multi-purpose drug	Play a role in improved access	Deliver regime treatment	Implement mass drug administrations	Once-off occasion	Limited to a number of years	Milestone related	Engage at given time instances	Collaborate and build a partnership	Fund R&D	Partially fund	Facilitate collaboration between innovators	Collaborate with innovator	Facilitate in regulatory process	Provide market exclusivity	Adjust policies and regulations	Provide market certainty	Limited to an amount	Full capacity	No capacity	Beginning once-off	End once-off	Once output provided	Incrementally, based on output	Incrementally, based on timing	Incrementally, as innovator requires	Clinical trial regulation policies	Market authorization policy	Market exclusivity policies	Pricing policies	Tax credit policies	National policies and legislations	National/International intellectual property policies	International trade law	Access to key data	Access to compounds	Access to intellectual property	Technology expertise and access	R&D expertise
Push interventions	2	2	0	2	2	2	2	1	2	0	2	2	1	2	2	2	1	2	2	2	2	0	0	0	1	1	2	0	0	2	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	1	0	1	0	0	2	2	2	2	2
1 Grant	1	0	0	1	0	0	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
2 Open-source initiative	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
3 Patent Pool	1	0	1	0	1	0	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1	1	1	0	0
4 PPP	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5 Tax credits	1	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Outcome-based pull strategies																																																									
6 Advanced market commitments	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0
7 Differential pricing	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
8 Patent buyouts	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	1	0	1	1	1	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1	0
9 Pooled fund	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0
10 Prize fund	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
11 Rating system	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lego-regulatory pull strategies																																																									
12 Intellectual property and market exclusivity	1	0	1	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	1	0	0	1	0	0
13 Policy instrument	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	0	0	0	0
14 Priority review voucher	1	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	0	1	1	0	0	0	1	0	0	0	0
15 Trade, tariff adjustments	1	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0
Hybrid strategies																																																									
16 Collaboration network and consortiums	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	1	0
17 Colloquium and symposium	0	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	1	0	1	1	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
18 Policy and legislation	0	0	1	0	1	0	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	1	1	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	0	0	0	0
19 Drug status designation	1	0	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0
20 Joint venture	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	1	1
21 Independent organization	0	0	0	1	0	0	1	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1
22 Hybrid PPP	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
23 Research laboratories	1	1	0	1	0	0	1	0	0	1	0	1	1	1	1	1	0	1	1	0	1	0	0	1	0	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
24 Treaty	1	1	1	0	1	0	0	1	0	1	0	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1
25 Working Group	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0
26 Coordination mechanism*	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1

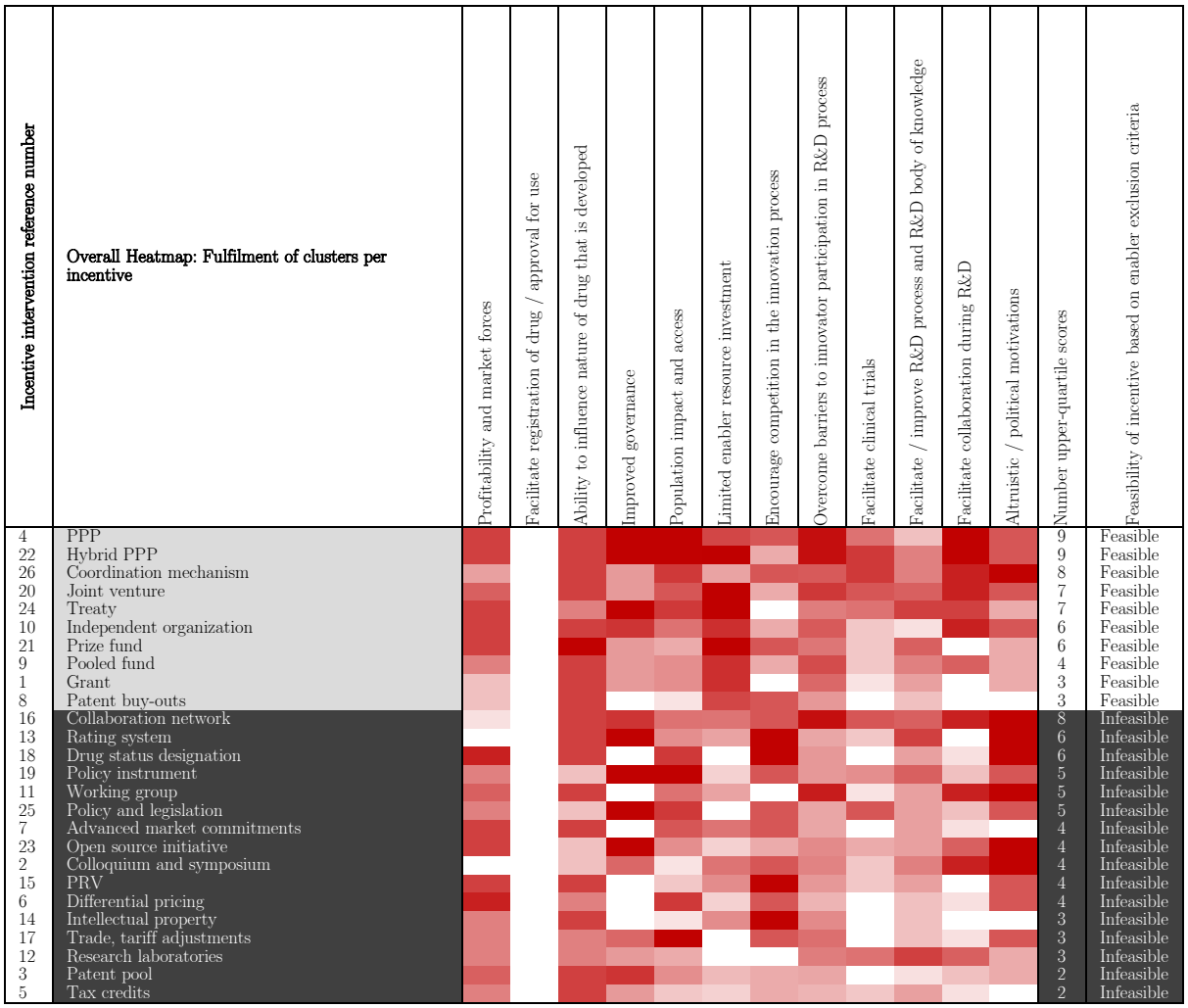
Domain 3 Innovator matrix: Prize fund results SME 11

DOMAIN 3: INNOVATOR INQUIRY FORM				
OBJECTIVES			**INTERNAL CAPABILITIES**	
1	**Reason for performing R&D for the disease?**		**1**	**Nature of innovator stakeholder?**
	Profit maximization	0		Small to medium organization (includes start-up)	2
	Corporate social responsibility	0		Large pharmaceutical organization	0
	Not for profit	1		Not-for-profit organization	2
	Profit improvement	0		Governmental institution	2
	Political obligations	0		Academic institution	2
2	**Focus area of R&D and intention for patients?**			Independent scientist (no organization linked)	2
	R&D of drug	2	**2**	**Capacity to provide own funding?**
	R&D of multi-purpose drug	1		No capacity	1
	Play a role in improved access	0		Limited to an amount	1
	Drug repurposing	2		Full capacity	1
	Deliver regime treatment	0	**3**	**R&D limitations?**
3	**Require from the enabler?**			Don't have research laboratory	1
	Fund all R&D costs	0		Don't have adequate equipment	1
	Partially fund R&D	2		Lack of information (knowledge) on disease	1
	Collaboration with enabler	0		Cumbersome nature of clinical trial regulations	1
	Adjust policies and regulations	0		Shortage of finances	1
	Facilitate regulatory process	0		Policies or regulatory limitations	1
	Provide market exclusivity	0		No market certainty	1
	Provide market certainty	0	**4**	**Authorization standards adhered to?**
	Provide a collaboration platform	1		None	1
	Provide risk insurance or security	0		Accredited authorisation organization	2
	Improve export potential	0			
4	**Preference or required funding timing?**				
	Beginning once-off	0			
	End once-off	2			
	Incrementally based on output	0			
	Incrementally based on timing	0			
	Incrementally as required	0			
	Once output provided	0			
	Don't require any funding	0			

Background Logic 3 Innovator matrix: Prize fund results SME 11

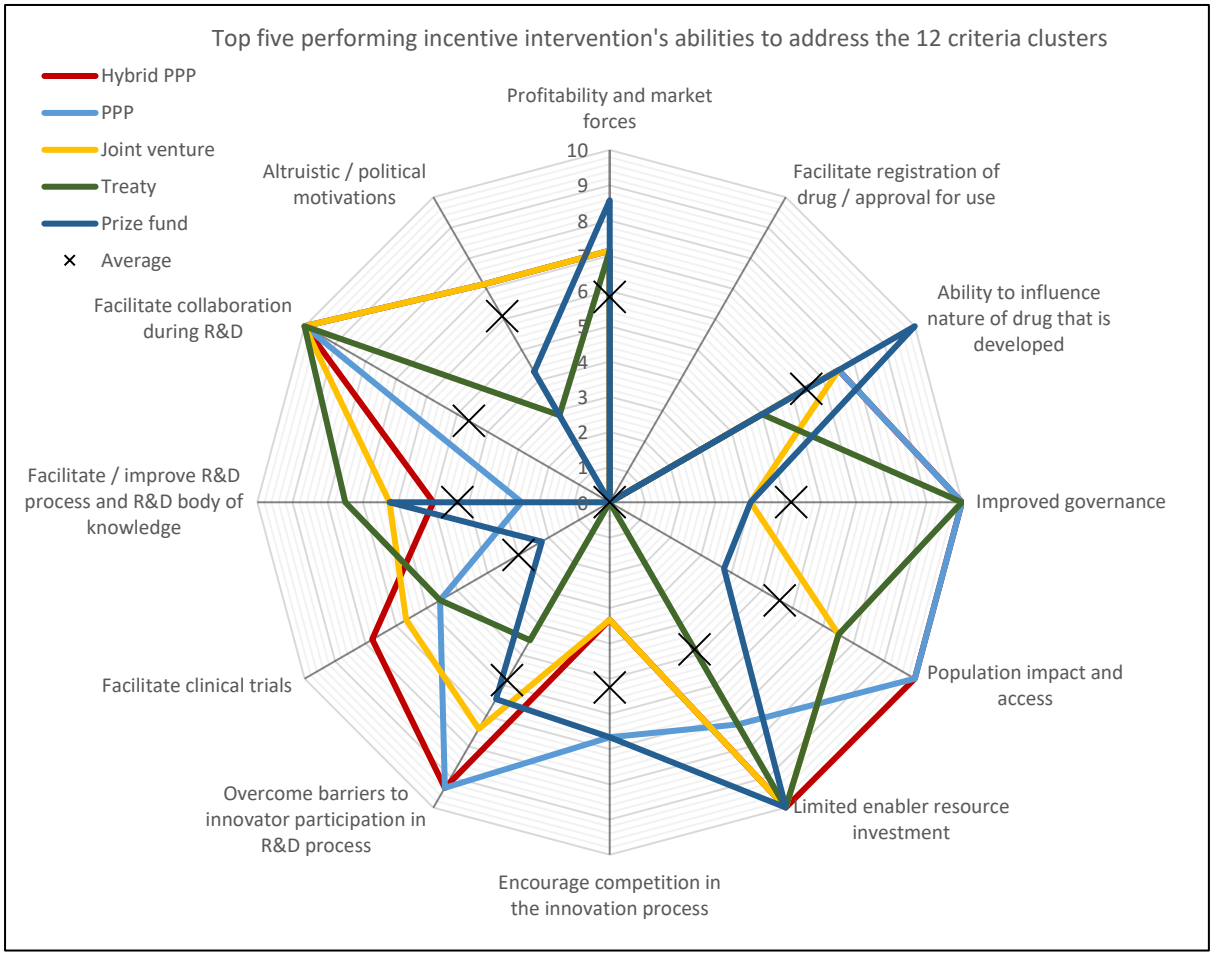
		1. Reason for performing R&D for the disease?	Profit maximization	Corporate or social responsibility	Not for profit	Profit improvement	Political obligations	**2. Focus area of R&D and intention for patients?**	R&D of drugs / novel drugs	Develop regime treatment	R&D a multi-purpose drug/vaccine	Play a role in improved access	Drug repurposing	**3. Require from enabler / incentive intervention**	Cover all R&D costs	Partly cover R&D costs	Collaboration with enabler	To adjust policies and regulations	To facilitate in the regulatory process	To provide market certainty	To provide market exclusivity	Collaboration platform	Risk insurance or security	Improve export potential	**4. Preference or required funding timing?**	Beginning once-off	End once-off	Incrementally based on output	Incrementally based on timing	Incrementally as required / incrementally	Once output provided	Do not require any funding	**1. Nature of organization?**	Large pharmaceutical organizations (private)	Small-and medium enterprise (private)	NGO	Governmental institution	Academic Institution	Scientist (no company)	**2. Capacity to provide own funding?**	No capacity	Limited to an amount	Full capacity	**3. R&D limitations?**	Don't have research laboratory	Don't have adequate equipment	Lack of information (knowledge) on disease	Cumbersome nature of clinical trial regulations	Shortage of finances	Policies or regulation limitations	No market certainty	**4. Which Authorization standards adhered to?**	None	Accredited authorisation organization
Push interventions			0	0	1	0	0	.	2	0	1	0	2	.	0	2	0	0	0	0	0	1	0	0	.	0	2	0	0	0	0	0	.	0	2	2	2	2	2	.	1	1	1	.	1	1	1	1	1	1	1	.	1	2
1	Grant		0	1	1	1	1		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		1	0	1	1	0	0	0		0	1	1	1	1	1		1	1	1		0	0	0	0	1	0	0		0	1
2	Open-source initiative		0	1	1	1	1		0	0	0	0	1		0	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	0		0	0	1	1	0	0	0		1	1
3	Patent Pool		0	1	1	1	0		1	1	1	1	1		0	0	0	0	0	0	1	1	0	1		0	0	0	0	1	0	1		1	1	1	1	0	0		0	0	0		0	0	0	0	0	0	0		0	1
4	PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
5	Tax credits		1	0	0	1	0		1	1	1	0	1		0	1	0	1	0	0	0	0	0	0		0	0	0	1	0	1	1		1	1	0	1	1	0		0	0	0		0	0	0	0	0	0	0		0	0
Outcome-based pull incentives																																																									
6	Advanced market commitments		1	1	0	1	1		1	1	1	1	1		0	0	0	0	0	1	0	0	1	0		0	1	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		0	1
7	Differential pricing		0	1	1	1	1		1	1	1	1	1		0	1	0	1	0	0	0	0	0	1		0	0	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	0		0	0
8	Patent buyouts		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	1	1	0	1	0		0	1	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	0	0		0	1
9	Pooled fund		0	1	1	0	1		1	1	1	1	1		1	1	0	0	0	0	0	1	1	0		1	1	1	1	1	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		1	1
10	Prize fund		1	1	1	1	0		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		0	1	1	0	0	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		0	1
11	Rating system		0	1	1	0	1		1	1	1	1	0		0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	1		1	1	1	1	1	0		0	0	1		0	0	0	0	0	0	0		1	1
Lego-regulatory pull strategies																																																								
12	Intellectual property and market exclusivity		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	0	1	0	1	1		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		0	1
13	Policy instrument		0	1	1	0	1		0	0	0	1	0		0	0	0	1	1	0	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	0	1		0	0	0	0	0	1	0		1	1
14	Priority review voucher		1	0	1	1	0		1	1	1	0	0		0	1	0	0	1	0	0	0	0	0		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	1	0	1	0		1	1
15	Trade, tariff adjustments		1	1	1	1	1		1	1	1	1	0		0	1	0	1	0	1	1	0	1	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		0	0	0	0	1	1	0		1	1
Hybrid strategies																																																								
16	Collaboration network and consortiums		0	1	1	0	1		1	1	1	1	1		1	1	1	0	0	0	0	1	1	1		0	0	1	1	1	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
17	Colloquium and symposium		0	1	1	0	0		0	0	0	0	0		0	0	1	0	1	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	1	1	0	0	0		1	1
18	Policy and legislation		0	1	1	0	1		0	1	0	1	1		0	0	0	1	1	1	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		1	1
19	Drug status designation		1	1	1	1	0		1	1	1	1	1		0	1	0	1	0	1	0	0	1	1		0	0	0	0	0	0	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		1	1
20	Joint venture		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	1	1	1	1	0	1		1	1	1	1	1	1		0	1	1		1	1	1	1	1	0	0		1	1
21	Independent organization		1	1	1	1	0		1	1	1	1	1		1	0	1	0	1	1	0	1	0	0		1	1	1	1	1	0	1		1	1	1	0	0	1		0	0	1		1	1	1	1	0	0	0		1	1
22	Hybrid PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	1	1		1	1
23	Research laboratories		1	1	0	1	1		1	1	1	0	1		0	0	1	0	0	0	0	0	0	0		0	0	0	0	0	0	1		0	1	1	1	1	1		0	0	1		1	1	0	0	0	0	0		1	1
24	Treaty		0	0	0	1	1		1	1	1	1	1		1	1	0	1	1	1	1	1	1	1		1	1	0	1	0	0	1		0	0	0	1	0	0		1	1	1		0	0	1	1	1	1	0		1	1
25	Working Group		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	0	1	1	1	0	1		0	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
26	Coordination mechanism		1	1	1	0	1		1	1	1	1	1		0	1	1	0	0	0	0	1	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	0		1	1

Domain 5 Solution set (1 of 2): Prize fund results SME 11



Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													9	Feasible
22	Hybrid PPP													9	Feasible
26	Coordination mechanism													8	Feasible
20	Joint venture													7	Feasible
24	Treaty													7	Feasible
10	Independent organization													6	Feasible
21	Prize fund													6	Feasible
9	Pooled fund													4	Feasible
1	Grant													3	Feasible
8	Patent buy-outs													3	Feasible
16	Collaboration network													8	Infeasible
13	Rating system													6	Infeasible
18	Drug status designation													6	Infeasible
19	Policy instrument													5	Infeasible
11	Working group													5	Infeasible
25	Policy and legislation													5	Infeasible
7	Advanced market commitments													4	Infeasible
23	Open source initiative													4	Infeasible
2	Colloquium and symposium													4	Infeasible
15	PRV													4	Infeasible
6	Differential pricing													4	Infeasible
14	Intellectual property													3	Infeasible
17	Trade, tariff adjustments													3	Infeasible
12	Research laboratories													3	Infeasible
3	Patent pool													2	Infeasible
5	Tax credits													2	Infeasible

Domain 5 solution set (2 of 2): Prize fund results SME 11



Background Logic 5: Prize fund (combined)

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	BL	1		1	3		2	2	2	3		2	3	2	2	2	2		1	3	3	4	1		2	2	4	4	4		1	2	1	3		2	3		3	2	1	4	3		1	1	1	1
	Cluster 1: Profitability and market forces	Delink revenue from sales volume	Incentive improves product export potential	Improve product export potential (Incentive ability)	Improve export potential (Innovator require)	Incentive allows market exclusivity over an innovation	Gain market exclusivity over an innovation (Enabler goal)	Provide market exclusivity (Enabler ability)	Market exclusivity policies (Enabler ability to alter)	Provide market exclusivity (Innovator require)	Incentive provides market certainty	Provide market certainty (Enabler role)	Provide market certainty (Innovator require)	Incentive involves/requires national/international intellectual property policies (Enabler ability)	Incentive involves/requires tax credit policies (Enabler ability)	Incentive involves/requires pricing policies (Enabler ability)	Incentive involves/requires international trade law (Enabler ability)	Incentive improves NPV of stakeholders	Improve NPV of stakeholders	Profit improvement (Innovator goal)	Profit maximization (Innovator goal)	Any profit margins allowed (Consumer require)	Minimizes barriers to implementation (implementation of incentive)	Cluster 2Facilitate registration of drug / approval for use	Incentive involves/requires market authorization policies (Enabler ability)	Incentive involves/requires national policies and legislations (Enabler ability)	Existing drugs not allowed in target area (Consumer availability)	Drug status designation required (Consumer availability)	IP regulation allows procurement of drugs to target area (Consumer availability)	Cluster 3: Ability to influence nature of drug that is developed	Incentive encourage R&D of a drug/intervention	Encourage R&D of a drug/intervention (Incentive ability)	Provide drug (Enabler goal)	R&D of drug (Innovator goal)	Incentives stimulates multi-purpose drug R&D	Multi-purpose drug (Enable goal)	R&D of multi-purpose drug (Innovator goal)	Incentive allows the delivery of regime treatment	Deliver regime treatment (Innovator goal)	Deliver regime treatment (Enabler goal)	Payoff to innovators based on cost-effectiveness	Contextual treatment criteria can be addressed by incentive (Consumer requirement)	Incentive allows drug repurposing (Innovator goal)	Cluster 4: Improved governance	Promote equitable health-focused governance (Incentive ability)	Promote transparency and accountability (Incentive ability)	Advances the priority of disease on health agenda (Incentive ability)	Advance proper functioning of domestic policy (Incentive ability)
	7	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	1	0	0	2	0	0	0	0	0	0	8	2	1	1	2	1	1	1	1	0	1	2	2	0	5	2	2	0	1
Push mechanisms																																															
Grant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	1	1	0
Open-source initiative		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1		0	0	0	0	1		0	0	0	0	0	0	0	0	0	0	0	1	1		1	1	1	1
Patent pool		1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0		0	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	1	0		1	1	0	0
PPP		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1		1	1	0	1	1		1	1	1	1	1	1	1	1	1	0	1	1	0		1	1	1	1
Tax credits		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	0	1		0	0	0	1	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	1	1	0
Outcome-based pull strategies																																															
Advanced market commitments (AMC)		1	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	1	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	0	1	0
Differential pricing		1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	0	1	0		0	0	1	0
Patent buy-outs		0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0		1	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	0	0		0	0	1	0
Pooled fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	1	1	0
Prize fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	1	1	0
Rating system		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	1	1	0		1	1	1	1	1	1	1	1	1	0	1	0	0		1	1	1	1
Lego-regulatory pull strategies																																															
Intellectual property		0	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0		0	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	0	0		0	0	1	0
Policy instrument		0	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	1	1		1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	1	0		1	1	0	1
PRV		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1		1	1	0	0	0		1	1	1	1	1	1	1	1	1	0	1	0	0		0	0	1	0
Trade, tariff adjustments		0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0		1	1	1	1	1		1	1	1	1	1	1	1	1	1	0	0	0	0		1	0	1	1
Hybrid strategies																																															
Collaboration network and consortiums		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		1	1	1	0
Colloquium and symposium		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	1	0		0	1	1	1
Policy and legislation		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1		1	1	0	1	1		0	0	0	0	0	0	0	0	1	0	0	1	1		1	1	0	1
Drug status designation		1	1	1	1	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	0	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	0	1	1	0		0	0	1	0
Joint venture		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	0	1		0	0	1	0	1		1	1	1	1	1	1	1	1	1	0	1	1	0		0	1	1	0
Independent organization		1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		1	1	1	0
Hybrid between PPP and other mechanisms		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	0	1	1	0		1	1	1	1
Research laboratories		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1		0	0	0	0	0		1	1	1	1	1	1	1	1	1	0	0	1	0		0	1	1	0
Treaty		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1		1	1	0	1	1		1	1	1	1	1	1	1	1	1	0	0	1	0		1	1	1	1
Working group		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	0	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	0	1	0
Coordination mechanism		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1		0	0	1	0	0		1	1	1	1	1	1	1	1	1	0	1	1	0		0	1	1	0

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 5: Population impact and access	Incentive improves consumer access	Improve consumer access (Incentive ability)	Play a role in improved access (Enabler goal)	Play a role in improved access (Innovator goal)	Incentive enables mass drug administration	Enable mass drug administration (Incentive ability)	Implement mass drug administrations (Enabler goal)	Incentive aims to reduce burden of disease in area	Incentive aims to minimize disruptive effects to	Incentive allows for differential pricing (Consumer	Incentive allows differential pricing (End-consumer	Incentive allows differential pricing (Procurer requirement)	Deliver affordable and accessible treatment (Enabler goal)	Incentive eliminates all financial risk (Consumer	Cluster 6: Limited enabler resource investment	Affordable to implement the incentive	Incentive allows resources to develop drugs to be	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be in the beginning,	Incentive allows payoff to innovator to be in the beginning,	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be at the end, once-	Incentive allows payoff to innovator to be at the end, once-	Incentive allows payoff to innovator to be incrementally,	Incentive allows payoff to innovator to be incrementally,	Incentive allows payoff to innovator to be incrementally,	Incentive does not require enabler funding (Enabler no	Incentive does not require enabler funding (Enabler has no	Innovator does not require any funding from enabler, or	Incentive requires/allows the enabler to partially fund	Incentive requires/allows the enabler to partially fund R&D	Incentive requires/ allows innovator to partially fund R&D	Incentive payout to innovator is a once-off occasion	Incentive payout to innovator occurs once output is	Incentive allows innovator payouts to be limited to a	Incentive allows innovator payouts to be milestone	Incentive allows enabler to engage with innovator at given	Incentive allows enabler funding to be limited to an	Cluster 7: Encourage competition in the innovation	Incentive encourages large firm participation	Incentive encourages large firm participation	Incentive allows large pharmaceutical organization	Incentive aimed at incentivising large pharmaceutical	Incentive allows competition among parallel experiments	Incentive enlarges the number of clinical trials registered	Incentive targets all organizations to participate (Enabler
	8	2	2	0	2	1	1	0	1	2	0	0	0	0	2	11	2	0	0	0	0	2	2	2	0	0	0	0	0	0	2	2	2	2	0	0	1	0	2	6	2	2	1	2	2	0	2
Push mechanisms																																														
Grant		1	1	1	1	1	1	1	1	0	0	0	0	0	0		1	1	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	1	0	1	1	0	1		0	0	0	0	0	0	0
Open-source initiative		0	0	0	0	0	0	0	1	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0		1	1	1	1	0	1	0
Patent pool		1	1	1	1	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0	1	1	0		1	1	1	1	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1		1	1	1	1	0	1	1
Tax credits		0	0	0	0	1	1	1	1	0	0	0	0	0	0		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	1	0		1	1	1	1	0	0	0
Outcome-based pull strategies		0				0					0								0			0			0			0			0											0						
Advanced market commitments (AMC)		1	1	1	1	1	1	1	1	1	0	0	0	0	0		1	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0		1	1	1	1	0	0	1
Differential pricing		1	1	1	1	1	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	0	0	0		1	1	1	1	0	0	1
Patent buy-outs		0	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	1	0	0	1	0	0		1	1	1	1	0	0	1
Pooled fund		1	1	1	1	1	1	1	1	0	0	0	0	0	0		1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	1
Prize fund		1	1	1	1	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	0	1	1		0	0	0	0	1	1	1
Rating system		1	1	1	1	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1	0	1	0	1		1	1	1	1	1	0	1
Lego-regulatory pull strategies		0				0					0								0			0			0			0			0											0						
Intellectual property		0	0	0	0	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	0	0		1	1	1	1	1	0	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1		1	1	1	1	0	1	1
PRV		0	0	0	0	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	1	1	0		1	1	1	1	1	0	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	1		1	1	1	1	0	0	1
Hybrid strategies		0				0					0								0			0			0			0			0											0						
Collaboration network and consortiums		1	1	1	1	1	1	1	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	0	1	0	1		1	1	1	1	0	0	1
Colloquium and symposium		0	0	0	0	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	0	0	1	0		1	1	1	1	0	0	1
Policy and legislation		1	1	1	1	1	1	1	1	1	0	0	0	1	0		0	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1		1	1	1	1	0	1	1
Drug status designation		1	1	1	1	1	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1		1	1	1	1	1	0	1
Joint venture		1	1	1	1	1	1	1	1	0	0	0	0	0	1		1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1		1	1	1	1	0	1	0
Independent organization		1	1	1	1	0	0	0	1	0	0	0	0	0	1		0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	0	1	1	0	1		1	1	1	1	0	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	1	1	1	1	1	0		1	1	1	1	0	1	0
Research laboratories		0	0	0	0	0	0	0	1	1	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0		0	0	0	0	0	1	0
Treaty		1	1	1	1	1	1	1	1	1	1	1	1	1	0		1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	1	1	1	0	1		0	0	0	0	0	1	0
Working group		1	1	1	1	1	1	1	1	0	0	0	0	1	0		1	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0		0	0	0	0	0	0	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0	1	0	1	1	0	1		1	1	1	1	0	1	1

Background Logic 5: Prize fund (combined)

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 8: Overcome barriers to innovator participation in R&D process	**Incentive allows small and medium organizations to be incentivized**	Incentive enables participation of small and medium organizations	Incentive enables participation of small and medium organizations (Enabler target)	Incentive enables participation of small and medium organizations (Innovator identity)	**Incentive allows governmental institutions to be incentivized**	Incentive allows governmental institutions to be incentivized (Enabler target)	Incentive allows governmental institutions to be incentivized (Innovator identity)	**Incentive allows independent scientists to be incentivized**	Incentive allows independent scientists to be incentivized (Enabler target)	Incentive allows independent scientists to be incentivized (Innovator identity)	**Incentive allows academic institutions to be incentivized**	Incentive allows academic institutions to be incentivized (Enabler target)	Incentive allows academic institutions to be incentivized (Innovator identity)	**Incentive allows NGO organizations to be incentivized**	Incentive allows NGO organizations to be incentivized (Enabler target)	Incentive allows NGO organizations to be incentivized (Innovator identity)	**Incentive financing is timed across drug lifecycle**	**Incentive provides long term R&D financing**	**Incentive provides sustainable financing for innovator**	**Incentive provides R&D project insurance**	Incentive provides R&D project insurance	Incentive provides risk insurance or security (Innovator requirement)	**Incentive de-risks the R&D process**	**Incentive requires/allows enabler to fund R&D**	Incentive allows enabler to fund R&D (Enabler goal)	Incentive requires enabler to fund all R&D costs (Innovator requirement)	**Incentive allows enabler to fully fund R&D (Enabler full capacity)**	Incentive allows enabler to fully fund R&D (Enabler full capacity)	Incentive requires enabler to completely fund R&D (Innovator no ability)	**Incentive requires enabler to partially fund R&D (Innovator ability)**	Incentive requires enabler to partially fund R&D (Innovator requirement)	Incentive requires enabler to partially fund R&D (Innovator ability)	**Incentive allows funding to be incremental, as innovator requires**	Incentive allows funding to be incremental, as innovator requires (Enabler ability)	Incentive allows funding to be incremental, as innovator requires (Innovator requirement)	**Incentive allows funding to be incremental, based on timing**	Incentive allows funding to be incremental, based on timing (Enabler ability)	Incentive allows funding to be incremental, based on timing (Innovator requirement)	**Incentive does not provide any funding (Innovator has full capacity to provide own funding)**	**Incentive allows enabler to increase bandwidth and network (Enabler goal)**	**Incentive utilizes enabler's ability to influence intellectual property (Enabler ability)**	**Incentive requires/ utilizes enabler's access to key data**	Incentive utilizes enabler's access to key data (Enabler ability)	Incentive provides innovator with information (knowledge) on disease (Innovator requirement)	**Incentive utilizes enabler's access to compounds (Enabler ability)**	**Incentive requires/ utilizes enabler technology expertise and access**	Incentive requires/ utilizes enabler technology expertise and access	Incentive provides innovator access to adequate equiptment (Innovator requirement)	Incentive provides innovator with access to research laboratory (innovator requirement)	**Incentive requires/ utilizes enablers R&D expertise**	Incentive requires/ utilizes enablers R&D expertise	Incentive aids innovator with cumbersome nature of clinical trial regulations (innovator requirement)	**Incentive addresses innovator's policy or regulatory limitations (innovator requirement)**	**Incentive provides innovator with market certainty (innovator requirement)**	**Innovator does not adhere to any authorization standards (innovator nature)**	**Innovator has accredited authorisation organization (innovator nature)**	**Incentive rewards innovation**
			1	2	3		2	3		2	3		2	3		2	3	1	1	1		1	2	2		2	3		2	3		3	3		2	3		2	3	3	2	2		2	3	2		2	3	3		2	3	3	3	3	3	1
	31	2	2	2	2	2	1	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	0	0	2	2	0	2	0	2	2	2	2	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	2	2
Push mechanisms																																																										
Grant		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Open-source initiative		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	1	0
Patent pool		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0
Tax credits		1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Outcome-based pull strategies		0				0			0			0			0						0				0			0			0			0			0						0				0				0							
Advanced market commitments (AMC)		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1
Differential pricing		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Patent buy-outs		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1
Pooled fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Prize fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1
Rating system		1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Lego-regulatory pull strategies		0				0			0			0			0						0				0			0			0			0			0						0				0				0							
Intellectual property		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
PRV		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1
Hybrid strategies		0				0			0			0			0						0				0			0			0			0			0						0				0				0							
Collaboration network and consortiums		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Colloquium and symposium		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	1	1	1	0	0	1	1	0
Policy and legislation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
Drug status designation		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Joint venture		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Independent organization		1	1	1	1	0	0	0	0	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	1	0	1	0	0	0	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Research laboratories		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	0
Treaty		0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0	1	1	0
Working group		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0

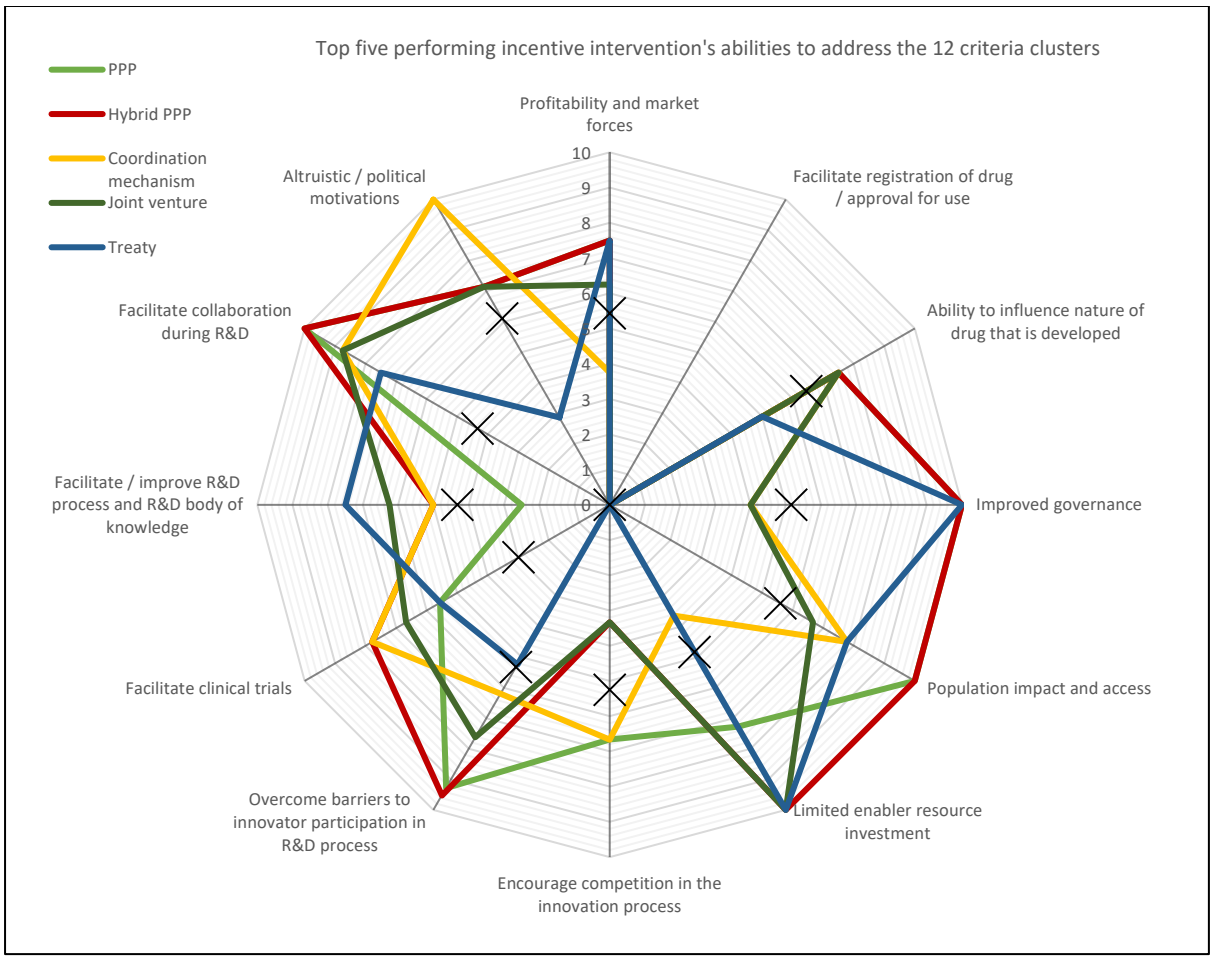
Background Logic 5: Prize fund (combined)

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING		1	1	1	1	1	1	1	2			1	1	1	1	1	1	2	2	2			1	2	2		2	3		1	3		2	3		2		2	3	3		4	4
	Cluster 9: Facilitate clinical trials	**Incentive allows provision of public subsidies for clinical trials**	**Incentive reduces clinical trial risk involved**	**Incentive assist in registration and monitor of trials**	**Incentive globalizes clinical trial methods**	**Incentive reduces clinical trial activation difficulty**	**Incentive enhances or prompt the quality of clinical trials**	**Incentive aids in clinical trial regulation**	**Clinical trial regulation policies (Enablers ability to influence)**		**Cluster 10: Facilitate / improve R&D process and R&D body of knowledge**	**Incentive aims to/ allows improvement of R&D productivity**	**Incentive provides regulatory oversight to promote R&D**	**Incentive provides regulatory exclusivity provisions for R&D**	**Incentive encourages efficient innovation**	**Incentive ensures the conservation of resources in R&D process**	**Incentive requires/ allows green R&D of drugs**	**Incentive enables organizations to innovate easier (Enabler goal)**	**Incentive advances the R&D field & body of knowledge (Enabler goal)**	**Incentive can improve the state of the R&D pipeline (Enabler goal)**		**Cluster 11: Facilitate collaboration during R&D**	**Incentive facilitates cooperation and synergy between all stakeholders**	Facilitates cooperation and synergy between all stakeholders	Incentive facilitates collaboration between innovators (Enabler goal)	**Incentive allows enabler to collaborate and build a partnership/s (Enabler goal)**	**Incentive allows enabler to collaborate with innovator**	Incentive allows enabler to collaborate with innovator (Enabler goal)	Incentive allows innovator to collaborate with enabler (Innovator requirement)	**Incentive provides a platform for coordinating innovators**	Incentive provides a platform for coordinating innovators	Incentive provides a collaboration platform (Innovator requirement)	**Incentive allows/ requires enabler to facilitate in regulatory process**	Incentive allows/ requires enabler to facilitate in regulatory process (Enabler goal)	Incentive allows/ requires enabler to facilitate innovator in regulatory process (Innovator requirement)	**Incentive requires enabler to adjust policies and regulations**	Enabler has ability to adjust policies and regulations	Innovator requires enabler to adjust policies and regulations (should be allowed by incentive)		**Cluster 12: Altruistic / political motivations**	**Incentive convey an important message (Enabler goal)**	**Incentive allows corporate social responsibility to be fulfilled**	Incentive allows corporate social responsibility (Enabler goal)	Incentive allows innovator to fulfil corporate social responsibility (Innovator goal)	**Incentive allows enabler to fulfil political obligations**	Incentive allows enabler to fulfil political obligations (Enabler goal)	Incentive allows innovator to fulfil political obligations (Innovator goal)	**Incentive allows not for profit R&D (Innovator goal)**	**Incentive allows not for profit/ restricted profit margins for drug procurers**	Incentive enables/ allows restricted profit margins for drug procurers	Incentive enables no profit margins for drug procurers
	9	2	2	1	0	1	2	1	0		16	0	2	2	2	2	2	2	2	2		4	2	2	0	0	0	0	0	2	2	0	0	0	0	0		7	2	1	1	0	0	0	0	2	2	0	2
Push mechanisms																																													
Grant		0	0	0	0	1	0	0	0			0	1	0	0	0	0	0	1	1			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	0	0	0
Open-source initiative		0	1	1	1	0	0	0	0			1	0	0	0	0	0	0	1	1			1	1	1	0	0	0	0	1	1	1	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1
Patent pool		0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	1			0	0	0	0	0	0	0	1	1	1	1	1	0	0	0			0	1	1	1	1	0	0	0	1	0
PPP		1	0	1	1	1	0	1	1			0	0	0	0	0	0	0	1	1			1	1	1	1	1	1	1	1	1	1	0	0	1	1	1			1	1	1	1	1	1	1	0	1	0
Tax credits		1	0	0	0	0	0	0	1			0	1	1	0	0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	0	0	0	1	1			0	0	0	0	0	0	0	0	1	0
Outcome-based pull strategies																							0				0			0			0			0				0				0					
Advanced market commitments (AMC)		0	0	0	0	0	0	0	0			0	0	0	1	1	0	0	0	1			0	0	0	1	0	0	0	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	0	1	0
Differential pricing		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	0	0	0	1	1			1	1	1	1	1	1	1	0	1	0
Patent buy-outs		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	1	0
Pooled fund		0	1	0	0	0	0	0	0			0	0	0	1	1	0	1	0	1			1	1	1	0	1	0	0	0	1	1	0	0	0	0	0			0	1	1	1	1	1	0	0	0	0
Prize fund		0	0	0	1	0	1	0	0			0	0	0	1	1	0	1	1	1			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	1	1	1	1	0	0	1	0	0
Rating system		0	0	0	0	0	1	0	0			1	1	1	1	1	1	0	1	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1
Lego-regulatory pull strategies																							0				0			0			0			0				0				0					
Intellectual property		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	1	0
Policy instrument		0	0	1	1	0	1	1	1			0	1	0	1	1	1	0	1	0			0	0	0	1	0	0	0	0	0	0	1	1	1	1	1			0	1	1	1	1	1	1	1	1	1
PRV		0	0	0	0	1	0	1	1			0	0	1	0	0	0	0	1	1			0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0			1	0	0	0	0	0	1	0	1	0
Trade, tariff adjustments		0	0	0	0	0	0	0	0			0	0	1	0	0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	0	0	1	1	1			0	1	1	1	1	1	1	1	1	1
Hybrid strategies																							0				0			0			0			0				0				0					
Collaboration network and consortiums		0	1	1	1	0	1	1	0			1	0	0	1	1	0	1	1	1			1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1
Colloquium and symposium		0	0	0	1	0	1	0	0			1	1	0	1	0	0	1	1	0			1	1	1	1	1	1	1	1	1	1	1	1	0	0	0			1	1	1	1	0	0	0	1	1	1
Policy and legislation		1	0	1	1	1	1	0	1			0	1	0	1	0	1	0	0	0			0	0	0	1	0	0	0	0	0	0	1	1	1	1	1	1			0	1	1	1	1	1	1	1	1	1
Drug status designation		0	0	0	0	0	0	0	1			0	0	1	0	0	0	0	1	1			0	0	0	0	0	0	0	0	0	0	0	0	1	1	1			1	1	1	1	0	0	0	1	1	0
Joint venture		0	1	0	1	1	1	1	0			0	0	0	1	1	0	1	1	1			1	1	1	1	1	1	1	1	1	1	1	1	0	0	0			0	1	1	1	1	1	1	1	1	1
Independent organization		0	0	0	0	0	1	0	0			0	0	0	0	0	0	0	1	0			1	1	1	1	1	1	1	1	1	1	1	1	1	1	0			0	1	1	1	0	0	0	1	1	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	0	1	1			0	1	0	0	0	0	1	1	1			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			0	1	1	1	1	1	1	1	1	1
Research laboratories		0	0	1	1	1	1	1	0			0	0	0	1	1	1	1	1	1			1	1	1	1	1	1	1	0	0	0	0	0	0	0	0			0	1	1	1	1	1	1	0	1	0
Treaty		1	0	0	1	0	1	1	1			0	1	0	1	1	1	1	0	1			1	1	1	1	0	0	0	1	1	1	1	1	1	1	1			0	0	0	0	1	1	1	0	1	1
Working group		0	0	0	1	1	0	0	0			0	0	0	0	0	0	1	1	1			1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1
Coordination mechanism		0	1	1	1	1	1	1	0			0	0	0	1	1	1	1	0	0			1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0			1	1	1	1	1	1	1	1	1	1

Domain 5 solution set (1 of 2): Prize fund results (combined)

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													9	Feasible
22	Hybrid PPP													9	Feasible
26	Coordination mechanism													8	Feasible
20	Joint venture													7	Feasible
24	Treaty													7	Feasible
10	Prize fund													6	Feasible
21	Independent organization													5	Feasible
9	Pooled fund													4	Feasible
1	Grant													3	Feasible
8	Patent buy-outs													3	Feasible
16	Collaboration network													8	Infeasible
11	Rating system													6	Infeasible
19	Drug status designation													6	Infeasible
13	Policy instrument													5	Infeasible
25	Working group													5	Infeasible
18	Policy and legislation													5	Infeasible
6	Advanced market commitments													4	Infeasible
2	Open source initiative													4	Infeasible
17	Colloquium and symposium													4	Infeasible
14	PRV													4	Infeasible
7	Differential pricing													4	Infeasible
12	Intellectual property													3	Infeasible
15	Trade, tariff adjustments													3	Infeasible
23	Research laboratories													3	Infeasible
3	Patent pool													2	Infeasible
5	Tax credits													2	Infeasible

Domain 5 solution set (2 of 2): Prize fund results (combined)



Non-incentive-based interventions (1 of 8): Prize fund results (combined)

1. Country economic status		*For further reference*	
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)	1
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

2. Burden fully characterized		*For further reference*	
Meaning	The affected patients are diagnosed, being monitored and documented properly.	(Olmsted et al., 2006; RAND Corporation, 2007; Novak et al., 2013)	1
Relevance	Once the burden of a disease is fully characterized, consumer demand can be estimated. Consumer demand will have an influence on how profitable the perceived market is. Fully characterizing the burden also assists in the planning, distribution and implementation of control strategies.		
Intervention considerations	Diagnostic tools and technology, availability and access there of		
	Diagnostic intervention and intervention strategies		
	Availability of health facilities (option is to consider mobile health facilities)		
	Educate populations on disease side-effects, risks, and necessity of health interventions		
	Capture burden characterization data		

3. Physicians per 1000 population		*For further reference*	
Meaning	The number of physicians available per capita / 1000 of people	(Al-Shamsi, 2017)	1
Relevance	The higher the availability of physicians in a country, the higher the likelihood that the population will have access to adequate care.		
Intervention considerations	Recruit international medical graduates		
	Modify postgraduate majors to allow physicians to enter the practice in areas of need		
	Shorten the preparatory under-graduate medical education years and introduce modern methods of teaching.		

4. Quality of existing drugs		*For further reference*	
Meaning	Drugs should not pose significant health risks to patients and should be effective in treating the disease.	(van Olmen et al., 2010); (Dorlo et al., 2012); (Rauscher, Walkowiak and Djara, 2018); (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	1
Relevance	Patients depend on drugs for disease mitigation. If quality is not up-to-standard, then disease burden might increase or might not decrease.		
Intervention considerations	Repeat final clinical trial stages to monitor effects of medicine in a controlled environment		
	Remove drugs from market		
	Improve monitoring of ADR		
	Pharmacovigilance		
	Quality control of current manufacturing procedures		
	Enforce international clinical trial and manufacturing practices and regulations		

5. Availability of drugs for the desired population		*For further reference*	
Meaning	Drugs are available in the right quantities, on the right time for patients to access.	(Jackson, 2018) ; (Niëns and Brouwer, 2013), (Holt, Gillam and Ngondi, 2012)	1
Relevance	If drugs are adequate but not available, then patients might not be effectively treated. Possible resistance to medicines.		
Intervention considerations	Supply chain management		
	Distribution networks		
	Inventory management at health facilities		
	Replenishment systems at health facilities		
	Burden characterization assists in inventory planning		

Non-incentive-based interventions (2 of 8): Prize fund results (combined)

6. Affordability of current drugs to desired population		*For further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	2
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

7. Appropriateness of drugs to the desired population		*For further reference*	
Meaning	Drugs must target the disease intended for. Intervention must be understandably explained and not interfere with culture.	(Jackson, 2018), (Hotez, 2008)	1
Relevance	If drugs are not appropriate, then patients won't use it or, if they use it, improvements in disease burden will not be made.		
Intervention considerations	Screen culture and explore possible cultural and ethical issues		
	Improve diagnostics of patients		
	Communication in understandable language for population group		
	Survey to understand the feelings of patients		

8. Acceptability of drugs to the desired population		*For further reference*	
Meaning	Drugs are not acceptable because of cultural values norms or stigmas.	(Jackson, 2018) ; (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	1
Relevance	If patients do not accept drugs, then intervention strategies go to waste.		
Intervention considerations	Educate people to reduce stigmas.		
	Educate people to understand potential of drugs.		
	Respect and honour the norms and values of the patient group.		

9. Comprehensiveness of services delivered		*For further reference*	
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004), (WHO, 2010)	1
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.		
Intervention considerations	Education of prevention measures.		
	Address root-cause of disease (e.g. water and sanitation)		
	Investigate the needs of the affected population group		
	Address social needs of patients		
	Repeat prevention or mass drug administration interventions, if deemed necessary.		

10 Continuity of patients' access to health services [Check in Case study 1 Appendix]		*For further reference*	
Meaning	For health interventions where once-off treatment is not adequate, follow-up treatments must be scheduled and adhered to.	(Jackson, 2018, (Holt, Gillam and Ngondi, 2012, Stevens, 2004)	1
Relevance	If follow-up treatments are not provided, then patient health might not improve as desired.		
Intervention considerations	Scheduling of follow-up interventions		
	Mobile health facilities		
	Track patient health records and data		
	Monitor and track patients		

11. Coordination of service delivery networks		*For further reference*	
Meaning	Service delivery is done in an organized, timely, professional and appropriate manner.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; WHO, 2010a; Rauscher et al., 2018)	1
Relevance	If service delivery is not coordinated properly, then some patients might be overlooked for treatment, not have access, or might miss the opportunity to meet with health care workers (if not properly communicated)		
Intervention considerations	Communication services		
	Scheduling of health workers		
	Monitor service delivery per area		
	Monitor drug distribution or mass drug administrations per region.		

Non-incentive-based interventions (3 of 8): Prize fund results (combined)

12. Minimize waste of resources in service delivery		*For further reference*	
Meaning	Any resource that is not used or used in an effective or efficient manner, leads to waste and possible financial losses.	(Priya, Nandini and Selvamani, 2012)	2
Relevance	Given that most waste is preventable, resources could be used in a more effective manner.		
Intervention considerations	Monitor service delivery to identify and address waste.		
	Coordinate service delivery actions		
	Waste management		

13. Demand size or sales force (relates to disease burden)		*For further reference*	
Meaning	The size of the burdened population, and patients who needs medicines, or intervention strategies.	(Novak et al., 2013; RAND Corporation, 2007)	0
Relevance	By determining the size of the burdened population, service delivery and intervention strategies can be planned more accurately. Also, service delivery waste can be reduced.		
Intervention considerations	Characterization of the burden of disease		
	Diagnostic interventions		
	Target repurposing		
	The size of the burdened population, and patients who needs medicines, or intervention strategies.		

14. The role of brand loyalty		*For further reference*	
Meaning	Brand loyalty of consumers to certain brands / drugs means that consumers buy certain drugs, based on previous experience, or perceived value. (relevant to other brands).	(Griffiths, 2008; Panchal *et al.*, 2012)	1
Relevance	If a product does not have brand loyalty, it might have the necessary characteristics to mitigate disease, but patients are not using it as a result of not 'trusting' the drug.		
Intervention considerations	Awareness amongst physicians of the value of the drug		
	Build trust in the communities		
	Well planned market strategies		

15. Bargaining power of the suppliers (chemical entities)		*For further reference*	
Meaning	The ability of suppliers to influence the prizing of the entities that they offer the pharmaceutical innovators and manufacturers.	(Whiteside, 2016)	1
Relevance	The stronger the bargaining power of the suppliers; the higher the prizes of resources, and the higher the total cost of drug interventions.		
Intervention considerations	Research alternative suppliers.		
	Support local suppliers.		
	Consider importing of goods.		
	Ensure quality of suppliers, if weak bargaining power.		

16. Existence of competitors		*For further reference*	
Meaning	Competitors refer to other pharmaceutical innovators completing R&D in the same field, thus, targeting the same disease.	(Thakor and Lo, 2018; (Whiteside, 2016)	1
Relevance	Strong competition exists because of intellectual property rights that are gained for new chemical entities innovated.		
Intervention considerations	Explore and compare for similar drugs being marketed as different products.		
	Competition is not always a bad thing (speeds up discovery)		
	Collaboration and open innovation		

17. Political will and contribution to improve R&D for disease		*For further reference*	
Meaning	The effort and contribution that the government of a country is willing to make towards R&D of diseases.	(Brinkerhoff, 2003; (Emmanuel and Emmanuel, 1996; World Health Organization, 2018)	1
Relevance	Governments should be obligated to make significant efforts to reduce disease burden within a country		
Intervention considerations	Enforce SDGs		
	Ministry of Health audit		
	Policy reform		
	Political accountability systems		

Non-incentive-based interventions (4 of 8): Prize fund results (combined)

18. Effective national budget allocation		*For further reference*	
Meaning	The financial plan of a country should include planning and financial allocations to the health and health care of citizens.	(World Health Organization, 2018; Emmanuel and Emmanuel, 1996; Becker, 2015)	1
Relevance	The health care of a country is the responsibility of its government. Without budget allocation, health care advancement is less likely.		
Intervention considerations	Implement SDGs		
	Policy reform		
	Strategic resource allocation options		
	Global health governance		

19. Regulation of strategic health policy		*For further reference*	
Meaning	The goals, visions, priorities and budgetary decisions of a country needs to be regulated, to be in line with health needs.	(Liang and Mackey, 2012; World Health Organization, 2018; Nagpal, Sinclair and Garner, 2013)	1
Relevance	If the strategic plans and actions to undertake and achieve are not taken, then the health of the country will lack improvement.		
Intervention considerations	Global health governance		
	Strategic political interventions		
	Domestic, private, and global policy interventions		

20. Adequate supply of the health service		*For further reference*	
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Jacobs et al., 2012; RAND Corporation, 2007; Manjit Kaur; Sarah Hall, 2002)	2
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

21. Monitoring of the actual health system and system performance		*For further reference*	
Meaning	The observation and measurement of health system performance.	(WHO, 2010a; International Federation *et al.*, 2015; Jones *et al.*, 2015; Newman *et al.*, 2016)	1
Relevance	By observing and measuring performance of the health system, problems can be located faster and more easily.		
Intervention considerations	Information systems and data handling		
	Pharmacovigilance		
	Reporting networks		
	Personnel training		
	Accountability networks and schedules		

22. Current investment capital and returns		*For further reference*	
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Vischer et al., 2017; Bates et al., 2015; Ho, Zarrinpar and Chow, 2016; Payne et al., 2015)	2
Relevance	This factor refers to the current ROI being profitable or not, if not then more investment in a similar research area is not likely.		
Intervention considerations	Financial analysis		
	Cost analysis of activities		
	Reduce indirect and operational costs		

23. Stakeholder demand		*For further reference*	
Meaning	Stakeholder demand refer to whether the public desires, and needs the product being developed.	(Thakor and Lo, 2018; Whiteside, 2016)	1
Relevance	The higher the demand for the products being delivered, the greater the perceived potential ROI.		
Intervention considerations	Target market analysis		
	Marketing strategies		
	Inform governments and the public that require this drug.		
	Pricing of the product		

Non-incentive-based interventions (5 of 8): Prize fund results (combined)

24. Established marketing and distribution network		*For further reference*	
Meaning	The marketing and distribution of drugs are important, to inform patients, and provide access and availability.	(Ravn, 2012; Radulescu, 2012)	1
Relevance	Distribution adds to effective service delivery; and marketing creates and enlarges the market demand.		
Intervention considerations	Marketing strategies		
	Effective distribution networks		
	Supply chain management		
	Coordination of service delivery, inventory management and distribution services		

25. Consistency and recommendations on choosing metrics for clinical trials		*For further reference*	
Meaning	Clinical trials are the most timeous procedure of drug R&D, using the correct metrics are essential in innovation productivity.	(Gupta et al., 2016; Moatti et al., 2016; Mayo et al., 2017; Clifton, Kohrt and Peoples, 2015; Zhou et al., 2015)	0
Relevance	Guidelines and regulations should be followed to advance in clinical trial phases. If not consistent then clinical trials might be trivial.		
Intervention considerations	Structured regulations and policy recommendations		
	Standardized clinical trial metrics		
	Market authorization regulation		
	Capture data of clinical trial methods and metric outputs		

26. Transparency of clinical trial information		*For further reference*	
Meaning	Clinical trial information is openly available, reliable and does not entail any suspicious information.	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	0
Relevance	Transparent clinical trial information assures that products being developed adhere to safety, efficacy and regulatory requirements.		
Intervention considerations	Annual, and unannounced firm audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

27. Accountability of clinical trial information		*For further reference*	
Meaning	Clinical trial information should be trustworthy	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	1
Relevance	There should be clear accountability for the information of clinical trials.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

28. Accessibility of clinical trial information		*For further reference*	
Meaning	The clinical trial information should be made available (within the market exclusivity agreements)	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	1
Relevance	Secrecy on critical clinical trial information not allowed, especially if it alters the safety and efficacy of the drugs.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

29. The use of innovative clinical trial tools and technology		*For further reference*	
Meaning	Advanced tools and technologies exist for performing clinical trials.	(McKinsey&Company, 2017)	0
Relevance	Modern technology and tools assist in clinical trial and drug discovery processes and might enhance the R&D process.		
Intervention considerations	Research on tools and technology available		
	Reliability of current tools and technology used in clinical trials		
	Break-even of getting new equipment, tools and technologies		
	Cost-benefit analysis of getting new equipment, tools and technologies		

Non-incentive-based interventions (6 of 8): Prize fund results (combined)

30. Struggling to prove efficacy		*For further reference*	
Meaning	The ability of pharmaceutical innovators to prove that the drug fulfils the intended result.	(PhRMA, 2016)	1
Relevance	Drugs should target the intended disease and be effective in treating the patients.	(Hay et al., 2014)	
Intervention considerations	Clinical trial information quality	(von Ranke, Fierro and Antunes, 2016) (Ho, Zarrinpar and Chow, 2016)	
	Clinical trial design		
	Tools, technology and equipment used for clinical trials		
	Adhere to international regulation standards		

31. Legal and ethical regulations for clinical trials too difficult		*For further reference*	
Meaning	Extensive laws and regulations exist for the development of drugs.	(Califf and Sugarman, 2015), (Salas, 2017), (Tsukamoto et al., 2016), (Cheng and Xie, 2017), (Tsourounis et al., 2015)	1
Relevance	A lot of difficulty is experienced in bridging legal and ethical barriers in drug R&D.		
Intervention considerations	Collaborate with bigger pharmaceutical organizations		
	Availability of third parties to adhere to regulations and laws		
	Complete annual audits		
	Ensure data transparency, accuracy and accountability		

32. Safety assessments standards		*For further reference*	
Meaning	Safety assessment standards should be adhered to, to quantify and measure risks involved in the drug being developed.	(Singh and Loke, 2012)	1
Relevance	Drugs that does not adhere to safety standards might pose a health risk to patients.	(PhRMA, 2016)	
Intervention considerations	Health authority standards and regulations	(Hay et al., 2014)	
	Clinical trial practices and designs		
	Randomized controlled trials		
	Global health governance		

33. Adaptive clinical trials occurrence		*For further reference*	
Meaning	Clinical trials that involves observing participant outcomes and adjusting drug parameters in accordance.	(Gokhale and Gokhale, 2016)	1
Relevance	Without adaptive clinical trials, important observations cannot be made; and drug safety not improved to the extent necessary.	(Baylor College of Medicine, 2009)	
Intervention considerations	Amount of participants part of adaptive clinical trials	(Hay et al., 2014)	
	Procedures of adaptive clinical trials		
	Data capturing		
	Health authority standards and regulations		

34. Recruitment and retention of participants		*For further reference*	
Meaning	Clinical trials require participants to perform drug safety and adequacy tests.	(Kurt et al., 2017) (Hammer, Eckardt and Barton-Burke, 2016) (Jennings et al., 2015), (Thacker, T., Wegele, A.R., Pirio Richardson, 2016)	1
Relevance	Effort should be done to recruit the right number of participants for clinical trial tests		
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Ensure safety of participants		
	Build trustworthy relationships with participants		

35. Racial differences in participation in clinical trial		*For further reference*	
Meaning	A variety of ethnicity groups, races and both genders' response on the drugs needs to be tested	(Kurt, Semler, et al., 2017)	1
Relevance	Given that drugs can be used by anyone, tests should be performed on various people to test for any difference in reactions or dosage requirements.	(Baylor College of Medicine, 2009)	
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Build trustworthy relationships with participants		

Non-incentive-based interventions (7 of 8): Prize fund results (combined)

36. Relationships between innovators and participants		*For further reference*	
Meaning	Innovators should strive to have a professional, and trustworthy relationship with participants	(Kurt, Semler, et al., 2017) (Tsukamoto et al., 2016) (Califf and Sugarman, 2015) (Salas, 2017)	1
Relevance	If the relationship between innovators and participants is not appropriate; then participants might not agree to complete more trials.		
Intervention considerations	Build trust with participants, by following standard clinical trial procedures		
	Adhere to safety and regulation standards		
	Monitor participants closely		
	Capture data		

37. Physician participation		*For further reference*	
Meaning	Qualified medical practitioners should be present in clinical trial tests on humans.	(Baylor College of Medicine, 2009)	1
Relevance	Qualified physicians will be able to monitor the health and wellbeing of patients in clinical trials, as well as respond if ADR occur.		
Intervention considerations	Incentivize physicians to participate		
	Provide proper training to physicians		
	Adhere to correct clinical trial procedures		

38. Skilled workforce		*For further reference*	
Meaning	Workforce, part of drug R&D process should be skilled to adequately perform tasks.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001), International Labour Office, 2010)	1
Relevance	If workforce is not skilled, preventable problems in the R&D process might arise.		
Intervention considerations	Train workforce (workshops, training programs)		
	Encourage mentorship in work environment		
	Ethical conduct		

39. Existence of manufacturing plants		*For further reference*	
Meaning	Manufacturing plants exists to perform adequate drug manufacturing.	(World Health Organization, 2016), (WHO, 2011)	1
Relevance	If no manufacturing plants exists, then producing drugs on large scale might be difficult.		
Intervention considerations	Encourage/ Incentivize SME drug manufacturers		
	Consider international manufacturing organizations		

40. Drug manufacturing adheres to regulatory requirements		*For further reference*	
Meaning	Drug manufacturing should adhere to regulatory requirements to ensure safety.	(Koeberle and Schiemenz, 2017) (Burnham et al., 2015), (Wechsler, 2015)	0
Relevance	Unregulated manufacturing practices poses potential risks to the drugs.		
Intervention considerations	Audit Manufacturing organizations		
	Global manufacturing practices		
	Comply to cGMPs (Current good manufacturing practices)		
	Unannounced visits by regulatory authorities to manufacturing facilities		

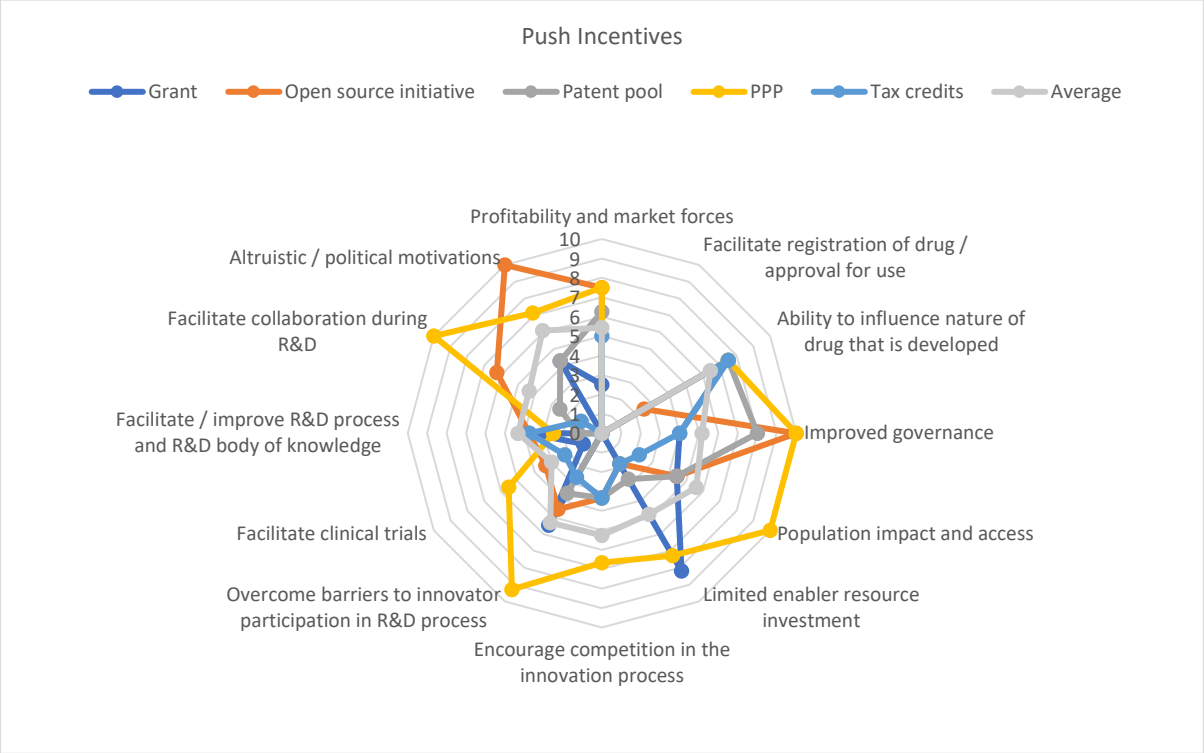
41. Appropriate technology used for the manufacturing of drugs		*For further reference*	
Meaning	A lot of technologies are available to manufacture drugs, some are advised by regulatory agencies.	(World Health Organization, 2011)	1
Relevance	Appropriate technology might improve the safety, productivity and quality of the drugs being manufactured.		
Intervention considerations	Comply to cGMPs		
	Research technology that is available		
	Complete cost-benefit analysis to ensure new technologies are strategic choices		
	Ensure compliance of all regulations and policies		

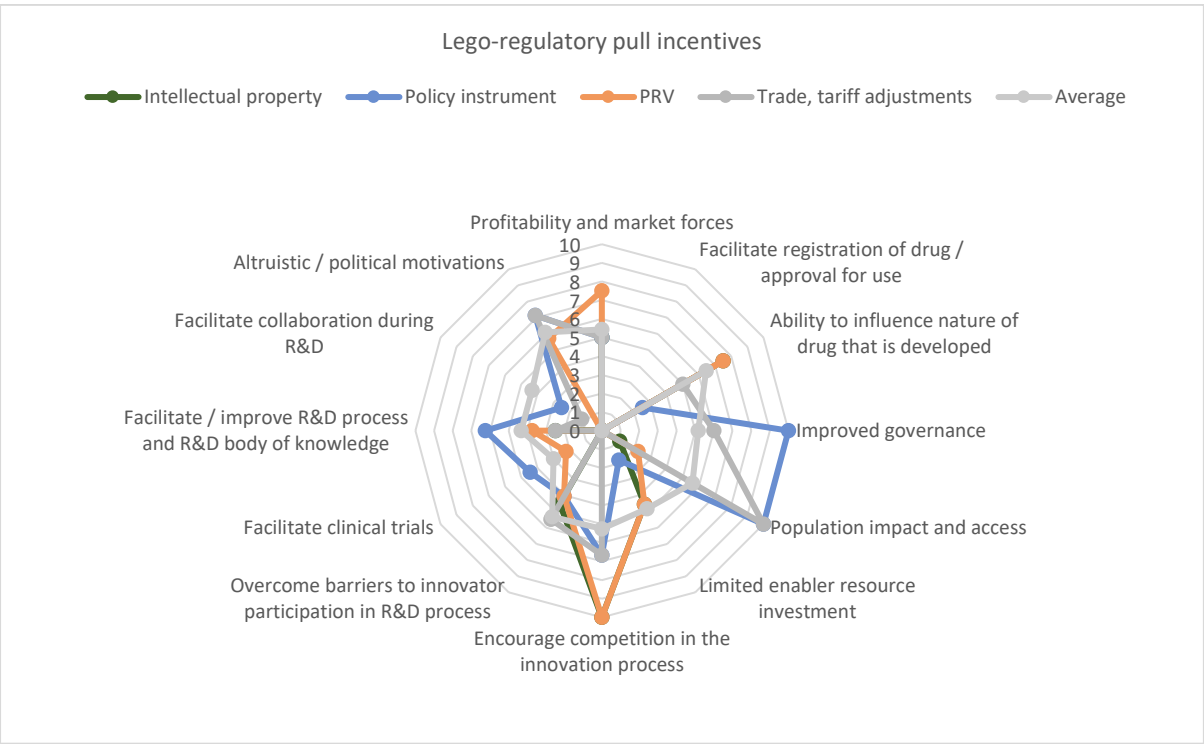
42. Health data generation		*For further reference*	
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	0
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

Non-incentive-based interventions (8 of 8): Prize fund results (combined)

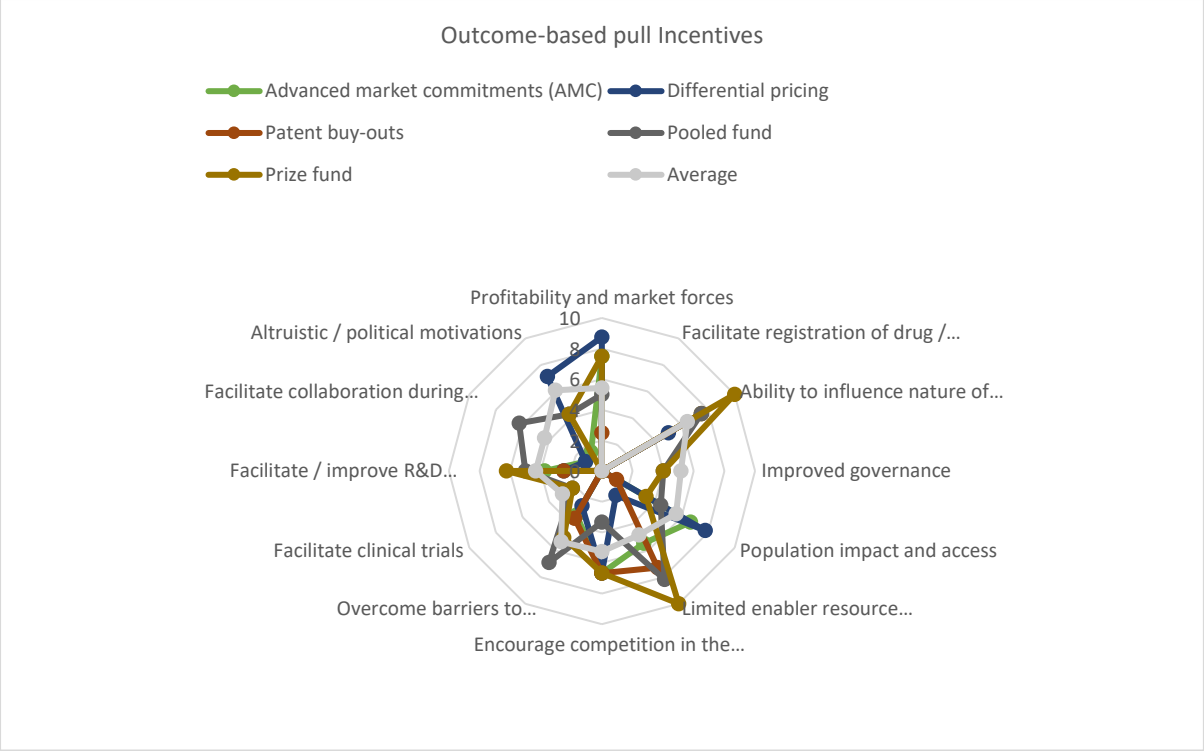
43. Communication and use of public health data		*For further reference*	
Meaning	Analysing, synthesising and validating health data	(WHO, 2010a)	1
Relevance	By evaluating health data, important measures can be implemented to satisfy growing needs, or gaps within the health system.		
Intervention considerations	Establish national sets of indicators with targets and accurate reporting which will inform health sector reviews and improve the planning of future interventions		
	Assess the health systems performance, to determine the success of current interventions		
	Adjust health system operation, based on accurate data.		
	Communicate health statistics to the public for awareness.		

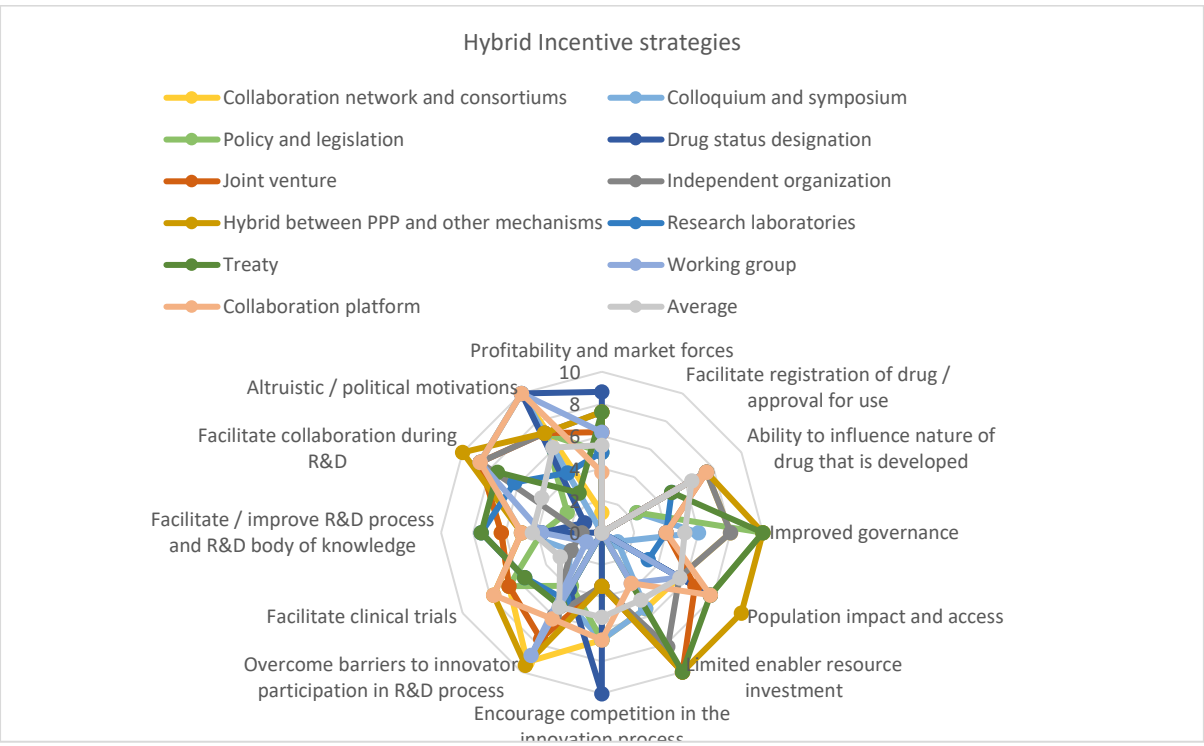
Supplementary material 1 (1 of 2): Prize fund results (combined)



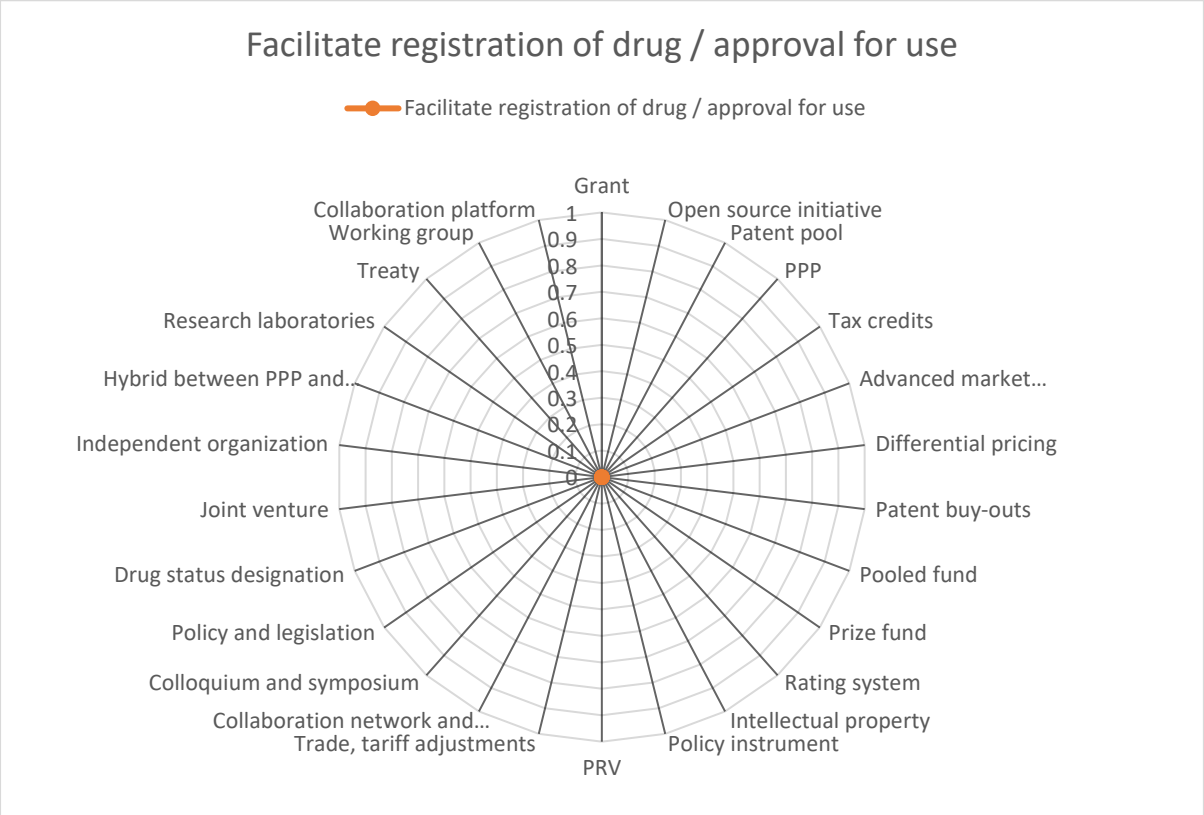


Supplementary material 1 (1 of 2): Prize fund results (combined)

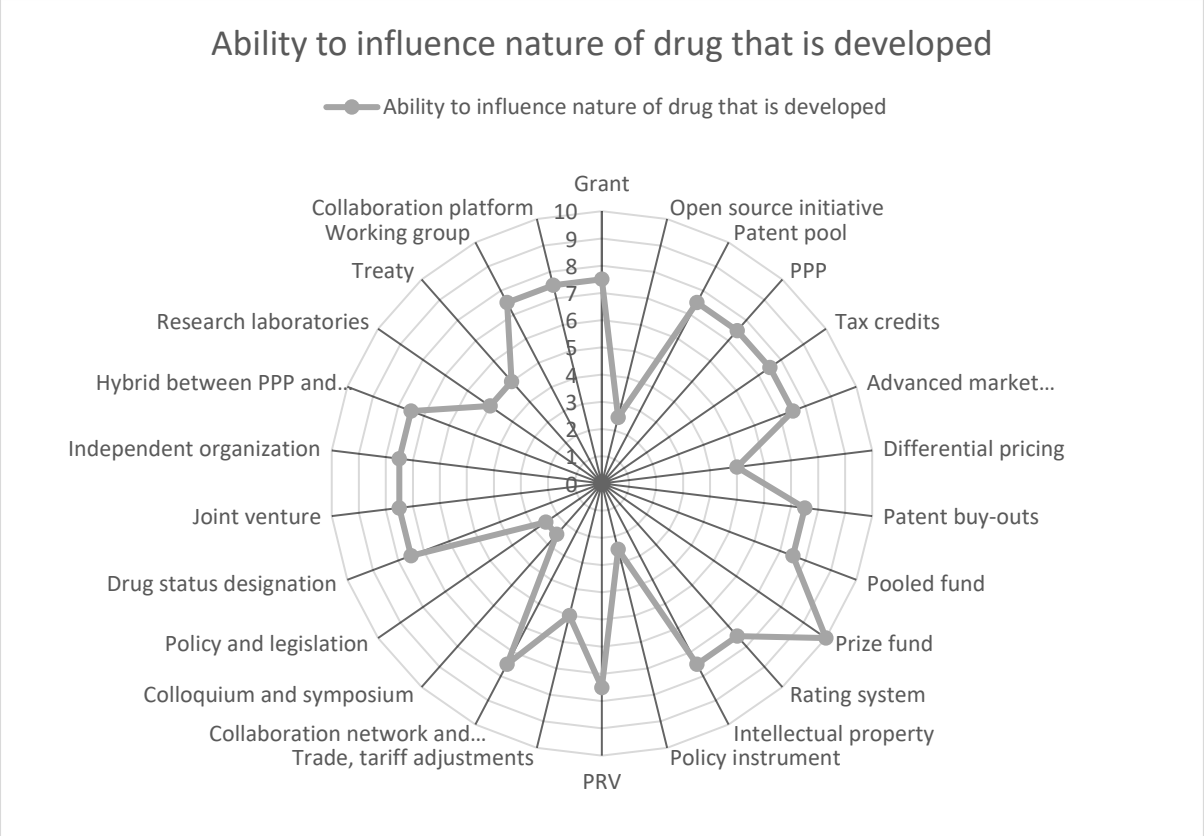


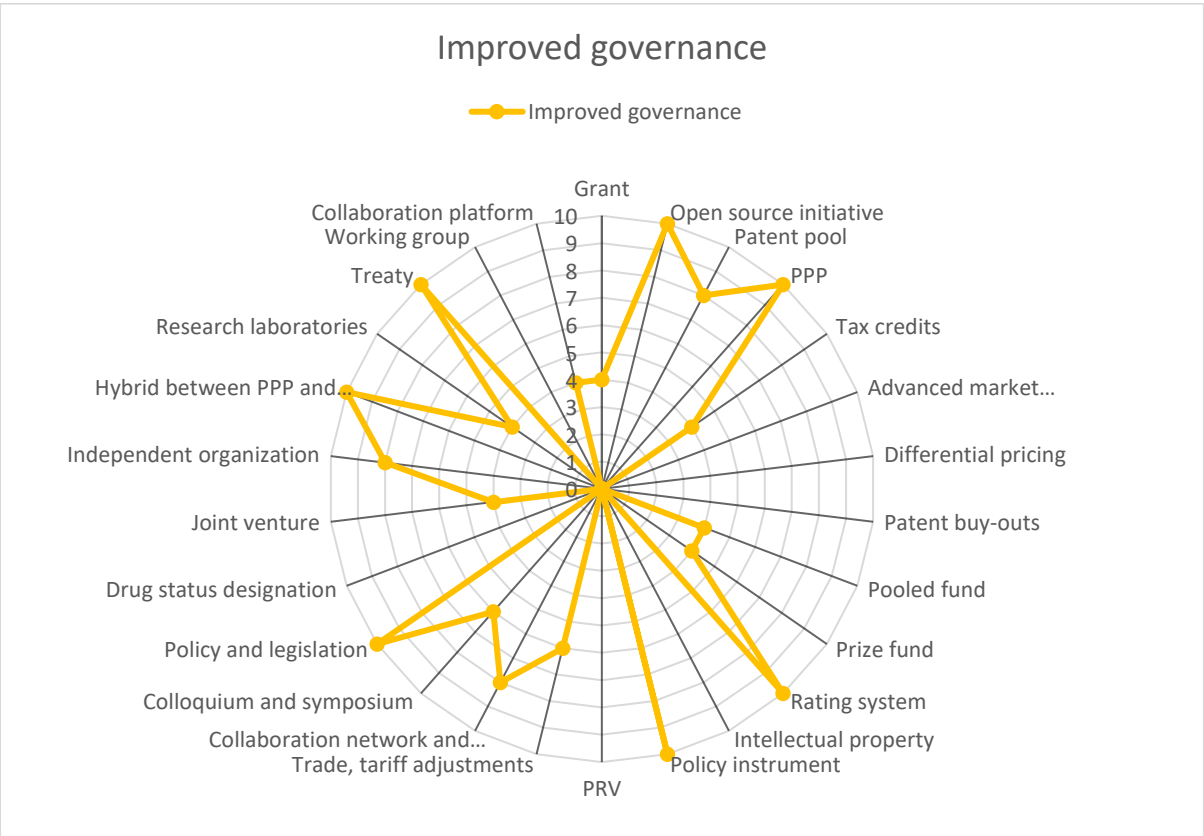


Supplementary material 2 (1 of 6): Prize fund results (combined)



Supplementary material 2 (2 of 6): Prize fund results (combined)





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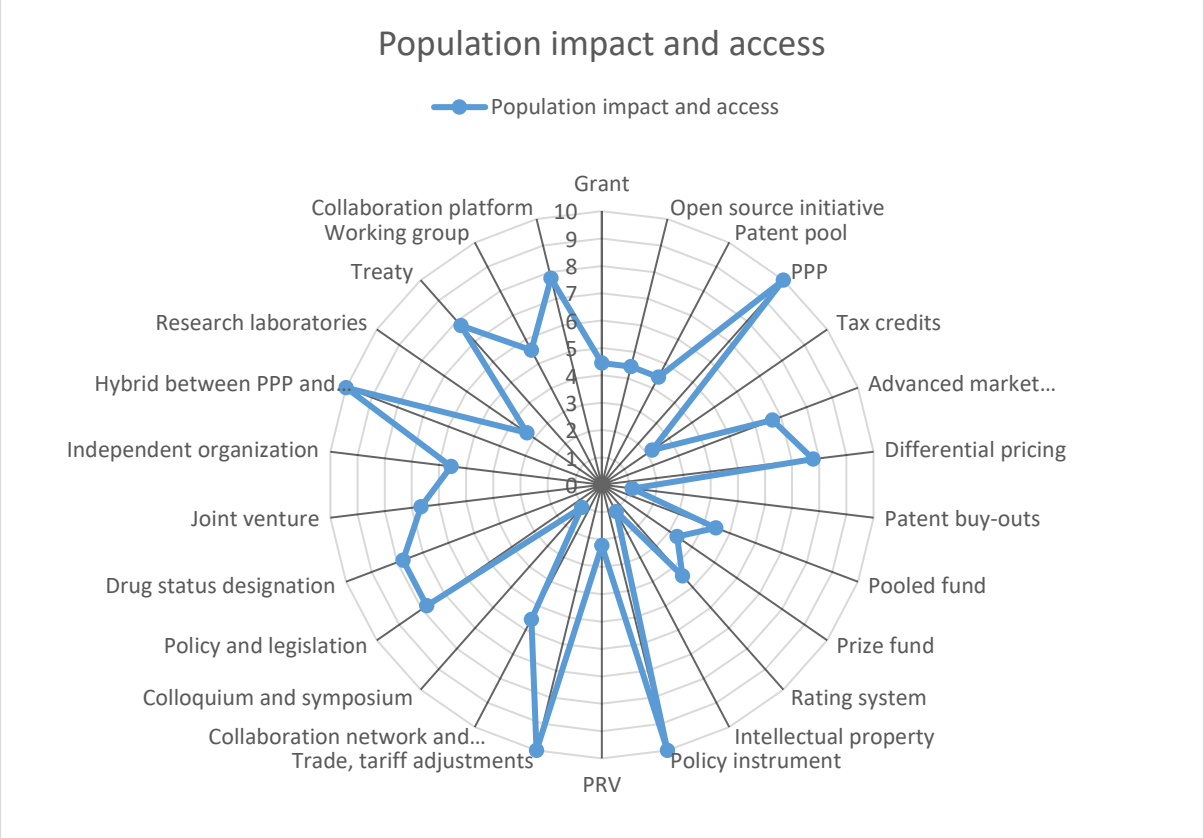
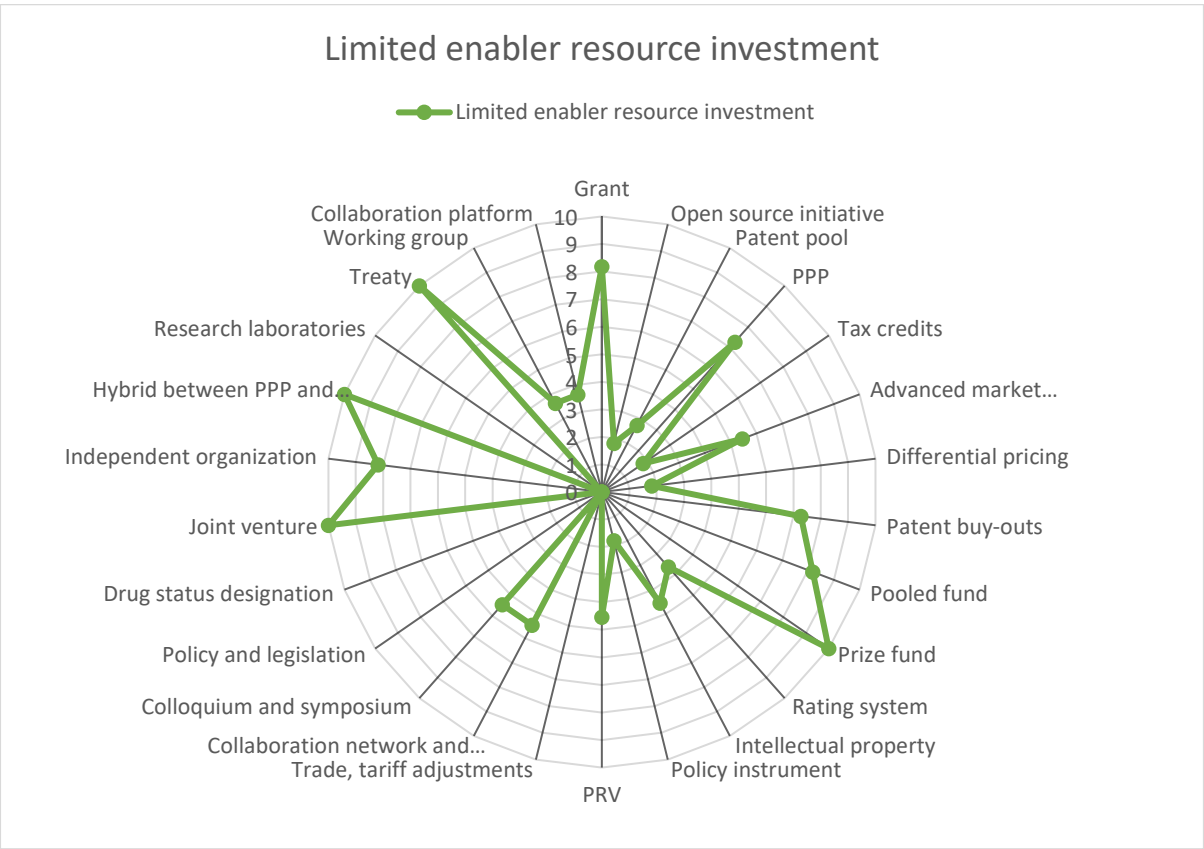
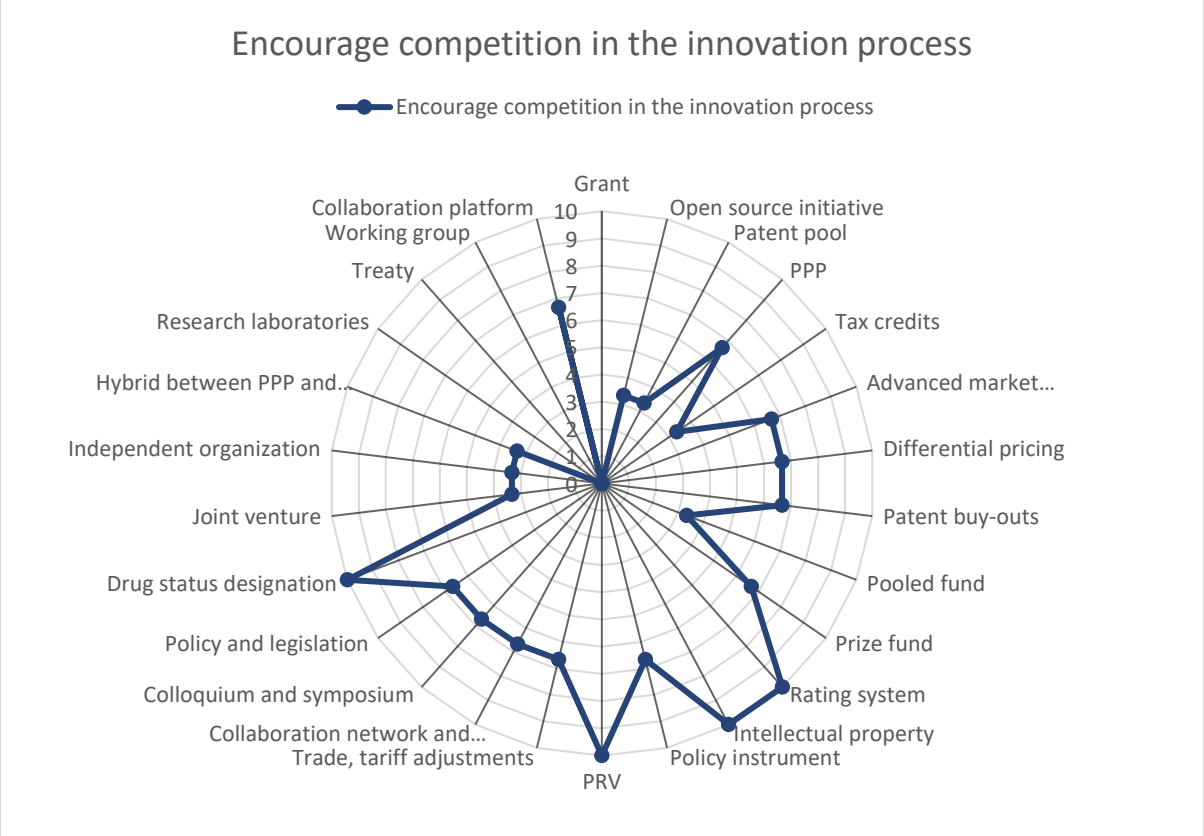
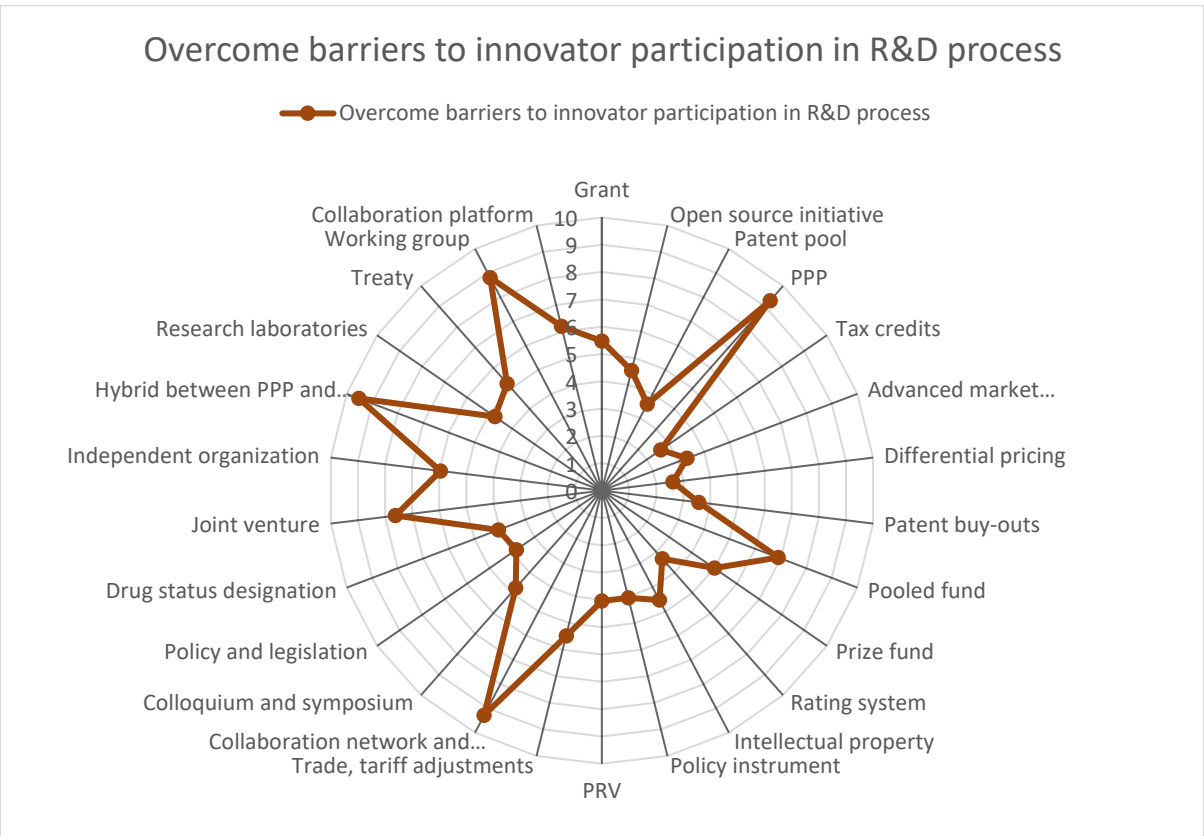




Supplementary material 2 (4 of 6): Prize fund results (combined)





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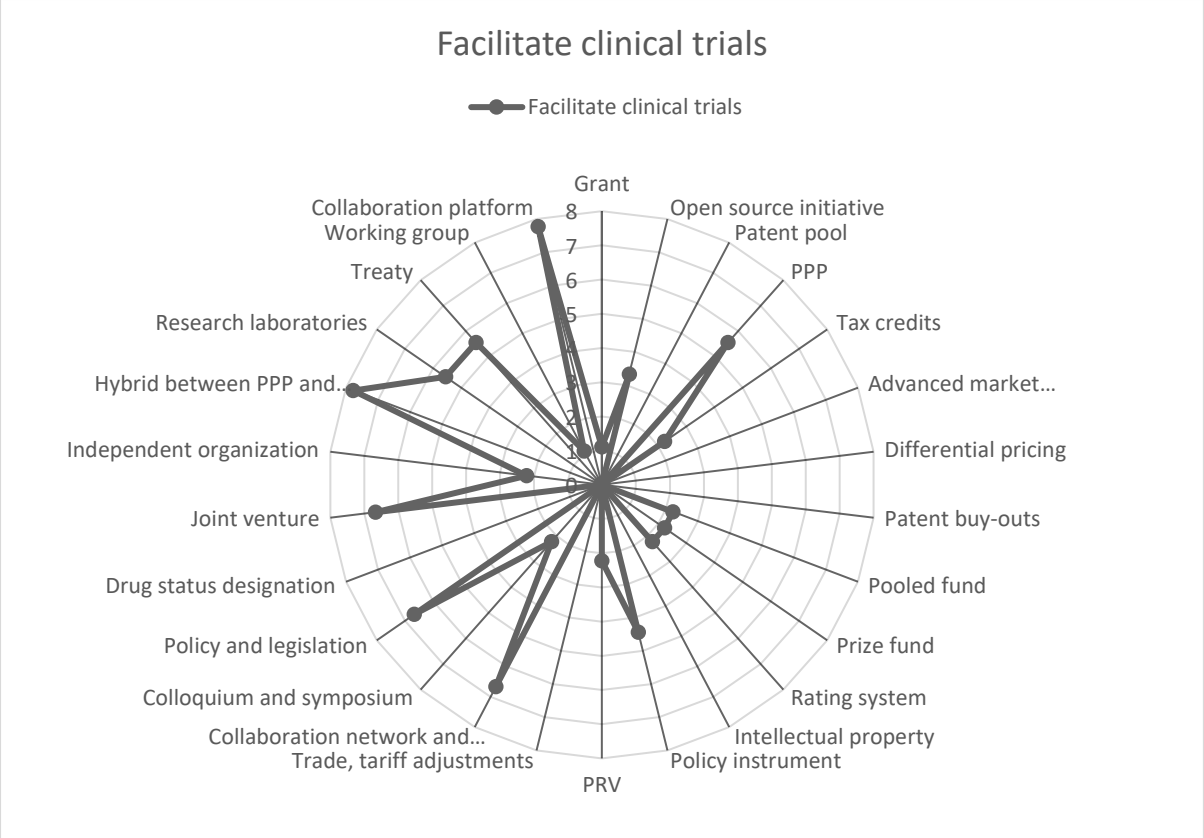

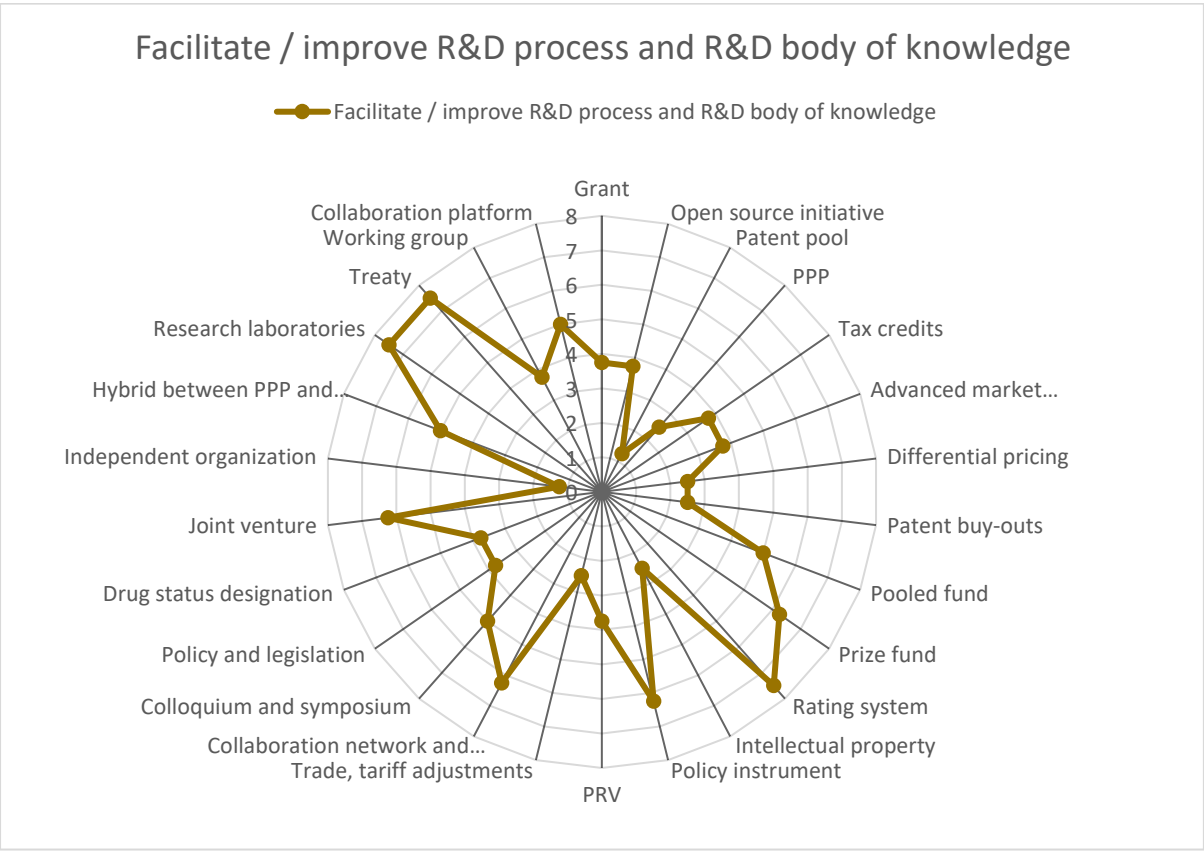

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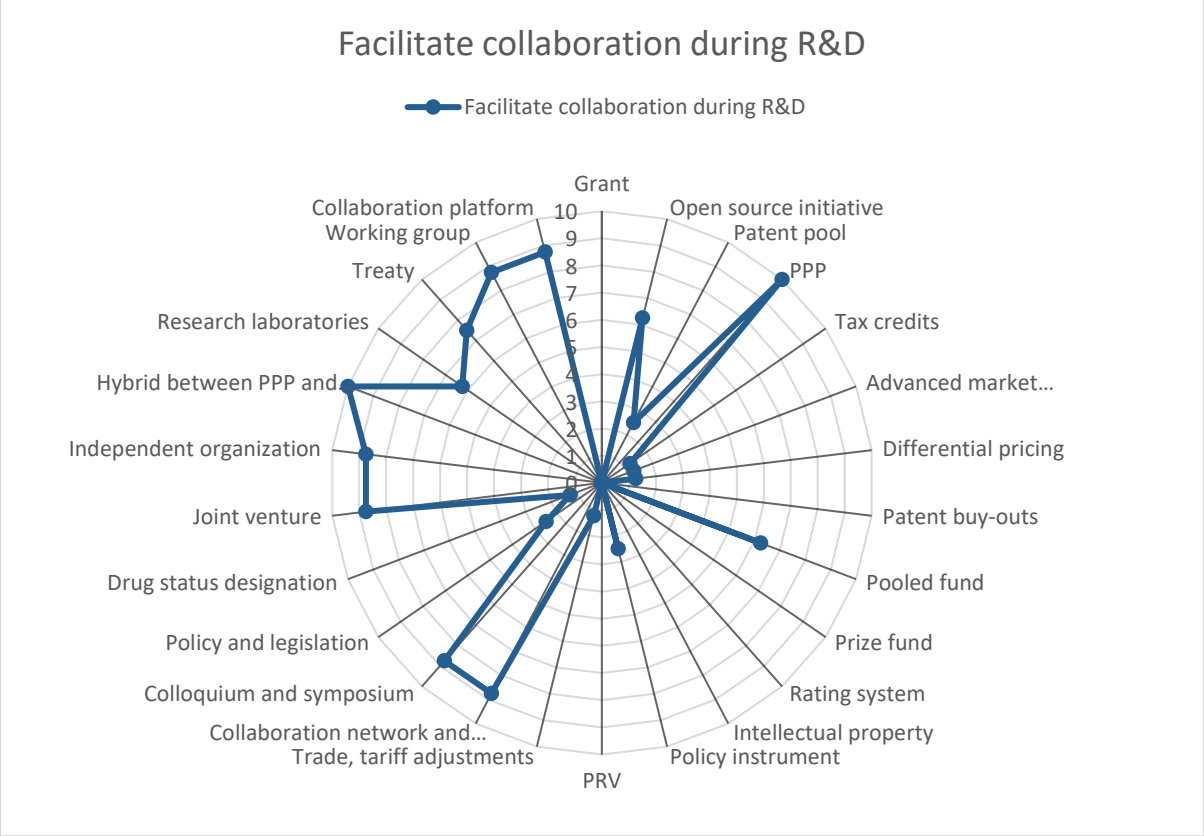
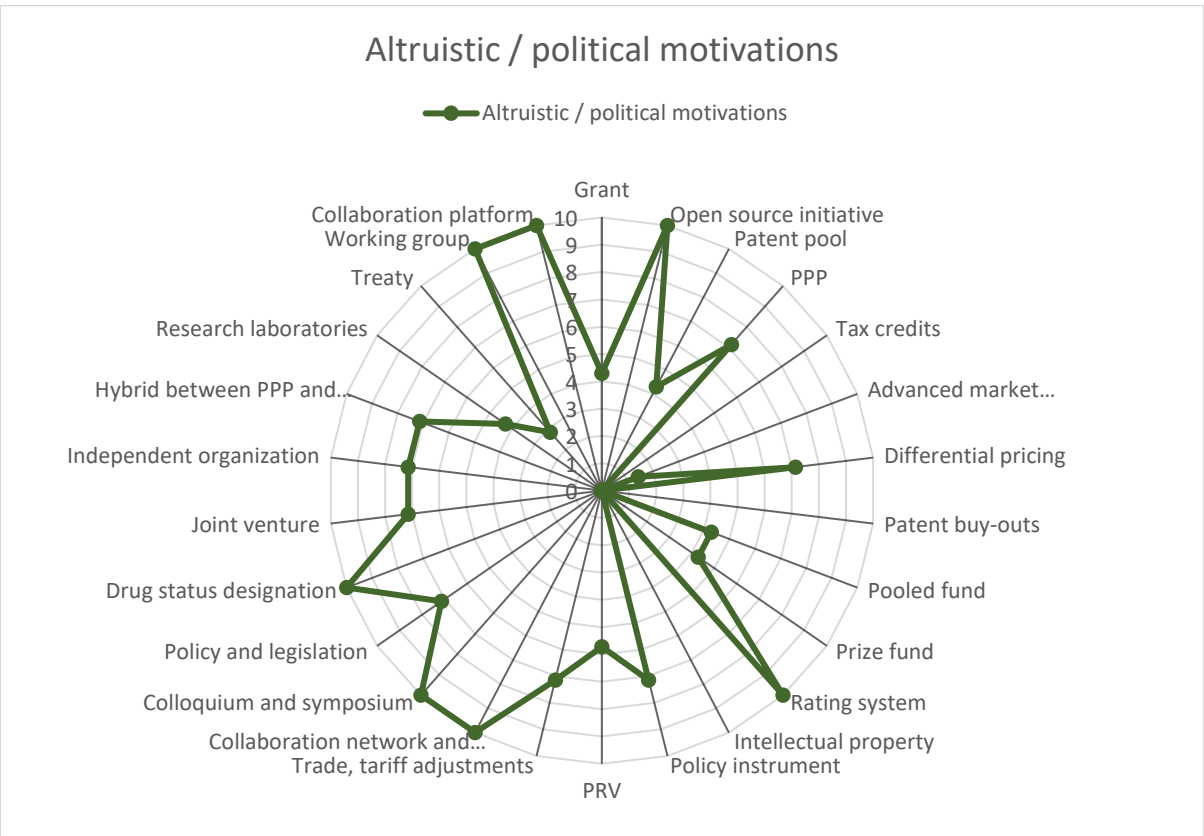
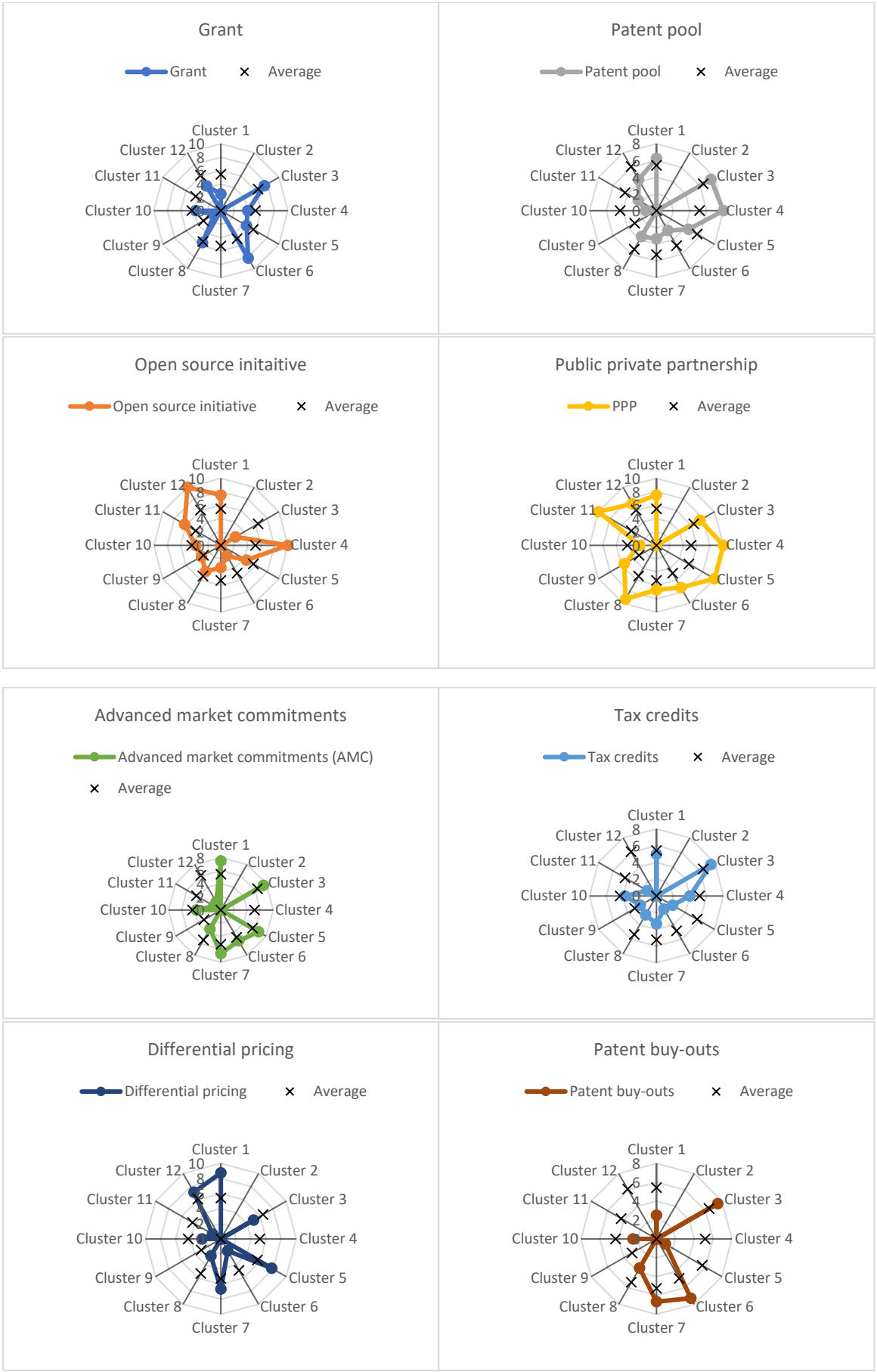




Supplementary material 3 (1 of 4): Prize fund results (combined)



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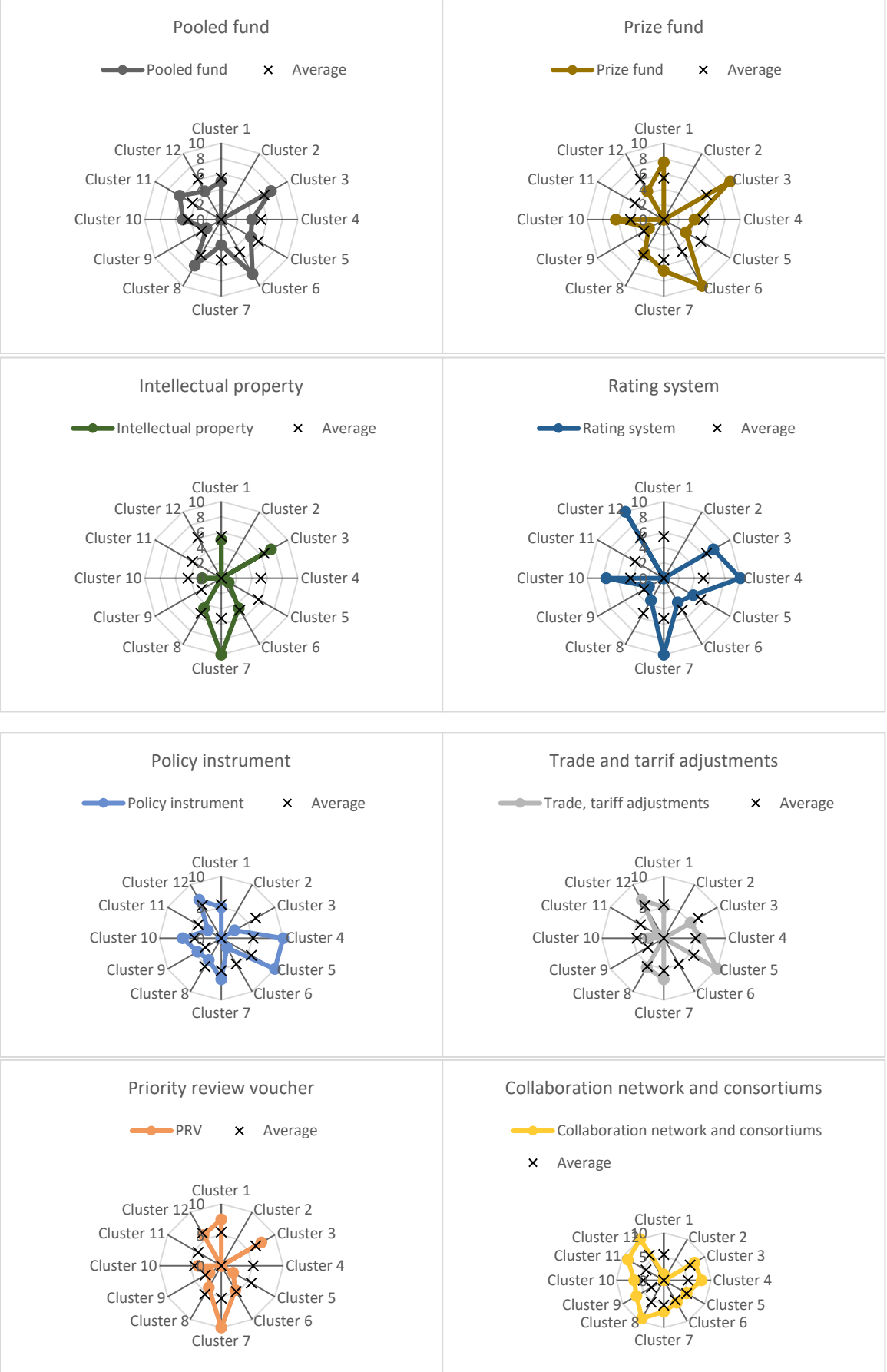

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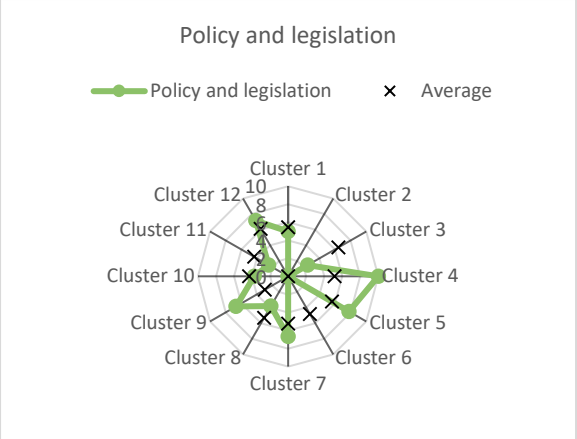
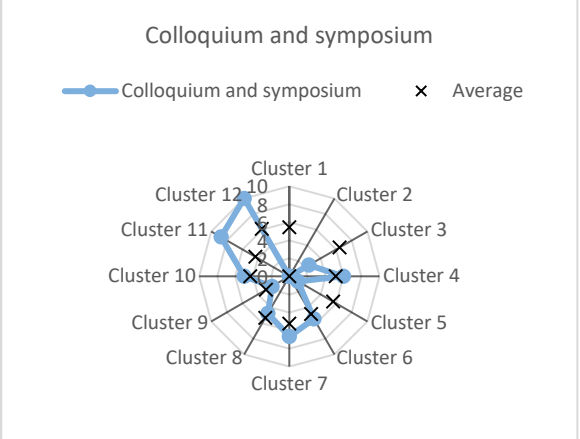
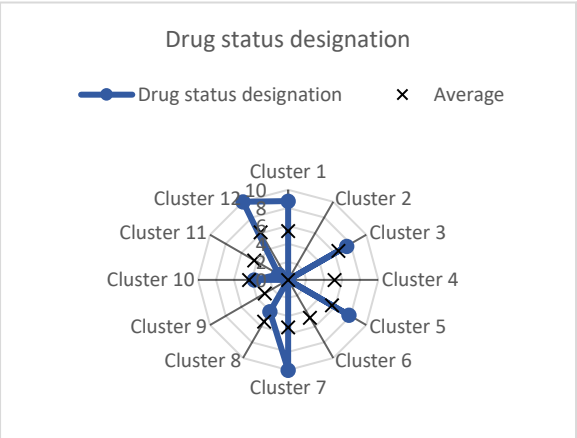
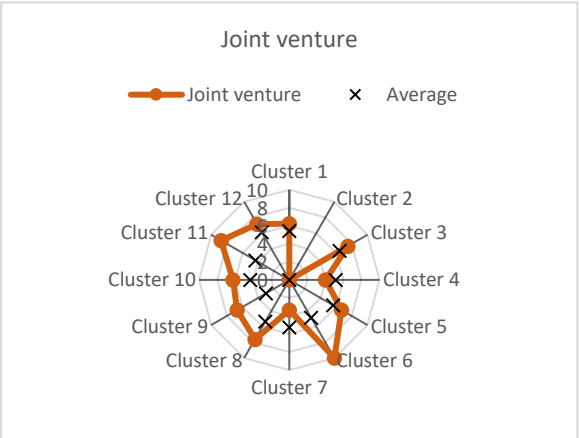
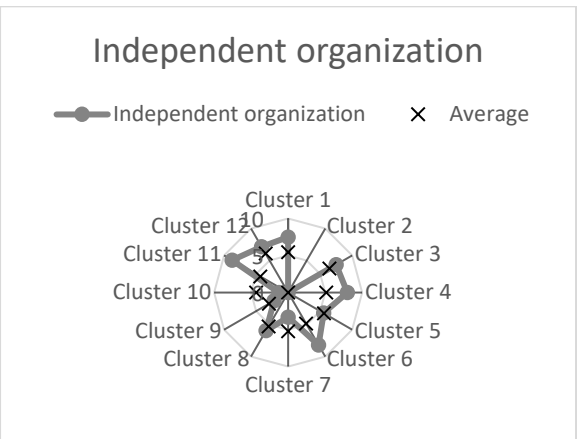
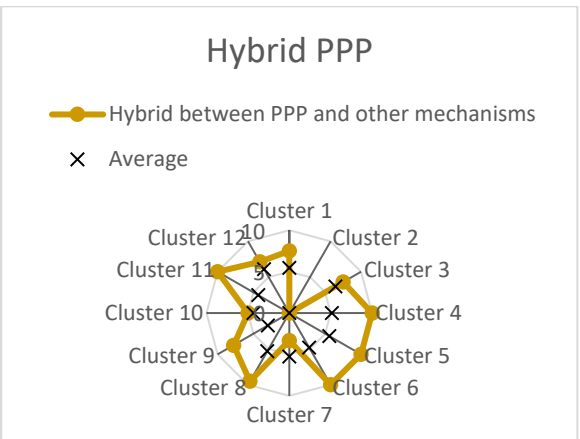


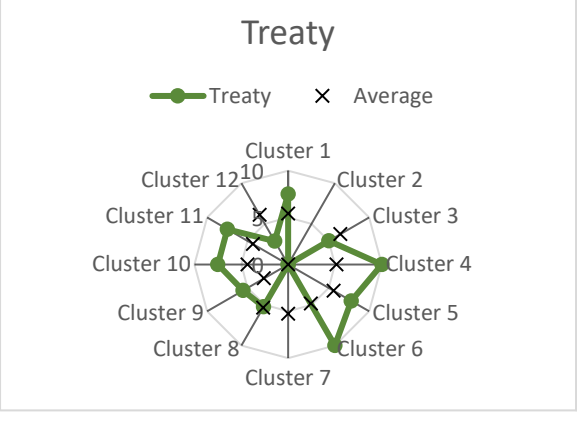


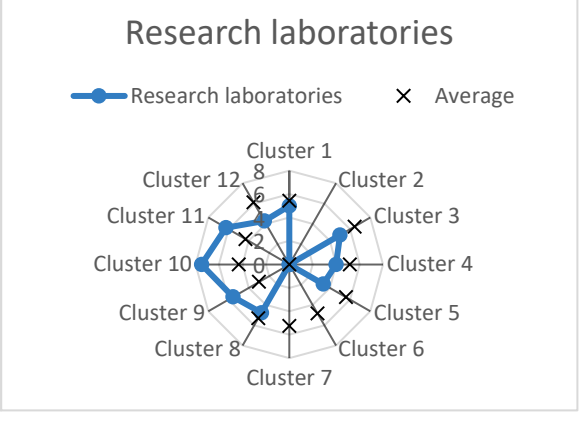




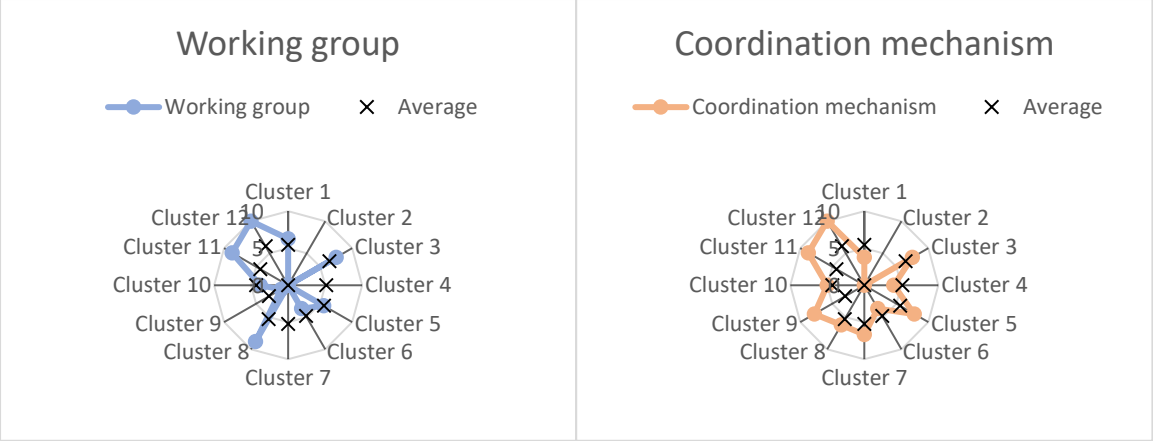








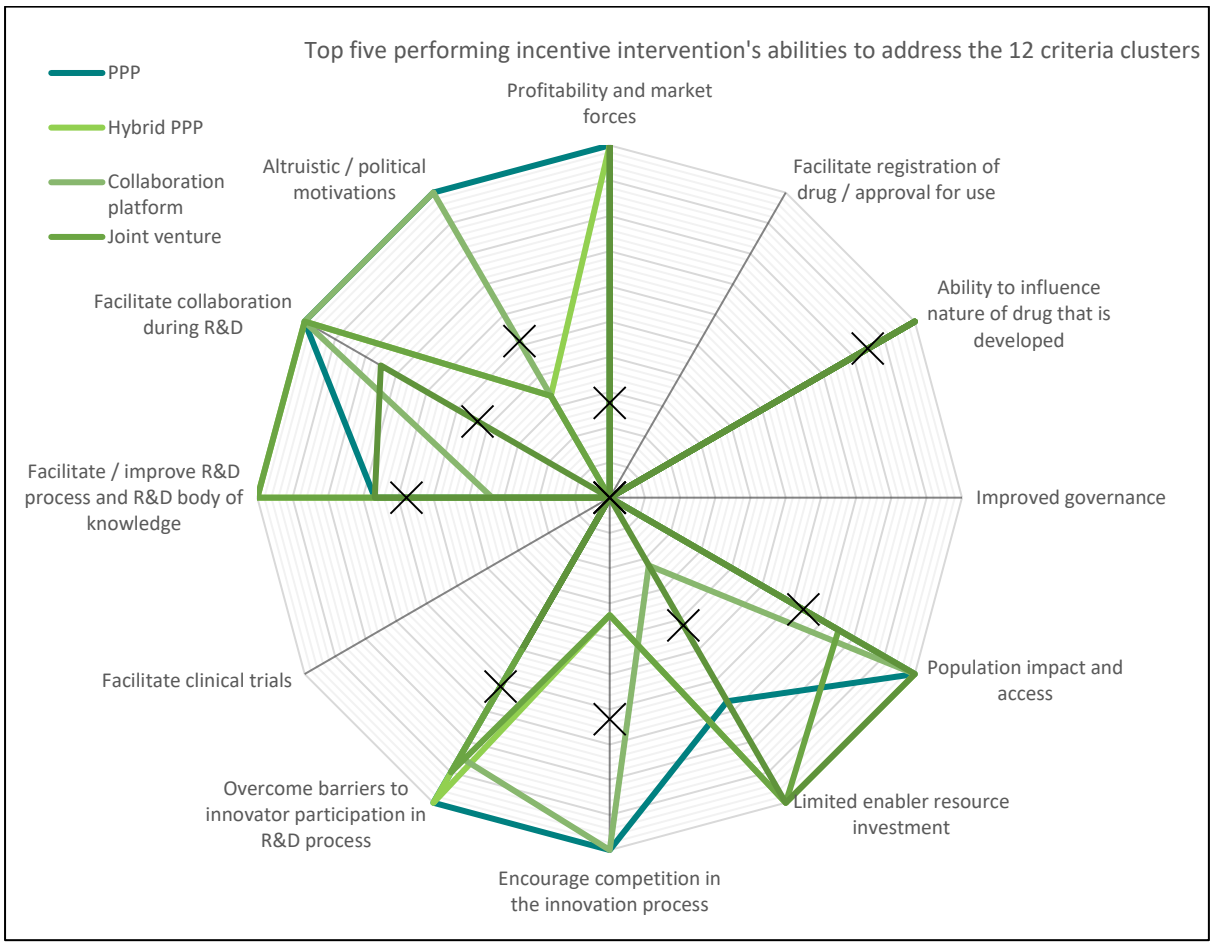
Supplementary material 3 (4 of 4): Prize fund results (combined)



Supplementary material 4 (1 of 2): Prize fund results (combined)

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													10	Feasible
22	Hybrid PPP													10	Feasible
26	Collaboration platform													9	Feasible
20	Joint venture													8	Feasible
24	Treaty													7	Feasible
21	Independent organization													6	Feasible
10	Prize fund													6	Feasible
8	Patent buy-outs													6	Feasible
1	Grant													5	Feasible
9	Pooled fund													5	Feasible
16	Collaboration network and consortiums													10	Infeasible
25	Working group													9	Infeasible
17	Colloquium and symposium													7	Infeasible
7	Differential pricing													7	Infeasible
19	Drug status designation													7	Infeasible
15	Trade, tariff adjustments													7	Infeasible
23	Research laboratories													6	Infeasible
12	Intellectual property													6	Infeasible
13	Policy instrument													6	Infeasible
11	Rating system													6	Infeasible
2	Open source initiative													6	Infeasible
18	Policy and legislation													6	Infeasible
14	PRV													5	Infeasible
3	Patent pool													4	Infeasible
5	Tax credits													4	Infeasible
6	Advanced market commitments													4	Infeasible

Supplementary material 4 (2 of 2): Prize fund results (combined)



Appendix N: Hybrid PPP case study results

This appendix includes:

(i) Domain 1: Hybrid PPP results
(ii) Background logic 1AB: Hybrid PPP results
(iii) Domain 2: Hybrid PPP results
(iv) Background logic 2: Hybrid PPP results
(v) Domain 3: Hybrid PPP results
(vi) Background logic 3: Hybrid PPP results
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(viii) Domain 5: Hybrid PPP results
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Domain 1 system demarcation: Hybrid PPP results

DOMAIN 1: SYSTEM DEMARCATION						System evaluation	
	System elements	2	1	0	Aspect to address	Measure [0|1|2]	Sourced from section
Disease setting and affected population							
1	Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)	2	Chapter 3.6.2
2	Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact	2	Chapter 3.6.2
3	Burden fully characterized	< 40% of population within 5% of health facility	40% - 60% of population within 5% of health facility	> 60% of population within 5% of health facility	Non-incentive-based solutions (I)	1	Chapter 3.4.1.1 &3.6.2
4	Physicians per 1000 population	¡ 1 per 1 000	1 - 2 physicians per 1 000 population	¿ 2 physicians per 1 000 population	Non-incentive-based solutions (I)	1	SME 4
Existing drug characteristics							
5	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact	1	Chapter 3.6
6	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)	1	Chapter 3.6
7	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact	1	Chapter 2.1.2
8	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)	2	Chapter 2.2.5
9	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access	1	Chapter 2.2.5
10	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)	2	Chapter 2.2.5
11	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)	1	Chapter 2.2.5
12	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (Respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)	1	Chapter 2.2.5
13	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access	2	Chapter 3.6.2
Service delivery							
14	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)	1	Chapter 2.2.3
15	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)	1	Chapter 2.2.3
16	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)	1	Chapter 2.2.3
17	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)	1	Chapter 2.2.3
Consumers, Competitors, and suppliers							
18	Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)	0	Chapter 3.4.3 & 3.7.3
19	The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)	1	Chapter 3.7.3
20	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)	1	Chapter 3.4.3
21	Existence of competitors	No competitors	Some competitors	A lot of competition	Non-incentive-based solutions (V)	1	Chapter 3.4.3
22	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility	1	Chapter 3.4.3
23	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation	0	Chapter 3.4.3
24	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation	0	Chapter 3.4.3
Governance and leadership							
25	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)	2	Chapter 3.6.2
26	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership	0	Chapter 3.6.2
27	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership	2	Chapter 3.6.2
28	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership	1	Chapter 3.6.2
29	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
30	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
31	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership	0	Chapter 2.2.3
32	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)	2	Chapter 2.2.5
33	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)	1	Chapter 2.2.3
Profitability and market forces							
34	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces	2	Chapter 2.1 & 3.6.2
35	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)	1	Chapter 3.6.2
36	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)	0	Chapter 2.1.2
37	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)	1	Chapter 3.4.3
38	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces	1	Chapter 3.4.3 & 3.6.2
39	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership	0	Chapter 3.6.2
Research and development process							
40	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials	0	Chapter 2.1.2
41	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
42	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
43	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
44	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
45	Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials	0	Chapter 2.1.2
46	Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials	0	Chapter 2.1.2
47	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials	1	Chapter 2.1.2
48	Quality of clinical trials	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable	Good clinical trial quality	9. R&D and clinical trials	0	Chapter 2.1.2
49	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials	1	Chapter 3.6.2
50	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
51	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
52	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
53	Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
54	Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
55	Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
56	Racial differences in participation in clinical trial	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
57	Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
58	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
59	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)	1	Chapter 3.4.3
60	R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials	1	Chapter 2.1.3
61	Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials	0	Chapter 2.1.2 & 2.1.3
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)	1	Chapter 2.1.2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)	0	Chapter 2.1.2
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)	0	Chapter 3.4.3
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs	2	Chapter 3.4.3
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)	2	Chapter 2.2.3
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)	1	Chapter 2.2.3

Background Logic 1AB: Hybrid PPP results

	BACKGROUND LOGIC 1A&B: CRITERIA MATRIX	1. Profitability and market forces	Improve NPV	Delink revenue from sales volume	Improve product export potential	2. Implementation feasibility and security	Minimizes barriers to implementation	Minimize disruptive effects to population	Affordable to implement the incentive	Provide R&D project insurance	3. Green and sustainability	Ensure conservation of resources in R&D process	Encourage efficient innovation	Green R&D of drugs	4. Population impact and access	Potential to reduce burden of disease	Encourage R&D of a drug/novel drug	Improve consumer access	Enable mass drug administration	5. Participation and cooperation	Enables participation of small and medium organization	Encourage large firm participation	Facilitates cooperation and synergy	Platform for coordinating innovators	Allow competition among parallel experiments	6. Governance and leadership	Promote equitable health-focused governance	Promote transparency and accountability	Advances the priority of disease on health agenda	Advance proper functioning of domestic policy	Regulatory oversight to promote R&D	Regulatory exclusivity provisions for R&D	Resources to develop drug government financed	7. Rewards focus	Payoff to innovators based on cost-effectiveness	Reward innovation	Financing timed across drug lifecycle	Provide long term R&D financing	Provide sustainable financing	Provide public subsidies for clinical trials	8. Impact on R&D process and clinical trials	Reduce clinical trial risk involved	Assist in registration and monitor of trials	Globalize clinical trial methods	Reduce clinical trials activation difficulty	Enhance or prompt the quality of clinical trials	Assist in expensive clinical trial regulation	Improves R&D productivity	Enlarge number of clinical trials registered
			2	2	1		2	2	2	2		2	2	2		1	1	2	1		2	2	2	2	2		2	2	0	1	2	2	0		2	2	2	2	2	2		2	1	0	1	2	1	0	0
1	**Grants:** Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting		1	0	0		0	0	1	0		0	0	0		1	1	1	1		1	0	0	0	0		0	1	1	0	1	0	1		0	0	0	1	0	0		0	0	0	1	0	0	0	0
2	**Open-source initiative:** Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets have the ability to benefit all participants.		1	1	0		1	1	1	0		0	0	0		1	0	0	0		1	1	1	1	0		1	1	1	1	0	0	0		0	0	0	0	0	0		1	1	1	0	0	0	1	1
3	**Patent pool:** Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.		1	1	1		0	0	1	0		0	0	0		1	1	1	0		1	1	0	1	0		1	1	0	0	0	0	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
4	**Public-private partnership:** Public-private partnerships is any arrangement between one or more public and private entities. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.		1	0	1		1	1	1	1		0	0	0		1	1	1	1		1	1	1	1	0		1	1	1	1	0	0	1		0	0	1	1	1	1		0	1	1	1	0	1	0	1
5	**Tax credits:** Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.		1	0	0		1	0	0	0		0	0	0		1	1	0	1		1	1	0	0	0		0	1	1	0	1	1	1		0	1	1	0	0	1		0	0	0	0	0	0	0	0
6	**Advanced market commitments:** Advanced market commitments are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.		1	1	0		1	1	1	1		1	1	0		1	1	1	1		1	1	0	0	0		0	0	1	0	0	0	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
7	**Differential pricing:** Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.		1	1	1		1	0	0	0		0	0	0		1	1	1	1		1	1	0	0	0		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
8	**Patent buyouts:** IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.		1	0	0		0	0	0	1		0	0	0		1	1	0	0		1	1	0	0	0		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
9	**Pooled fund:** When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.		0	1	0		1	0	1	1		1	1	0		1	1	1	1		1	0	1	1	0		0	1	1	0	0	0	0		0	0	1	1	1	0		1	0	0	0	0	0	0	0
10	**Prize fund:** Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.		1	1	0		1	0	1	0		1	1	0		1	1	1	0		1	0	0	0	1		0	1	1	0	0	0	0		1	1	1	0	0	0		0	0	1	0	1	0	0	1
11	**Rating system:** Pharmaceutical organizations are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.		0	0	0		0	0	1	0		1	1	1		1	1	1	0		1	1	0	0	1		1	1	1	1	1	1	0		0	0	0	0	0	0		0	0	0	0	1	0	1	0
12	**Intellectual property and market exclusivity:** Intellectual property refers to the right that the innovator receives when a new innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.		1	0	1		0	0	1	1		0	0	0		1	1	0	0		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
13	**Policy instrument:** Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy. Instruments can also include altering and enforcing domestic policies.		0	0	1		1	1	1	0		1	1	1		1	0	1	1		1	1	0	0	0		1	1	0	1	1	0	0		0	0	0	0	0	0		0	1	1	0	1	1	0	1
14	**Priority review voucher:** Law under which companies that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.		1	1	0		1	0	1	0		0	0	0		1	1	0	0		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	1	0	1	0	0
15	**Trade, tariff adjustments:** Adjustments made to the trading or the taxes and required costs associated with trading of specified manufactured drugs.		1	0	1		0	1	0	1		0	0	0		1	1	1	1		1	1	0	0	0		1	0	1	1	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
16	**Collaboration and consortiums:** A collaboration network refer to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a goal.		0	0	1		0	0	1	1		1	1	0		1	1	1	1		1	1	1	1	0		1	1	1	0	0	0	0		0	1	0	1	1	0		1	1	1	0	1	1	1	0
17	**Colloquium and symposium:** An academic conference or seminar held, focussing on one topic.		0	0	0		0	0	1	0		0	1	0		1	0	0	0		1	1	1	1	0		0	1	1	1	1	0	0		0	0	0	0	0	0		0	0	1	0	1	0	1	0
18	**Policy and legislation:** Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.		0	0	1		1	1	0	0		0	1	1		1	0	1	1		1	1	0	0	0		1	1	0	1	1	0	1		0	0	0	0	0	1		0	1	1	1	1	0	0	1
19	**Drug status designation:** Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.		1	1	1		1	0	0	1		0	0	0		1	1	1	1		1	1	0	0	1		0	0	1	0	0	1	0		0	1	0	0	0	0		0	0	0	0	0	0	0	0
20	**Joint venture:** Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.		1	0	1		1	0	1	1		1	1	0		1	1	1	1		1	1	1	1	0		0	1	1	0	0	0	0		0	1	1	0	0	0		1	0	1	1	1	1	0	1
21	**Independent organization:** Independent organizations does not require the approval of a government agency for decision-making and financial planning.		1	1	0		1	0	0	0		0	0	0		1	1	1	0		1	1	1	1	0		1	1	1	0	0	0	0		0	1	1	1	1	0		0	0	0	0	1	0	0	0
22	**Hybrid public-private partnership:** This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention, the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.		1	0	1		1	1	1	1		0	0	0		1	1	1	1		1	1	1	1	0		1	1	1	1	1	0	1		0	0	1	1	1	1		1	1	1	1	0	1	0	1
23	**Research laboratories:** Research laboratories are scientifically orientated facilities equipped with equipment to complete experiments aimed at R&D of drugs.		1	0	0		1	1	0	0		1	1	1		1	1	0	0		1	0	1	0	0		0	1	1	0	0	0	0		0	0	0	1	1	0		0	1	1	1	1	1	0	1
24	**Treaty:** Formal agreement between two or more political authorities, subject to international law.		1	0	1		1	1	1	1		1	1	1		1	1	1	1		0	0	1	1	0		1	1	1	1	1	0	1		0	0	0	0	0	1		0	0	1	0	1	1	0	1
25	**Working Group:** Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.		1	0	1		1	0	1	1		0	0	0		1	1	1	1		1	0	1	1	0		0	0	1	0	0	0	0		0	0	1	0	1	0		0	0	1	1	0	0	0	0
26	**Coordination mechanism and platform:** Initiatives to coordinate R&D investments and activities. Operate to clarify priorities, increase transparency, and diversify stakeholders.		0	0	1		1	1	1	0		1	1	1		1	1	1	1		1	1	1	1	0		0	1	1	0	0	0	0		0	0	0	0	0	0		1	1	1	1	1	1	0	1

Domain 2 Enabler profile: Hybrid PPP results

DOMAIN 2: ENABLER INQUIRY FORM					
OBJECTIVES			**INTERNAL CAPABILITIES**		
1	**Goal of the incentive strategy? (Inclusion)**		**1**	**Available funding. (Exclusion)**	
	Improve the state of the R&D pipeline	2		Limited to an amount	2
	Enable organizations to innovate easier	2		Full capacity	0
	Gain market exclusivity over an innovation	0		No capacity	0
	Advance the R&D field	2	**2**	**Payoff to innovators. (Inclusion)**	
	Deliver affordable and accessible treatment	0		Beginning once-off	0
	Convey an important message	2		End once-off	2
	Fulfil corporate social responsibility	0		Once output is provided	0
	Increase bandwidth and network	0		Incrementally, based on output	0
	De-risk R&D process	0		Incrementally, based on timing	0
	Political obligations	0		Incrementally, as innovator requires	0
2	**Which innovators are targeted? (Inclusion)**		**3**	**Ability to influence policy. (Inclusion)**	
	Large pharmaceutical organizations (private)	1		Clinical trial regulation policies	0
	SMEs (private)	2		Market authorization policies	0
	Governmental institutions	1		Market exclusivity policies	0
	Independent scientists	2		Pricing policies	0
	Academic institutions	2		Tax credit policies	0
	NGO organizations	2		National/international intellectual property policies	0
	Everyone	2		National policies and legislation	0
3	**Intention for the consumers? (Exclusion)**			International trade law	0
	Provide drug	1		**Access and expertise. (Inclusion)**	
	Multi-purpose drug	1	**4**	Access to key data	0
	Play a role in improved access	0		Access to compounds	0
	Implement mass drug administrations	0		Access to intellectual property	0
	Deliver regime treatment	1		Technology expertise and access	1
4	**Desired relationship with innovators? (Inclusion)**			R&D expertise	0
	Once-off occasion	2			
	Limited to a number of years	0			
	Milestone related	1			
	Engage at given time instances	0			
	Collaborate and build a partnership	0			
5	**Role and Responsibility willing to play? (Exclusion)**				
	Fund R&D	2			
	Partially fund R&D	2			
	Facilitate collaboration between innovators	0			
	Collaborate with innovator	0			
	Facilitate in regulatory process	0			
	Provide market exclusivity	0			
	Adjust policies and regulations	0			
	Provide market certainty	0			

Background Logic 1AB: Hybrid PPP results

	Background Logic 2: Enabler Matrix	1. Goal of the incentive strategy										2. Which innovators are targeted?							3. Intention for the patients?						4. Desired relationship with innovator?					5. Role & responsibility willing to play?									1. Available funding?			2. Funding timing?				3. Ability to influence /provide guidance in policies?								4. Access to aspects?				
		Improve the state of the R&D pipeline	Enable organizations to innovate easier	Gain market exclusivity over an innovation	Advance the R&D field & body of knowledge	Deliver affordable and accessible treatment	Convey an important message	Fulfil corporate social responsibility	Increase bandwidth and network	De-risk R&D process	Political obligations	Large pharmaceutical organizations(private)	SMEs (private)	Governmental institutions	Independent scientists	Academic institutions	NGO organizations	Everyone	Provide drug/novel drug	Multi-purpose drug	Play a role in improved access	Deliver regime treatment	Implement mass drug administrations	Once-off occasion	Limited to a number of years	Milestone related	Engage at given time instances	Collaborate and build a partnership	Fund R&D	Partially fund	Facilitate collaboration between innovators	Collaborate with innovator	Facilitate in regulatory process	Provide market exclusivity	Adjust policies and regulations	Provide market certainty	Limited to an amount	Full capacity	No capacity	Beginning once-off	End once-off	Once output provided	Incrementally, based on output	Incrementally, based on timing	Incrementally, as innovator requires	Clinical trial regulation policies	Market authorization policy	Market exclusivity policies	Pricing policies	Tax credit policies	National policies and legislations	National/International intellectual property policies	International trade law	Access to key data	Access to compounds	Access to intellectual property	Technology expertise and access	R&D expertise
	Push interventions	2	2	0	2	0	2	0	0	0	0	1	2	1	2	2	2	2	1	1	0	1	0	2	0	1	0	0	0	2	2	0	0	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
1	Grant	1	0	0	1	0	0	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	Open-source initiative	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
3	Patent Pool	1	0	1	0	1	0	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1	1	0
4	PPP	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	Tax credits	1	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0
	Outcome-based pull strategies																																																										
6	Advanced market commitments	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
7	Differential pricing	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0	1	1	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
8	Patent buyouts	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	1	0	1	1	1	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	1	1	0
9	Pooled fund	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0
10	Prize fund	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0
11	Rating system	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lego-regulatory pull strategies																																																										
12	Intellectual property and market exclusivity	1	0	1	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0	1	1	0	0	1	0	0	0	0	1	0	0
13	Policy instrument	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
14	Priority review voucher	1	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0	0	0	1	1	0	0	1	0	0	0	1	1	0	0	0	1	0	0	0	0	1	0
15	Trade, tariff adjustments	1	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0	0
	Hybrid strategies																																																										
16	Collaboration network and consortiums	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	1	0	1	1
17	Colloquium and symposium	0	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	1	0	1	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1
18	Policy and legislation	0	0	1	0	1	0	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
19	Drug status designation	1	0	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	0	0	0
20	Joint venture	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1
21	Independent organization	0	0	0	1	0	0	1	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1
22	Hybrid PPP	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
23	Research laboratories	1	1	0	1	0	0	1	0	0	1	0	1	1	1	1	1	0	1	1	0	1	0	0	1	0	1	1	0	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
24	Treaty	1	1	1	0	1	0	0	1	0	1	0	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	0	1	1
25	Working Group Coordination mechanism*	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	1
26		0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1

Domain 3 Innovator matrix: Hybrid PPP results

DOMAIN 3: INNOVATOR INQUIRY FORM					
OBJECTIVES			**INTERNAL CAPABILITIES**		
1	**Reason for performing R&D for the disease?**		**1**	**Nature of innovator stakeholder?**	
	Profit maximization	0		Small to medium organization (includes start-up)	0
	Corporate social responsibility	0		Large pharmaceutical organization	0
	Not for profit	2		Not-for-profit organization	0
	Profit improvement	0		Governmental institution	0
	Political obligations	0		Academic institution	2
2	**Focus area of R&D and intention for patients?**			Independent scientist (no organization linked)	0
	R&D of drug	1	**2**	**Capacity to provide own funding?**	
	R&D of multi-purpose drug	0		No capacity	1
	Play a role in improved access	1		Limited to an amount	1
	Drug repurposing	0		Full capacity	0
	Deliver regime treatment	0	**3**	**R&D limitations?**	
3	**Require from the enabler?**			Don't have research laboratory	0
	Fund all R&D costs	2		Don't have adequate equipment	1
	Partially fund R&D	2		Lack of information (knowledge) on disease	0
	Collaboration with enabler	1		Cumbersome nature of clinical trial regulations	0
	Adjust policies and regulations	0		Shortage of finances	2
	Facilitate regulatory process	0		Policies or regulatory limitations	0
	Provide market exclusivity	0		No market certainty	0
	Provide market certainty	0	**4**	**Authorization standards adhered to?**	
	Provide a collaboration platform	2		None	0
	Provide risk insurance or security	0		Accredited authorisation organization	2
	Improve export potential	0			
4	**Preference or required funding timing?**				
	Beginning once-off	0			
	End once-off	0			
	Incrementally based on output	2			
	Incrementally based on timing	2			
	Incrementally as required	1			
	Once output provided	0			
	Don't require any funding	0			

Background Logic 3 Innovator matrix: Hybrid PPP results

	1. Reason for performing R&D for the disease?	Profit maximization	Corporate or social responsibility	Not for profit	Profit improvement	Political obligations	2. Focus area of R&D and intention for patients?	R&D of drugs / novel drugs	Develop regime treatment	R&D a multi-purpose drug/vaccine	Play a role in improved access	Drug repurposing	3. Require from enabler / incentive intervention	Cover all R&D costs	Partly cover R&D costs	Collaboration with enabler	To adjust policies and regulations	To facilitate in the regulatory process	To provide market certainty	To provide market exclusivity	Collaboration platform	Risk insurance or security	Improve export potential	4. Preference or required funding timing?	Beginning once-off	End once-off	Incrementally based on output	Incrementally based on timing	Incrementally as required / incrementally	Once output provided	Do not require any funding	1. Nature of organization?	Large pharmaceutical organizations (private)	Small-and medium enterprise (private)	NGO	Governmental institution	Academic Institution	Scientist (no company)	2. Capacity to provide own funding?	No capacity	Limited to an amount	Full capacity	3. R&D limitations?	Don't have research laboratory	Don't have adequate equipment	Lack of information (knowledge) on disease	Cumbersome nature of clinical trial regulations	Shortage of finances	Policies or regulation limitations	No market certainty	4. Which Authorization standards adhered to?	None	Accredited authorisation organization
Push interventions		0	0	2	0	0		1	0	0	1	0		2	2	1	0	0	0	0	2	0	0		0	0	2	2	1	0	0		0	0	0	0	2	0		1	1	0		0	1	0	0	2	0	0		0	2
1 Grant		0	1	1	1	1		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		1	0	1	1	0	0	0		0	1	1	1	1	1		1	1	1		0	0	0	0	1	0	0		0	1
2 Open-source initiative		0	1	1	1	1		0	0	0	0	1		0	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	0		0	0	1	1	0	0	0		1	1
3 Patent Pool		0	1	1	1	0		1	1	1	1	1		0	0	0	0	0	0	1	1	0	1		0	0	0	0	1	0	1		1	1	1	1	0	0		0	0	0		0	0	0	0	0	0	0		0	1
4 PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
5 Tax credits		1	0	0	1	0		1	1	1	0	1		0	1	0	1	0	0	0	0	0	0		0	0	0	1	0	1	1		1	1	0	1	1	0		0	0	0		0	0	0	0	0	0	0		0	0
Outcome-based pull incentives																																																							
6 Advanced market commitments		1	1	0	1	1		1	1	1	1	1		0	0	0	0	0	1	0	0	1	0		0	1	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		0	1
7 Differential pricing		0	1	1	1	1		1	1	1	1	1		0	1	0	1	0	0	0	0	0	1		0	0	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	0		0	0
8 Patent buyouts		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	1	1	0	1	0		0	1	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	0	0		0	1
9 Pooled fund		0	1	1	0	1		1	1	1	1	1		1	1	0	0	0	0	0	1	1	0		1	1	1	1	1	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		1	1
10 Prize fund		1	1	1	1	0		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		0	1	1	0	0	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		0	1
11 Rating system		0	1	1	0	1		1	1	1	1	0		0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	1		1	1	1	1	1	0		0	0	1		0	0	0	0	0	0	0		1	1
Lego-regulatory pull strategies																																																						
12 Intellectual property and market exclusivity		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	0	1	0	1	1		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		0	1
13 Policy instrument		0	1	1	0	1		0	0	0	1	0		0	0	0	1	1	0	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	0	1		0	0	0	0	0	1	0		1	1
14 Priority review voucher		1	0	1	1	0		1	1	1	0	0		0	1	0	0	1	0	0	0	0	0		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	1	0	1	0		1	1
15 Trade, tariff adjustments		1	1	1	1	1		1	1	1	1	0		0	1	0	1	0	1	1	0	1	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		0	0	0	0	1	1	0		1	1
Hybrid strategies																																																						
16 Collaboration network and consortiums		0	1	1	0	1		1	1	1	1	1		1	1	1	0	0	0	0	1	1	1		0	0	1	1	1	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
17 Colloquium and symposium		0	1	1	0	0		0	0	0	0	0		0	0	1	0	1	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	1	1	0	0	0		1	1
18 Policy and legislation		0	1	1	0	1		0	1	0	1	1		0	0	0	1	1	1	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		1	1
19 Drug status designation		1	1	1	1	0		1	1	1	1	1		0	1	0	1	0	1	0	0	1	1		0	0	0	0	0	0	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		1	1
20 Joint venture		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	1	1	1	1	0	1		1	1	1	1	1	1		0	1	1		1	1	1	1	1	0	0		1	1
21 Independent organization		1	1	1	1	0		1	1	1	1	1		1	0	1	0	1	1	0	1	0	0		1	1	1	1	1	0	1		1	1	1	0	0	1		0	0	1		1	1	1	1	0	0	0		1	1
22 Hybrid PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	1	1		1	1
23 Research laboratories		1	1	0	1	1		1	1	1	0	1		0	0	1	0	0	0	0	0	0	0		0	0	0	0	0	0	1		0	1	1	1	1	1		0	0	1		1	1	0	0	0	0	0		1	1
24 Treaty		0	0	0	1	1		1	1	1	1	1		1	1	0	1	1	1	1	1	1	1		1	1	0	1	0	0	1		0	0	0	1	0	0		1	1	1		0	0	1	1	1	1	0		1	1
25 Working Group		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	0	1	1	1	0	1		0	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
26 Coordination mechanism		1	1	1	0	1		1	1	1	1	1		0	1	1	0	0	0	0	1	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	0		1	1

Background Logic 5: Hybrid PPP results

ACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	BL	1		1	3		2	2	2	3		2	3	2	2	2	2		1	3	3	4	1		2	2	4	4	4		1	2	3		2	3		3	2	1	4	3		1	1	1	1
	Cluster 1: Profitability and market forces	Delink revenue from sales volume	Incentive improves product export potential	Improve product export potential (Incentive ability)	Improve export potential (Innovator require)	Incentive allows market exclusivity over an innovation	Gain market exclusivity over an innovation (Enabler goal)	Provide market exclusivity (Enabler ability)	Market exclusivity policies (Enabler ability to alter)	Provide market exclusivity (Innovator require)	Incentive provides market certainty	Provide market certainty (Enabler role)	Provide market certainty (Innovator require)	Incentive involves/requires national/international intellectual property policies (Enabler ability)	Incentive involves/requires tax credit policies (Enabler ability)	Incentive involves/requires pricing policies (Enabler ability)	Incentive involves/requires international trade law (Enabler ability)	Incentive improves NPV of stakeholders	Improve NPV of stakeholders	Profit improvement (Innovator goal)	Profit maximization (Innovator goal)	Any profit margins allowed (Consumer require)	Minimizes barriers to implementation (implementation of incentive)		Cluster 2Facilitate registration of drug / approval for use	Incentive involves/requires market authorization policies (Enabler ability)	Incentive involves/requires national policies and legislations (Enabler ability)	Existing drugs not allowed in target area (Consumer availability)	Drug status designation required (Consumer availability)	IP regulation allows procurement of drugs to target area (Consumer availability)		Cluster 3: Ability to influence nature of drug that is developed	Incentive encourage R&D of a drug/intervention	Encourage R&D of a drug/intervention (Incentive ability)	Provide drug (Enabler goal)	R&D of drug (Innovator goal)	Incentives stimulates multi-purpose drug R&D	Multi-purpose drug (Enable goal)	R&D of multi-purpose drug (Innovator goal)	Incentive allows the delivery of regime treatment	Deliver regime treatment (Innovator goal)	Deliver regime treatment (Enabler goal)	Payoff to innovators based on cost-effectiveness	Contextual treatment criteria can be addressed by incentive (Consumer requirement)	Incentive allows drug repurposing (Innovator goal)		Cluster 4: Improved governance	Promote equitable health-focused governance (Incentive ability)	Promote transparency and accountability (Incentive ability)	Advances the priority of disease on health agenda (Incentive ability)	Advance proper functioning of domestic policy (Incentive ability)
	7	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0	2		0	0	0	0	0	0		3	1	1	0	1	0	0	0	0	0	0	2	0	0		4	2	2	0	0
Push mechanisms																																															
Grant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0		0	0	0	0	0	0		1	1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Open-source initiative		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1		0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	0	1	1		1	1	1	1
Patent pool		1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0		0	0	1	0	1			1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	0	0
PPP		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1		1	1	0	1	1			1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1
Tax credits		0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	0	1		0	0	0	1	0			1	1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Outcome-based pull strategies																																															
Advanced market commitments (AMC)		1	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	1	1		0	0	1	0	0			1	1	1	1	1	1	1	1	1	1	0	1	1		0	0	1	0
Differential pricing		1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1		0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	0	0	1		0	0	1	0
Patent buy-outs		0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0		1	0	1	0	1			1	1	1	1	1	1	1	1	1	1	0	1	0		0	0	1	0
Pooled fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1		0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Prize fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1		0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	1	1	1		0	1	1	0
Rating system		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	1	1	0			1	1	1	1	1	1	1	1	1	1	0	1	0		1	1	1	1
Lego-regulatory pull strategies																																															
Intellectual property		0	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0		0	0	1	0	1			1	1	1	1	1	1	1	1	1	1	0	1	0		0	0	1	0
Policy instrument		0	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	1	1		1	1	1	1	1			0	0	0	0	0	0	0	0	0	0	0	1	0		1	1	0	1
PRV		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1		1	1	0	0	0			1	1	1	1	1	1	1	1	1	1	0	1	0		0	0	1	0
Trade, tariff adjustments		0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0		1	1	1	1	1			1	1	1	1	1	1	1	1	1	1	0	0	0		1	0	1	1
Hybrid strategies																																															
Collaboration network and consortiums		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	0
Colloquium and symposium		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0			0	0	0	0	0	0	0	0	0	0	0	1	0		0	1	1	1
Policy and legislation		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1		1	1	0	1	1			0	0	0	0	0	0	0	1	1	0	0	1	1		1	1	0	1
Drug status designation		1	1	1	1	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	0	1		1	1	1	1	1			1	1	1	1	1	1	1	1	1	1	0	1	1		0	0	1	0
Joint venture		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	0	1		0	0	1	0	1			1	1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0
Independent organization		1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1		0	0	1	0	0			1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	0
Hybrid between PPP and other mechanisms		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1	1			1	1	1	1	1	1	1	1	1	1	0	1	1		1	1	1	1
Research laboratories		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	0	0	1		0	1	1	0
Treaty		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1		1	1	0	1	1			1	1	1	1	1	1	1	1	1	1	0	0	1		1	1	1	1
Working group		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	0	1		0	0	1	0	0			1	1	1	1	1	1	1	1	1	1	0	1	1		0	0	1	0
Coordination mechanism		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1		0	0	1	0	0			1	1	1	1	1	1	1	1	1	1	0	1	1		0	1	1	0

Background Logic 5: Hybrid PPP results

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 5: Population impact and access	Incentive improves consumer access	Improve consumer access (Incentive ability)	Play a role in improved access (Enabler goal)	Play a role in improved access (Innovator goal)	Incentive enables mass drug administration	Enable mass drug administration (Incentive ability)	Implement mass drug administrations (Enabler goal)	Incentive aims to reduce burden of disease in area	Incentive aims to minimize disruptive effects to	Incentive allows for differential pricing (Consumer	Incentive allows differential pricing (End-consumer	Incentive allows differential pricing (Procurer	Deliver affordable and accessible treatment (Enabler	Incentive eliminates all financial risk (Consumer	Cluster 6: Limited enabler resource investment	Affordable to implement the incentive	Incentive allows resources to develop drugs to be	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be	Incentive allows payoff to innovator to be incrementally,	Incentive allows payoff to innovator to be incrementally,	Incentive does not require enabler funding (Enabler no	Incentive does not require enabler funding (Enabler has	Innovator does not require any funding from enabler, or	Incentive requires/allows the enabler to partially fund	Incentive requires/allows the enabler to partially fund	Incentive requires/ allows innovator to partially fund	Incentive payout to innovator is a once-off occasion	Incentive payout to innovator occurs once output is	Incentive allows innovator payouts to be limited to a	Incentive allows innovator payouts to be milestone	Incentive allows enabler to engage with innovator at	Incentive allows enabler funding to be limited to an	Cluster 7: Encourage competition in the innovation	Incentive encourages large firm participation	Incentive encourages large firm participation	Incentive allows large pharmaceutical organization	Incentive aimed at incentivising large pharmaceutical	Incentive allows competition among parallel	Incentive enlarges the number of clinical trials	Incentive targets all organizations to participate
	8	2	2	0	1	2	2	0	2	2	0	0	0	0	0	12	2	0	0	0	0	0	0	0	2	1	2	0	0	0	2	2	2	0	0	2	1	1	2	4	2	2	0	0	2	0	0
Push mechanisms																																														
Grant		1	1	1	1	1	1	1	1	0	0	0	0	0	0		1	1	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	1	1	0	1		0	0	0	0	0	0	0
Open-source initiative		0	0	0	0	0	0	0	1	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0		1	1	1	1	0	1	0
Patent pool		1	1	1	1	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0	0		1	1	1	1	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1		1	1	1	1	0	1	1
Tax credits		0	0	0	0	1	1	1	1	0	0	0	0	0	0		0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	0	1	0		1	1	1	1	0	0	0
Outcome-based pull strategies																																														
Advanced market commitments (AMC)		1	1	1	1	1	1	1	1	1	0	0	0	0	0		1	0	0	0	0	1	1	1	0	0	0	1	1	0	0	0	1	1	1	0	0	0		1	1	1	1	0	0	1
Differential pricing		1	1	1	1	1	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	0	0	0		1	1	1	1	0	0	1
Patent buy-outs		0	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1		1	1	1	1	0	0	1
Pooled fund		1	1	1	1	1	1	1	1	0	0	0	0	0	0		1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	1		0	0	0	0	0	0	1
Prize fund		1	1	1	1	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	0		0	0	0	0	1	1	1
Rating system		1	1	1	1	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0	0	1	0	1		1	1	1	1	1	0	1
Lego-regulatory pull strategies																																														
Intellectual property		0	0	0	0	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1	1	0		1	1	1	1	1	0	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1		1	1	1	1	0	1	1
PRV		0	0	0	0	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	1	1	0		1	1	1	1	1	0	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	1		1	1	1	1	0	0	1
Hybrid strategies																																														
Collaboration network and consortiums		1	1	1	1	1	1	1	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	0		1	1	1	1	0	0	1
Colloquium and symposium		0	0	0	0	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	0	0		1	1	1	1	0	0	1
Policy and legislation		1	1	1	1	1	1	1	1	1	0	0	0	1	0		0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1		1	1	1	1	0	1	1
Drug status designation		1	1	1	1	1	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0		1	1	1	1	1	0	1
Joint venture		1	1	1	1	1	1	1	1	0	0	0	0	0	1		1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	1	1		1	1	1	1	0	1	0
Independent organization		1	1	1	1	0	0	0	1	0	0	0	0	0	1		0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0		1	1	1	1	0	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1		1	1	1	1	0	1	0
Research laboratories		0	0	0	0	0	0	0	1	1	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	0	1		0	0	0	0	0	1	0
Treaty		1	1	1	1	1	1	1	1	1	1	1	1	1	0		1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	1	1	1	1		0	0	0	0	0	1	0
Working group		1	1	1	1	1	1	1	1	0	0	0	0	1	0		1	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0		0	0	0	0	0	0	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	1	0	1		1	1	1	1	0	1	1

Background Logic 5: Hybrid PPP results

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 8: Overcome barriers to innovator participation in R&D process	Incentive allows small and medium organizations to be incentivized	Incentive enables participation of small and medium organizations	Incentive enables participation of small and medium organizations (Enabler target)	Incentive enables participation of small and medium organizations (Innovator identity)	Incentive allows governmental institutions to be incentivized	Incentive allows governmental institutions to be incentivized (Enabler target)	Incentive allows governmental institutions to be incentivized (Innovator identity)	Incentive allows independent scientists to be incentivized	Incentive allows independent scientists to be incentivized (Enabler target)	Incentive allows independent scientists to be incentivized (Innovator identity)	Incentive allows academic institutions to be incentivized	Incentive allows academic institutions to be incentivized (Enabler target)	Incentive allows academic institutions to be incentivized (Innovator identity)	Incentive allows NGO organizations to be incentivized	Incentive allows NGO organizations to be incentivized (Enabler target)	Incentive allows NGO organizations to be incentivized (Innovator identity)	Incentive financing is timed across drug lifecycle	Incentive provides long term R&D financing	Incentive provides sustainable financing for innovator	Incentive provides R&D project insurance	Incentive provides R&D project insurance	Incentive provides risk insurance or security (Innovator requirement)	Incentive de-risks the R&D process	Incentive requires/allows enabler to fund R&D	Incentive allows enabler to fund R&D (Enabler goal)	Incentive requires enabler to fund all R&D costs (Innovator requirement)	Incentive allows enabler to fully fund R&D (Enabler full capacity)	Incentive allows enabler to fully fund R&D (Enabler full capacity)	Incentive requires enabler to completely fund R&D (Innovator no ability)	Incentive requires enabler to partially fund R&D (Innovator ability)	Incentive requires enabler to partially fund R&D (Innovator requirement)	Incentive requires enabler to partially fund R&D (Innovator ability)	Incentive allows funding to be incremental, as innovator requires	Incentive allows funding to be incremental, as innovator requires (Enabler ability)	Incentive allows funding to be incremental, as innovator requires (Innovator requirement)	Incentive allows funding to be incremental, based on timing	Incentive allows funding to be incremental, based on timing (Enabler ability)	Incentive allows funding to be incremental, based on timing (Innovator requirement)	Incentive does not provide any funding (Innovator has full capacity to provide own funding)	Incentive allows enabler to increase bandwidth and network (Enabler goal)	Incentive utilizes enabler's ability to influence intellectual property (Enabler ability)	Incentive requires/ utilizes enabler's access to key data	Incentive utilizes enabler's access to key data (Enabler ability)	Incentive provides innovator with information (knowledge) on disease (Innovator requirement)	Incentive utilizes enabler's access to compounds (Enabler ability)	Incentive requires/ utilizes enabler technology expertise and access	Incentive requires/ utilizes enabler technology expertise and access	Incentive provides innovator access to adequate equipment (Innovator requirement)	Incentive provides innovator with access to research laboratory (Innovator requirement)	Incentive requires/ utilizes enablers R&D expertise	Incentive requires/ utilizes enablers R&D expertise	Incentive aids innovator with cumbersome nature of clinical trial regulations (Innovator requirement)	Incentive addresses innovator's policy or regulatory limitations (Innovator requirement)	Incentive provides innovator with market certainty (Innovator requirement)	Innovator does not adhere to any authorization standards (Innovator nature)	Innovator has accredited authorisation organization (Innovator nature)	Incentive rewards innovation
			1	2	3		2	3		2	3		2	3		2	3	1	1	1		1	2	2		2	3		2	3		3	3		2	3		2	3	3	2	2		2	3	2		2	3	3		2	3	3	3	3	3	1
	30	2	2	0	0	0	0	0	0	0	0	2	2	2	0	0	0	2	2	2	2	2	0	0	2	2	2	1	1	1	2	2	1	1	0	1	2	1	2	0	1	0	1	1	0	0	2	2	1	0	2	2	0	0	0	0	2	2
Push mechanisms																																																										
Grant		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Open-source initiative		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	1	0
Patent pool		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0
Tax credits		1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Outcome-based pull strategies																																																										
Advanced market commitments (AMC)		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1
Differential pricing		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Patent buy-outs		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1
Pooled fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Prize fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	1	1	1	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1
Rating system		1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Lego-regulatory pull strategies																																																									
Intellectual property		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
PRV		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1
Hybrid strategies																																																										
Collaboration network and consortiums		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Colloquium and symposium		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	1	1	1	0	0	1	1	0
Policy and legislation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
Drug status designation		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Joint venture		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Independent organization		1	1	1	1	0	0	0	0	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Research laboratories		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	0
Treaty		0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0	1	1	0
Working group		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0

Background Logic 5: Hybrid PPP results

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING

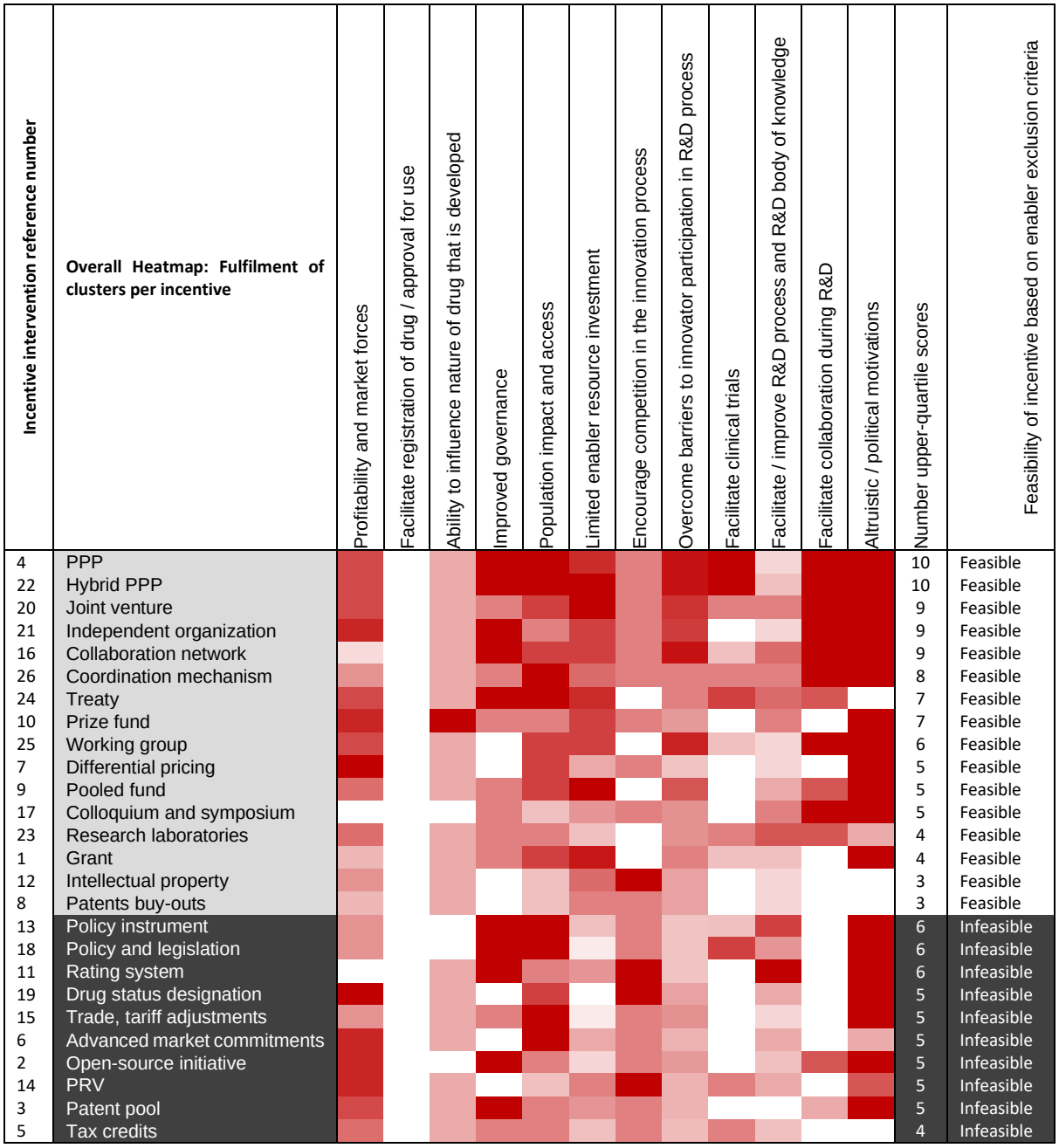
	Cluster 9: Facilitate clinical trials	Incentive allows provision of public subsidies for clinical trials	Incentive reduces clinical trial risk involved	Incentive assist in registration and monitor of trials	Incentive globalizes clinical trial methods	Incentive reduces clinical trial activation difficulty	Incentive enhances or prompt the quality of clinical trials	Incentive aids in clinical trial regulation	Clinical trial regulation policies (Enablers ability to influence)
		1	1	1	1	1	1	1	2
	4	2	0	0	0	1	0	1	0
Push mechanisms									
Grant		0	0	0	0	1	0	0	0
Open-source initiative		0	1	1	1	0	0	0	0
Patent pool		0	0	0	0	0	0	0	0
PPP		1	0	1	1	1	0	1	1
Tax credits		1	0	0	0	0	0	0	1
Outcome-based pull strategies									
Advanced market commitments (AMC)		0	0	0	0	0	0	0	0
Differential pricing		0	0	0	0	0	0	0	0
Patent buy-outs		0	0	0	0	0	0	0	0
Pooled fund		0	1	0	0	0	0	0	0
Prize fund		0	0	0	1	0	1	0	0
Rating system		0	0	0	0	0	1	0	0
Lego-regulatory pull strategies									
Intellectual property		0	0	0	0	0	0	0	0
Policy instrument		0	0	1	1	0	1	1	1
PRV		0	0	0	0	1	0	1	1
Trade, tariff adjustments		0	0	0	0	0	0	0	0
Hybrid strategies									
Collaboration network and consortiums		0	1	1	1	0	1	1	0
Colloquium and symposium		0	0	0	1	0	1	0	0
Policy and legislation		1	0	1	1	1	1	0	1
Drug status designation		0	0	0	0	0	0	0	1
Joint venture		0	1	0	1	1	1	1	0
Independent organization		0	0	0	0	0	1	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	0	1	1
Research laboratories		0	0	1	1	1	1	1	0
Treaty		1	0	0	1	0	1	1	1
Working group		0	0	0	1	1	0	0	0
Coordination mechanism		0	1	1	1	1	1	1	0

	Cluster 10: Facilitate / improve R&D process and R&D body of knowledge	Incentive aims to/ allows improvement of R&D productivity	Incentive provides regulatory oversight to promote R&D	Incentive provides regulatory exclusivity provisions for R&D	Incentive encourages efficient innovation	Incentive ensures the conservation of resources in R&D process	Incentive requires/ allows green R&D of drugs	Incentive enables organizations to innovate easier (Enabler goal)	Incentive advances the R&D field & body of knowledge (Enabler goal)	Incentive can improve the state of the R&D pipeline (Enabler goal)
		1	1	1	1	1	1	2	2	2
	12	1	1	2	2	2	2	0	2	0
Push mechanisms										
Grant		0	1	0	0	0	0	0	1	1
Open-source initiative		1	0	0	0	0	0	1	1	1
Patent pool		0	0	0	0	0	0	0	0	1
PPP		0	0	0	0	0	0	0	1	1
Tax credits		0	1	1	0	0	0	0	0	1
Outcome-based pull strategies										
Advanced market commitments (AMC)		0	0	0	1	1	0	0	0	1
Differential pricing		0	0	1	0	0	0	0	0	1
Patent buy-outs		0	0	1	0	0	0	0	0	1
Pooled fund		0	0	0	1	1	0	1	0	1
Prize fund		0	0	0	1	1	0	1	1	1
Rating system		1	1	1	1	1	1	0	1	0
Lego-regulatory pull strategies										
Intellectual property		0	0	1	0	0	0	0	0	1
Policy instrument		0	1	0	1	1	1	0	1	0
PRV		0	0	1	0	0	0	0	1	1
Trade, tariff adjustments		0	0	1	0	0	0	0	0	1
Hybrid strategies										
Collaboration network and consortiums		1	0	0	1	1	0	1	1	1
Colloquium and symposium		1	1	0	1	0	0	1	1	0
Policy and legislation		0	1	0	1	0	1	0	0	0
Drug status designation		0	0	1	0	0	0	0	1	1
Joint venture		0	0	0	1	1	0	1	1	1
Independent organization		0	0	0	0	0	0	0	1	0
Hybrid between PPP and other mechanisms		0	1	0	0	0	0	1	1	1
Research laboratories		0	0	0	1	1	1	1	1	1
Treaty		0	1	0	1	1	1	1	0	1
Working group		0	0	0	0	0	0	1	1	1
Coordination mechanism		0	0	0	1	1	1	1	0	0

	Cluster 11: Facilitate collaboration during R&D	Incentive facilitates cooperation and synergy between all stakeholders	Facilitates cooperation and synergy between all stakeholders	Incentive facilitates collaboration between innovators (Enabler goal)	Incentive allows enabler to collaborate and build a partnership/s (Enabler goal)	Incentive allows enabler to collaborate with innovator	Incentive allows enabler to collaborate with innovator (Enabler goal)	Incentive allows innovator to collaborate with enabler (Innovator requirement)	Incentive provides a platform for coordinating innovators	Incentive provides a platform for coordinating innovators	Incentive provides a collaboration platform (Innovator requirement)	Incentive allows/ requires enabler to facilitate in regulatory process	Incentive allows/ requires enabler to facilitate in regulatory process (Enabler ability)	Incentive allows/ requires enabler to facilitate innovator in regulatory process (Innovator requirement)	Incentive requires enabler to adjust policies and regulations	Enabler has ability to adjust policies and regulations	Innovator requires enabler to adjust policies and regulations (should be allowed by incentive)
			1	2	2		2	3		1	3		2	3		2	3
	6	2	2	2	0	2	2	1	2	2	2	0	0	0	0	0	0
Push mechanisms																	
Grant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Open-source initiative		1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0
Patent pool		0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1
Tax credits		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Outcome-based pull strategies																	
Advanced market commitments (AMC)		0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Differential pricing		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Patent buy-outs		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pooled fund		1	1	0	1	0	0	0	1	1	1	0	0	0	0	0	0
Prize fund		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rating system		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lego-regulatory pull strategies																	
Intellectual property		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Policy instrument		0	0	0	1	0	0	0	0	0	0	1	1	1	1	1	1
PRV		0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0
Trade, tariff adjustments		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Hybrid strategies																	
Collaboration network and consortiums		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Colloquium and symposium		1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0
Policy and legislation		0	0	0	1	0	0	0	0	0	0	1	1	1	1	1	1
Drug status designation		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Joint venture		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Independent organization		1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Research laboratories		1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
Treaty		1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1
Working group		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0

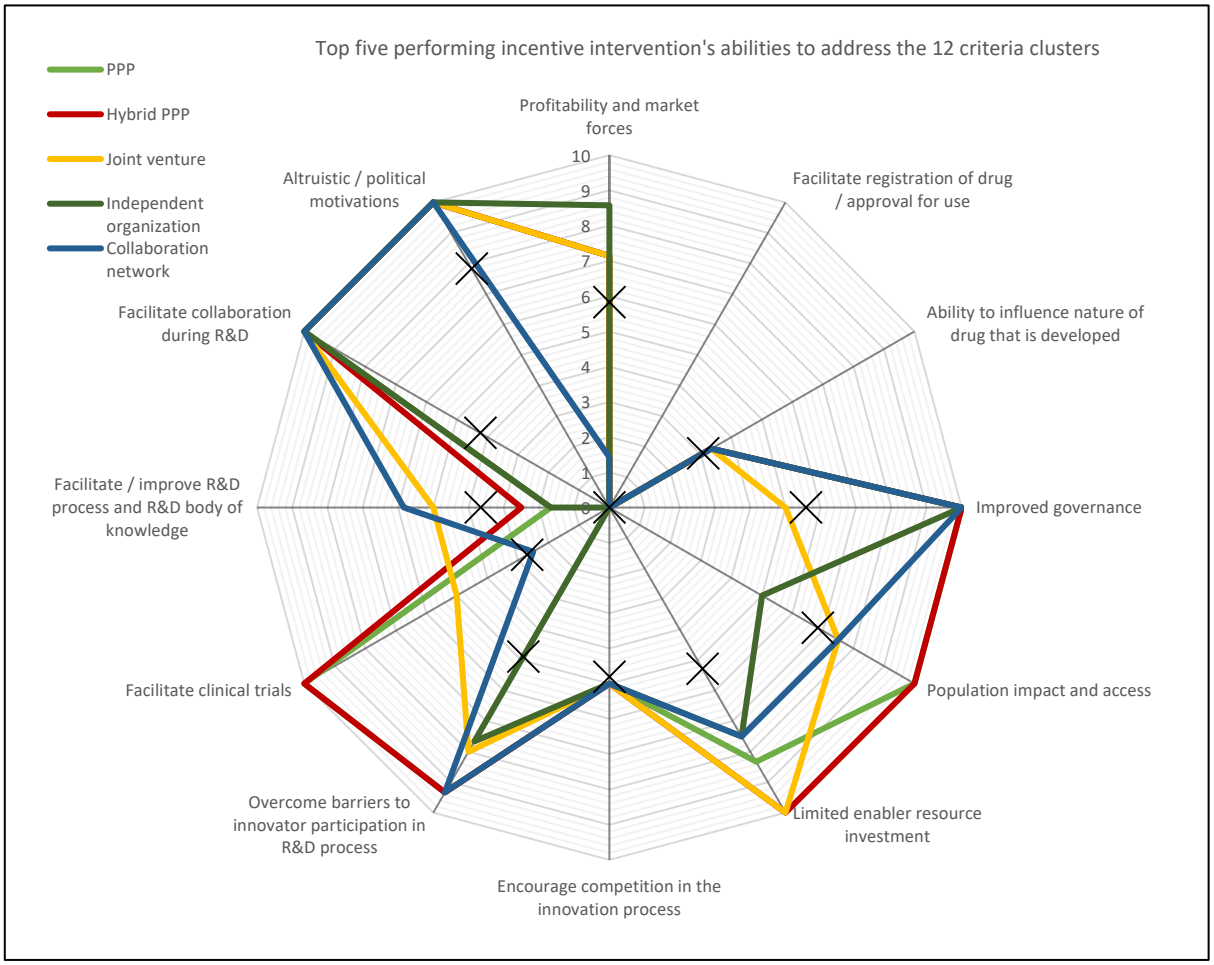
	Cluster 12: Altruistic / political motivations	Incentive convey an important message (Enabler goal)	Incentive allows corporate social responsibility to be fulfilled	Incentive allows enabler to fulfil corporate social responsibility (Enabler goal)	Incentive allows innovator to fulfil corporate social responsibility (Innovator goal)	Incentive allows enabler to fulfil political obligations	Incentive allows enabler to fulfil political obligations (Enabler goal)	Incentive allows innovator to fulfil political obligations (innovator goal)	Incentive allows not for profit R&D (Innovator goal)	Incentive allows not for profit/ restricted profit margins for drug procurers	Incentive enables/ allows restricted profit margins for drug procurers	Incentive enables no profit margins for drug procurers
		2		2	3		2	3	3		4	4
	3	0	1	1	0	0	0	0	2	0	0	0
Push mechanisms												
Grant		0	1	1	1	1	1	1	1	0	0	0
Open-source initiative		1	1	1	1	1	1	1	1	1	1	1
Patent pool		0	1	1	1	0	0	0	1	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	0
Tax credits		0	0	0	0	0	0	0	0	1	1	0
Outcome-based pull strategies												
Advanced market commitments (AMC)		0	1	1	1	1	1	1	0	1	1	0
Differential pricing		1	1	1	1	1	1	1	1	1	1	0
Patent buy-outs		0	0	0	0	0	0	0	0	1	1	0
Pooled fund		0	1	1	1	1	1	1	1	0	0	0
Prize fund		0	1	1	1	0	0	0	1	0	0	0
Rating system		1	1	1	1	1	1	1	1	0	0	1
Lego-regulatory pull strategies												
Intellectual property		0	0	0	0	0	0	0	0	1	1	0
Policy instrument		0	1	1	1	1	1	1	1	1	1	1
PRV		1	0	0	0	0	0	0	1	1	1	0
Trade, tariff adjustments		0	1	1	1	1	1	1	1	1	1	1
Hybrid strategies												
Collaboration network and consortiums		1	1	1	1	1	1	1	1	0	0	1
Colloquium and symposium		1	1	1	1	0	0	0	1	0	0	1
Policy and legislation		0	1	1	1	1	1	1	1	1	1	1
Drug status designation		1	1	1	1	0	0	0	1	0	0	1
Joint venture		0	1	1	1	1	1	1	1	1	1	1
Independent organization		0	1	1	1	0	0	0	1	0	0	1
Hybrid between PPP and other mechanisms		0	1	1	1	1	1	1	1	1	1	1
Research laboratories		0	1	1	1	1	1	1	0	0	0	1
Treaty		0	0	0	0	1	1	1	0	1	1	1
Working group		1	1	1	1	1	1	1	1	1	1	1
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	1

Domain 5 solution set (1 of 2): Hybrid PPP results



Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													10	Feasible
22	Hybrid PPP													10	Feasible
20	Joint venture													9	Feasible
21	Independent organization													9	Feasible
16	Collaboration network													9	Feasible
26	Coordination mechanism													8	Feasible
24	Treaty													7	Feasible
10	Prize fund													7	Feasible
25	Working group													6	Feasible
7	Differential pricing													5	Feasible
9	Pooled fund													5	Feasible
17	Colloquium and symposium													5	Feasible
23	Research laboratories													4	Feasible
1	Grant													4	Feasible
12	Intellectual property													3	Feasible
8	Patents buy-outs													3	Feasible
13	Policy instrument													6	Infeasible
18	Policy and legislation													6	Infeasible
11	Rating system													6	Infeasible
19	Drug status designation													5	Infeasible
15	Trade, tariff adjustments													5	Infeasible
6	Advanced market commitments													5	Infeasible
2	Open-source initiative													5	Infeasible
14	PRV													5	Infeasible
3	Patent pool													5	Infeasible
5	Tax credits													4	Infeasible

Domain 5 solution set (2 of 2): Hybrid PPP results



Non-incentive-based interventions (1 of 8): Hybrid PPP results

1. Country economic status		*For further reference*	
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)	2
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

2. Burden fully characterized		*For further reference*	
Meaning	The affected patients are diagnosed, being monitored and documented properly.	(Olmsted et al., 2006; RAND Corporation, 2007; Novak et al., 2013)	1
Relevance	Once the burden of a disease is fully characterized, consumer demand can be estimated. Consumer demand will have an influence on how profitable the perceived market is. Fully characterizing the burden also assists in the planning, distribution and implementation of control strategies.		
Intervention considerations	Diagnostic tools and technology, availability and access there of		
	Diagnostic intervention and intervention strategies		
	Availability of health facilities (option is to consider mobile health facilities)		
	Educate populations on disease side-effects, risks, and necessity of health interventions		
	Capture burden characterization data		

3. Physicians per 1000 population		*For further reference*	
Meaning	The number of physicians available per capita / 1000 of people	(Al-Shamsi, 2017)	1
Relevance	The higher the availability of physicians in a country, the higher the likelihood that the population will have access to adequate care.		
Intervention considerations	Recruit international medical graduates		
	Modify postgraduate majors to allow physicians to enter the practice in areas of need		
	Shorten the preparatory under-graduate medical education years and introduce modern methods of teaching.		

4. Quality of existing drugs		*For further reference*	
Meaning	Drugs should not pose significant health risks to patients and should be effective in treating the disease.	(van Olmen et al., 2010); (Dorlo et al., 2012); (Rauscher, Walkowiak and Djara, 2018); (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	1
Relevance	Patients depend on drugs for disease mitigation. If quality is not up-to-standard, then disease burden might increase or might not decrease.		
Intervention considerations	Repeat final clinical trial stages to monitor effects of medicine in a controlled environment		
	Remove drugs from market		
	Improve monitoring of ADR		
	Pharmacovigilance		
	Quality control of current manufacturing procedures		
	Enforce international clinical trial and manufacturing practices and regulations		

5. Availability of drugs for the desired population		*For further reference*	
Meaning	Drugs are available in the right quantities, on the right time for patients to access.	(Jackson, 2018) ; (Niëns and Brouwer, 2013), (Holt, Gillam and Ngondi, 2012)	2
Relevance	If drugs are adequate but not available, then patients might not be effectively treated. Possible resistance to medicines.		
Intervention considerations	Supply chain management		
	Distribution networks		
	Inventory management at health facilities		
	Replenishment systems at health facilities		
	Burden characterization assists in inventory planning		

Non-incentive-based interventions (2 of 8): Hybrid PPP results

6. Affordability of current drugs to desired population		*For further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	2
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

7. Appropriateness of drugs to the desired population		*For further reference*	
Meaning	Drugs must target the disease intended for. Intervention must be understandably explained and not interfere with culture.	(Jackson, 2018), (Hotez, 2008)	1
Relevance	If drugs are not appropriate, then patients won't use it or, if they use it, improvements in disease burden will not be made.		
Intervention considerations	Screen culture and explore possible cultural and ethical issues		
	Improve diagnostics of patients		
	Communication in understandable language for population group		
	Survey to understand the feelings of patients		

8. Acceptability of drugs to the desired population		*For further reference*	
Meaning	Drugs are not acceptable because of cultural values norms or stigmas.	(Jackson, 2018) ; (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	1
Relevance	If patients do not accept drugs, then intervention strategies go to waste.		
Intervention considerations	Educate people to reduce stigmas.		
	Educate people to understand potential of drugs.		
	Respect and honour the norms and values of the patient group.		

9. Comprehensiveness of services delivered		*For further reference*	
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004), (WHO, 2010)	1
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.		
Intervention considerations	Education of prevention measures.		
	Address root-cause of disease (e.g. water and sanitation)		
	Investigate the needs of the affected population group		
	Address social needs of patients		
	Repeat prevention or mass drug administration interventions, if deemed necessary.		

10 Continuity of patients' access to health services [Check in Case study 1 Appendix]		*For further reference*	
Meaning	For health interventions where once-off treatment is not adequate, follow-up treatments must be scheduled and adhered to.	(Jackson, 2018, (Holt, Gillam and Ngondi, 2012, Stevens, 2004)	1
Relevance	If follow-up treatments are not provided, then patient health might not improve as desired.		
Intervention considerations	Scheduling of follow-up interventions		
	Mobile health facilities		
	Track patient health records and data		
	Monitor and track patients		

11. Coordination of service delivery networks		*For further reference*	
Meaning	Service delivery is done in an organized, timely, professional and appropriate manner.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; WHO, 2010a; Rauscher et al., 2018)	1
Relevance	If service delivery is not coordinated properly, then some patients might be overlooked for treatment, not have access, or might miss the opportunity to meet with health care workers (if not properly communicated)		
Intervention considerations	Communication services		
	Scheduling of health workers		
	Monitor service delivery per area		
	Monitor drug distribution or mass drug administrations per region.		

Non-incentive-based interventions (3 of 8): Hybrid PPP results

12. Minimize waste of resources in service delivery		*For further reference*	
Meaning	Any resource that is not used or used in an effective or efficient manner, leads to waste and possible financial losses.	(Priya, Nandini and Selvamani, 2012)	1
Relevance	Given that most waste is preventable, resources could be used in a more effective manner.		
Intervention considerations	Monitor service delivery to identify and address waste.		
	Coordinate service delivery actions		
	Waste management		

13. Demand size or sales force (relates to disease burden)		*For further reference*	
Meaning	The size of the burdened population, and patients who needs medicines, or intervention strategies.	(Novak et al., 2013; RAND Corporation, 2007)	0
Relevance	By determining the size of the burdened population, service delivery and intervention strategies can be planned more accurately. Also, service delivery waste can be reduced.		
Intervention considerations	Characterization of the burden of disease		
	Diagnostic interventions		
	Target repurposing		
	The size of the burdened population, and patients who needs medicines, or intervention strategies.		

14. The role of brand loyalty		*For further reference*	
Meaning	Brand loyalty of consumers to certain brands / drugs means that consumers buy certain drugs, based on previous experience, or perceived value. (relevant to other brands).	(Griffiths, 2008; Panchal *et al.*, 2012)	1
Relevance	If a product does not have brand loyalty, it might have the necessary characteristics to mitigate disease, but patients are not using it as a result of not 'trusting' the drug.		
Intervention considerations	Awareness amongst physicians of the value of the drug		
	Build trust in the communities		
	Well planned market strategies		

15. Bargaining power of the suppliers (chemical entities)		*For further reference*	
Meaning	The ability of suppliers to influence the prizing of the entities that they offer the pharmaceutical innovators and manufacturers.	(Whiteside, 2016)	1
Relevance	The stronger the bargaining power of the suppliers; the higher the prizes of resources, and the higher the total cost of drug interventions.		
Intervention considerations	Research alternative suppliers.		
	Support local suppliers.		
	Consider importing of goods.		
	Ensure quality of suppliers, if weak bargaining power.		

16. Existence of competitors		*For further reference*	
Meaning	Competitors refer to other pharmaceutical innovators completing R&D in the same field, thus, targeting the same disease.	(Thakor and Lo, 2018; (Whiteside, 2016)	1
Relevance	Strong competition exists because of intellectual property rights that are gained for new chemical entities innovated.		
Intervention considerations	Explore and compare for similar drugs being marketed as different products.		
	Competition is not always a bad thing (speeds up discovery)		
	Collaboration and open innovation		

17. Political will and contribution to improve R&D for disease		*For further reference*	
Meaning	The effort and contribution that the government of a country is willing to make towards R&D of diseases.	(Brinkerhoff, 2003; (Emmanuel and Emmanuel, 1996; World Health Organization, 2018)	2
Relevance	Governments should be obligated to make significant efforts to reduce disease burden within a country		
Intervention considerations	Enforce SDGs		
	Ministry of Health audit		
	Policy reform		
	Political accountability systems		

Non-incentive-based interventions (4 of 8): Hybrid PPP results

18. Effective national budget allocation		*For further reference*	
Meaning	The financial plan of a country should include planning and financial allocations to the health and health care of citizens.	(World Health Organization, 2018; Emmanuel and Emmanuel, 1996; Becker, 2015)	1
Relevance	The health care of a country is the responsibility of its government. Without budget allocation, health care advancement is less likely.		
Intervention considerations	Implement SDGs		
	Policy reform		
	Strategic resource allocation options		
	Global health governance		

19. Regulation of strategic health policy		*For further reference*	
Meaning	The goals, visions, priorities and budgetary decisions of a country needs to be regulated, to be in line with health needs.	(Liang and Mackey, 2012; World Health Organization, 2018; Nagpal, Sinclair and Garner, 2013)	1
Relevance	If the strategic plans and actions to undertake and achieve are not taken, then the health of the country will lack improvement.		
Intervention considerations	Global health governance		
	Strategic political interventions		
	Domestic, private, and global policy interventions		

20. Adequate supply of the health service		*For further reference*	
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Jacobs et al., 2012; RAND Corporation, 2007; Manjit Kaur; Sarah Hall, 2002)	2
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

21. Monitoring of the actual health system and system performance		*For further reference*	
Meaning	The observation and measurement of health system performance.	(WHO, 2010a; International Federation *et al.*, 2015; Jones *et al.*, 2015; Newman *et al.*, 2016)	1
Relevance	By observing and measuring performance of the health system, problems can be located faster and more easily.		
Intervention considerations	Information systems and data handling		
	Pharmacovigilance		
	Reporting networks		
	Personnel training		
	Accountability networks and schedules		

22. Current investment capital and returns		*For further reference*	
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Vischer et al., 2017; Bates et al., 2015; Ho, Zarrinpar and Chow, 2016; Payne et al., 2015)	1
Relevance	This factor refers to the current ROI being profitable or not, if not then more investment in a similar research area is not likely.		
Intervention considerations	Financial analysis		
	Cost analysis of activities		
	Reduce indirect and operational costs		

23. Stakeholder demand		*For further reference*	
Meaning	Stakeholder demand refer to whether the public desires, and needs the product being developed.	(Thakor and Lo, 2018; Whiteside, 2016)	0
Relevance	The higher the demand for the products being delivered, the greater the perceived potential ROI.		
Intervention considerations	Target market analysis		
	Marketing strategies		
	Inform governments and the public that require this drug.		
	Pricing of the product		

Non-incentive-based interventions (5 of 8): Hybrid PPP results

24. Established marketing and distribution network		*For further reference*	
Meaning	The marketing and distribution of drugs are important, to inform patients, and provide access and availability.	(Ravn, 2012; Radulescu, 2012)	1
Relevance	Distribution adds to effective service delivery; and marketing creates and enlarges the market demand.		
Intervention considerations	Marketing strategies		
	Effective distribution networks		
	Supply chain management		
	Coordination of service delivery, inventory management and distribution services		

25. Consistency and recommendations on choosing metrics for clinical trials		*For further reference*	
Meaning	Clinical trials are the most timeous procedure of drug R&D, using the correct metrics are essential in innovation productivity.	(Gupta et al., 2016; Moatti et al., 2016; Mayo et al., 2017; Clifton, Kohrt and Peoples, 2015; Zhou et al., 2015)	0
Relevance	Guidelines and regulations should be followed to advance in clinical trial phases. If not consistent then clinical trials might be trivial.		
Intervention considerations	Structured regulations and policy recommendations		
	Standardized clinical trial metrics		
	Market authorization regulation		
	Capture data of clinical trial methods and metric outputs		

26. Transparency of clinical trial information		*For further reference*	
Meaning	Clinical trial information is openly available, reliable and does not entail any suspicious information.	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	0
Relevance	Transparent clinical trial information assures that products being developed adhere to safety, efficacy and regulatory requirements.		
Intervention considerations	Annual, and unannounced firm audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

27. Accountability of clinical trial information		*For further reference*	
Meaning	Clinical trial information should be trustworthy	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	1
Relevance	There should be clear accountability for the information of clinical trials.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

28. Accessibility of clinical trial information		*For further reference*	
Meaning	The clinical trial information should be made available (within the market exclusivity agreements)	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	1
Relevance	Secrecy on critical clinical trial information not allowed, especially if it alters the safety and efficacy of the drugs.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

29. The use of innovative clinical trial tools and technology		*For further reference*	
Meaning	Advanced tools and technologies exist for performing clinical trials.	(McKinsey&Company, 2017)	0
Relevance	Modern technology and tools assist in clinical trial and drug discovery processes and might enhance the R&D process.		
Intervention considerations	Research on tools and technology available		
	Reliability of current tools and technology used in clinical trials		
	Break-even of getting new equipment, tools and technologies		
	Cost-benefit analysis of getting new equipment, tools and technologies		

Non-incentive-based interventions (6 of 8): Hybrid PPP results

30. Struggling to prove efficacy		*For further reference*	
Meaning	The ability of pharmaceutical innovators to prove that the drug fulfils the intended result.	(PhRMA, 2016)	1
Relevance	Drugs should target the intended disease and be effective in treating the patients.	(Hay et al., 2014)	
Intervention considerations	Clinical trial information quality	(von Ranke, Fierro and Antunes, 2016) (Ho, Zarrinpar and Chow, 2016)	
	Clinical trial design		
	Tools, technology and equipment used for clinical trials		
	Adhere to international regulation standards		

31. Legal and ethical regulations for clinical trials too difficult		*For further reference*	
Meaning	Extensive laws and regulations exist for the development of drugs.	(Califf and Sugarman, 2015), (Salas, 2017), (Tsukamoto et al., 2016), (Cheng and Xie, 2017), (Tsourounis et al., 2015)	1
Relevance	A lot of difficulty is experienced in bridging legal and ethical barriers in drug R&D.		
Intervention considerations	Collaborate with bigger pharmaceutical organizations		
	Availability of third parties to adhere to regulations and laws		
	Complete annual audits		
	Ensure data transparency, accuracy and accountability		

32. Safety assessments standards		*For further reference*	
Meaning	Safety assessment standards should be adhered to, to quantify and measure risks involved in the drug being developed.	(Singh and Loke, 2012)	1
Relevance	Drugs that does not adhere to safety standards might pose a health risk to patients.	(PhRMA, 2016)	
Intervention considerations	Health authority standards and regulations	(Hay et al., 2014)	
	Clinical trial practices and designs		
	Randomized controlled trials		
	Global health governance		

33. Adaptive clinical trials occurrence		*For further reference*	
Meaning	Clinical trials that involves observing participant outcomes and adjusting drug parameters in accordance.	(Gokhale and Gokhale, 2016)	1
Relevance	Without adaptive clinical trials, important observations cannot be made; and drug safety not improved to the extent necessary.	(Baylor College of Medicine, 2009)	
Intervention considerations	Amount of participants part of adaptive clinical trials	(Hay et al., 2014)	
	Procedures of adaptive clinical trials		
	Data capturing		
	Health authority standards and regulations		

34. Recruitment and retention of participants		*For further reference*	
Meaning	Clinical trials require participants to perform drug safety and adequacy tests.	(Kurt et al., 2017) (Hammer, Eckardt and Barton-Burke, 2016) (Jennings et al., 2015), (Thacker, T., Wegele, A.R., Pirio Richardson, 2016)	1
Relevance	Effort should be done to recruit the right number of participants for clinical trial tests		
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Ensure safety of participants		
	Build trustworthy relationships with participants		

35. Racial differences in participation in clinical trial		*For further reference*	
Meaning	A variety of ethnicity groups, races and both genders' response on the drugs needs to be tested	(Kurt, Semler, et al., 2017)	1
Relevance	Given that drugs can be used by anyone, tests should be performed on various people to test for any difference in reactions or dosage requirements.	(Baylor College of Medicine, 2009)	
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Build trustworthy relationships with participants		

Non-incentive-based interventions (7 of 8): Hybrid PPP results

36. Relationships between innovators and participants		*For further reference*	
Meaning	Innovators should strive to have a professional, and trustworthy relationship with participants	(Kurt, Semler, et al., 2017) (Tsukamoto et al., 2016) (Califf and Sugarman, 2015) (Salas, 2017)	1
Relevance	If the relationship between innovators and participants is not appropriate; then participants might not agree to complete more trials.		
Intervention considerations	Build trust with participants, by following standard clinical trial procedures		
	Adhere to safety and regulation standards		
	Monitor participants closely		
	Capture data		

37. Physician participation		*For further reference*	
Meaning	Qualified medical practitioners should be present in clinical trial tests on humans.	(Baylor College of Medicine, 2009)	1
Relevance	Qualified physicians will be able to monitor the health and wellbeing of patients in clinical trials, as well as respond if ADR occur.		
Intervention considerations	Incentivize physicians to participate		
	Provide proper training to physicians		
	Adhere to correct clinical trial procedures		

38. Skilled workforce		*For further reference*	
Meaning	Workforce, part of drug R&D process should be skilled to adequately perform tasks.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001), International Labour Office, 2010)	1
Relevance	If workforce is not skilled, preventable problems in the R&D process might arise.		
Intervention considerations	Train workforce (workshops, training programs)		
	Encourage mentorship in work environment		
	Ethical conduct		

39. Existence of manufacturing plants		*For further reference*	
Meaning	Manufacturing plants exists to perform adequate drug manufacturing.	(World Health Organization, 2016), (WHO, 2011)	1
Relevance	If no manufacturing plants exists, then producing drugs on large scale might be difficult.		
Intervention considerations	Encourage/ Incentivize SME drug manufacturers		
	Consider international manufacturing organizations		

40. Drug manufacturing adheres to regulatory requirements		*For further reference*	
Meaning	Drug manufacturing should adhere to regulatory requirements to ensure safety.	(Koeberle and Schiemenz, 2017) (Burnham et al., 2015), (Wechsler, 2015)	0
Relevance	Unregulated manufacturing practices poses potential risks to the drugs.		
Intervention considerations	Audit Manufacturing organizations		
	Global manufacturing practices		
	Comply to cGMPs (Current good manufacturing practices)		
	Unannounced visits by regulatory authorities to manufacturing facilities		

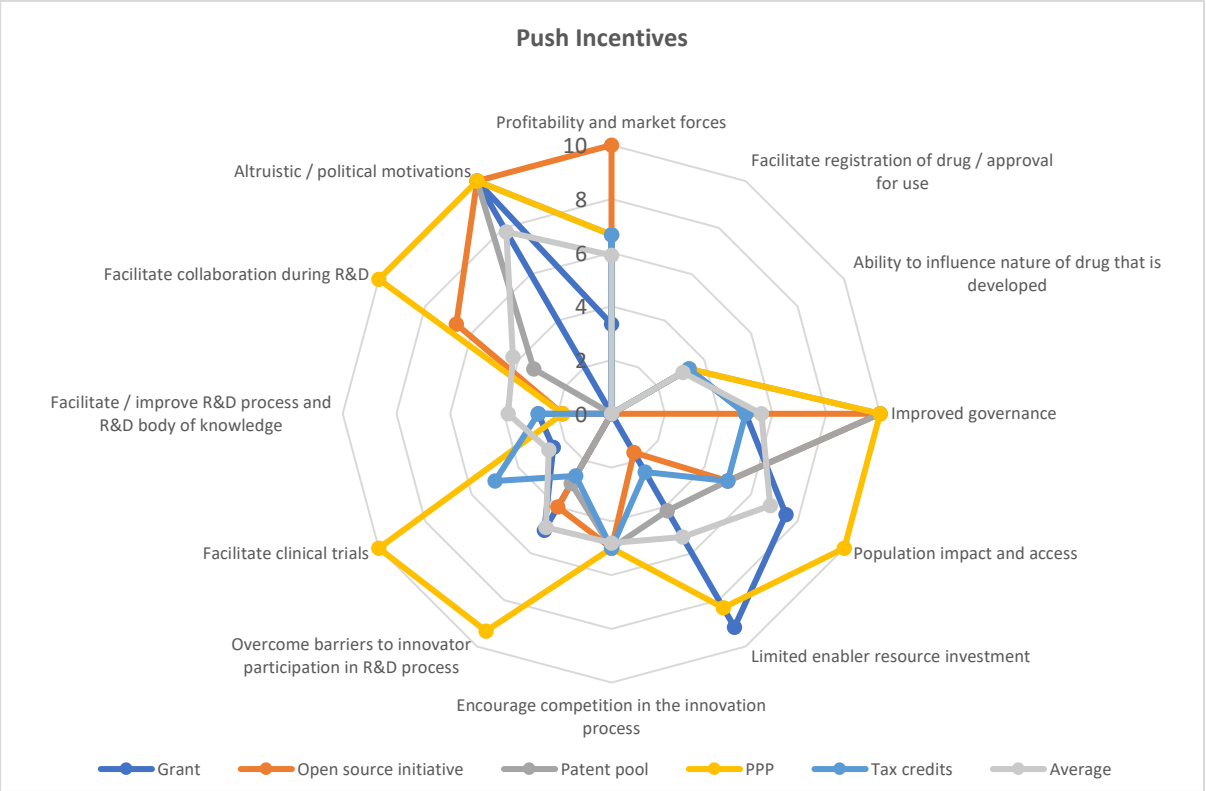
41. Appropriate technology used for the manufacturing of drugs		*For further reference*	
Meaning	A lot of technologies are available to manufacture drugs, some are advised by regulatory agencies.	(World Health Organization, 2011)	0
Relevance	Appropriate technology might improve the safety, productivity and quality of the drugs being manufactured.		
Intervention considerations	Comply to cGMPs		
	Research technology that is available		
	Complete cost-benefit analysis to ensure new technologies are strategic choices		
	Ensure compliance of all regulations and policies		

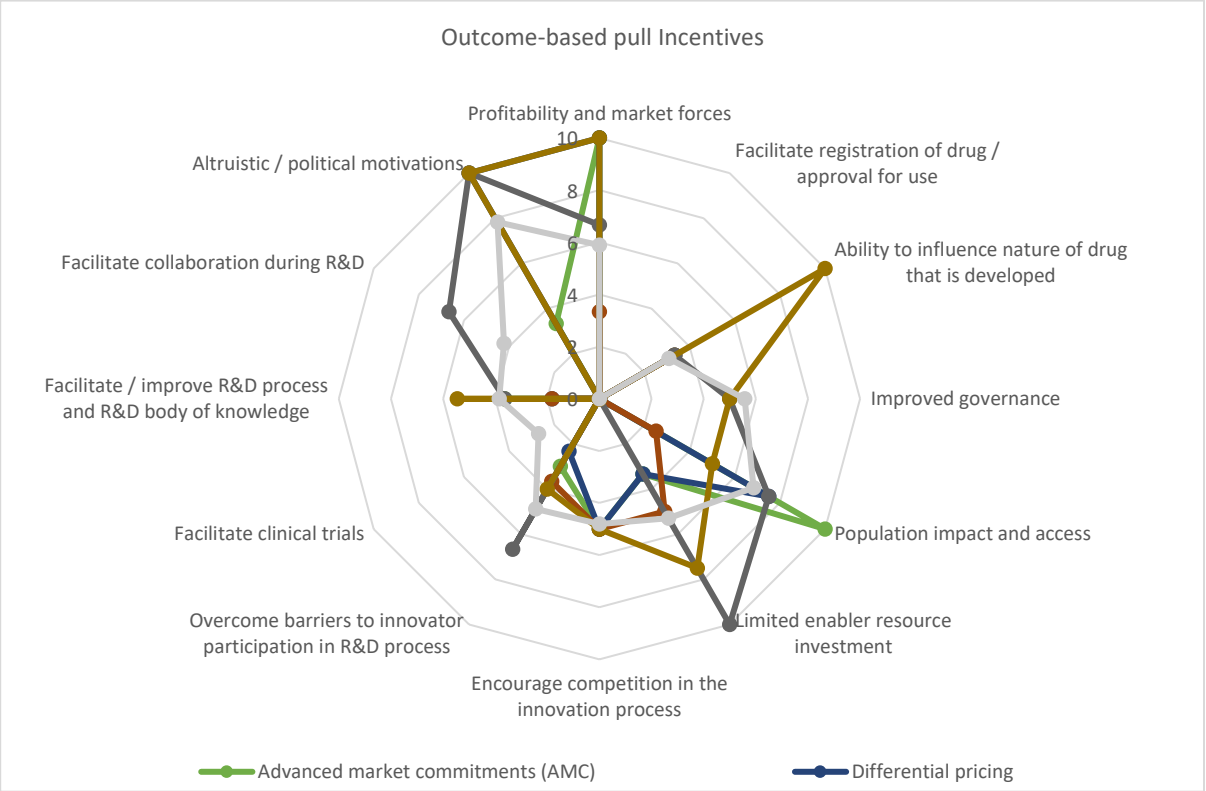
42. Health data generation		*For further reference*	
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	2
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

Non-incentive-based interventions (8 of 8): Hybrid PPP results

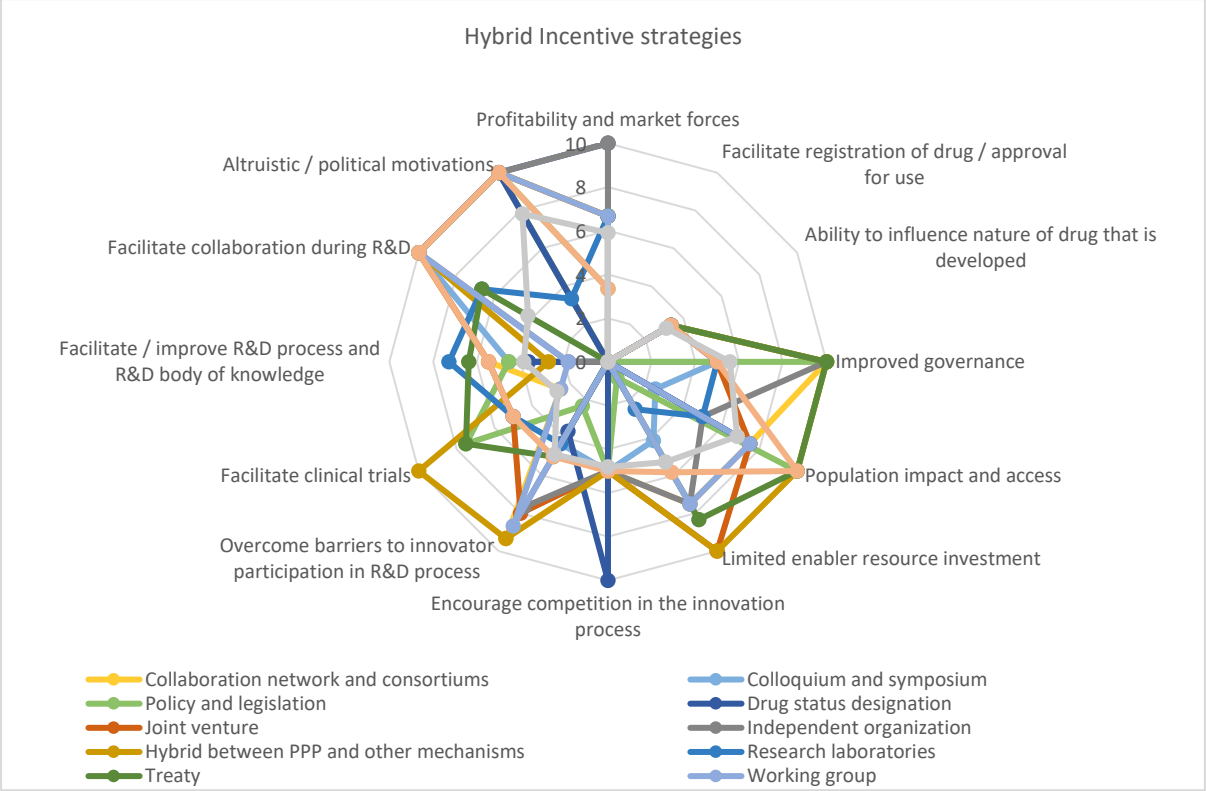
43. Communication and use of public health data		*For further reference*	
Meaning	Analysing, synthesising and validating health data	(WHO, 2010a)	1
Relevance	By evaluating health data, important measures can be implemented to satisfy growing needs, or gaps within the health system.		
Intervention considerations	Establish national sets of indicators with targets and accurate reporting which will inform health sector reviews and improve the planning of future interventions		
	Assess the health systems performance, to determine the success of current interventions		
	Adjust health system operation, based on accurate data.		
	Communicate health statistics to the public for awareness.		

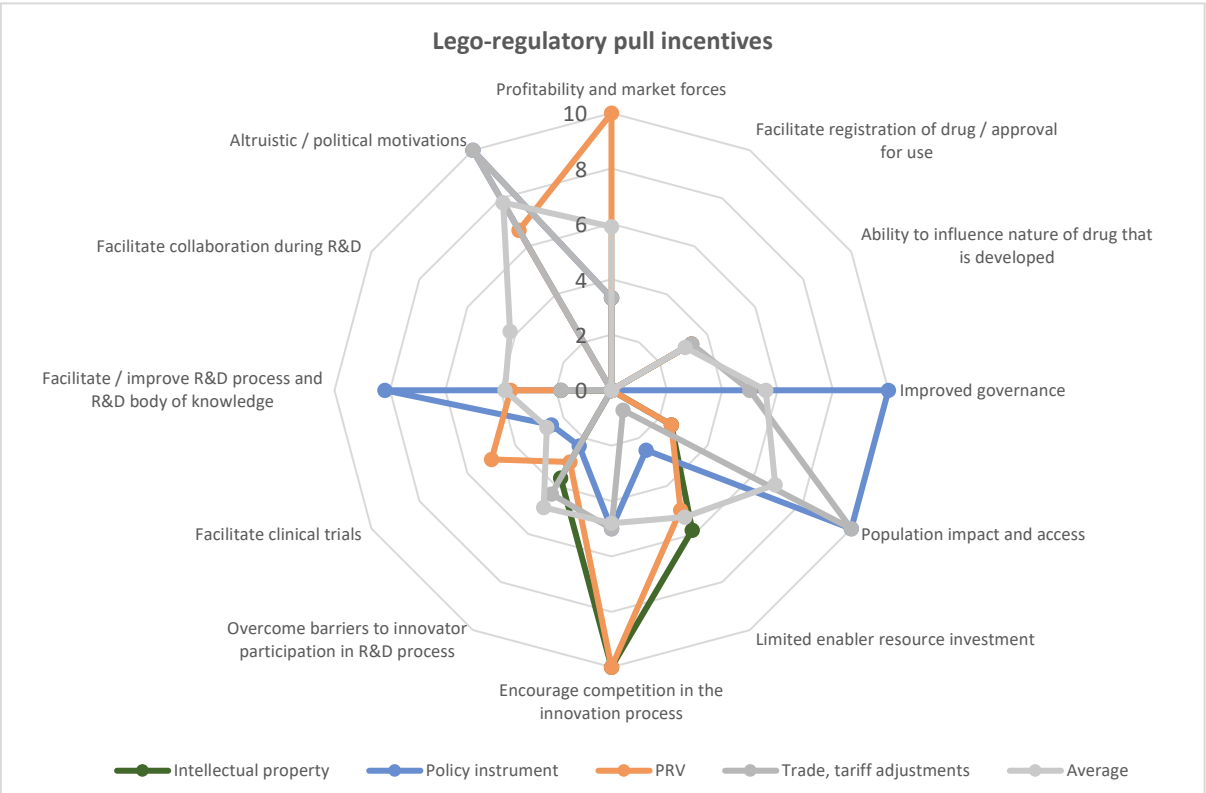
Supplementary material 1 (1 of 2): Hybrid PPP results



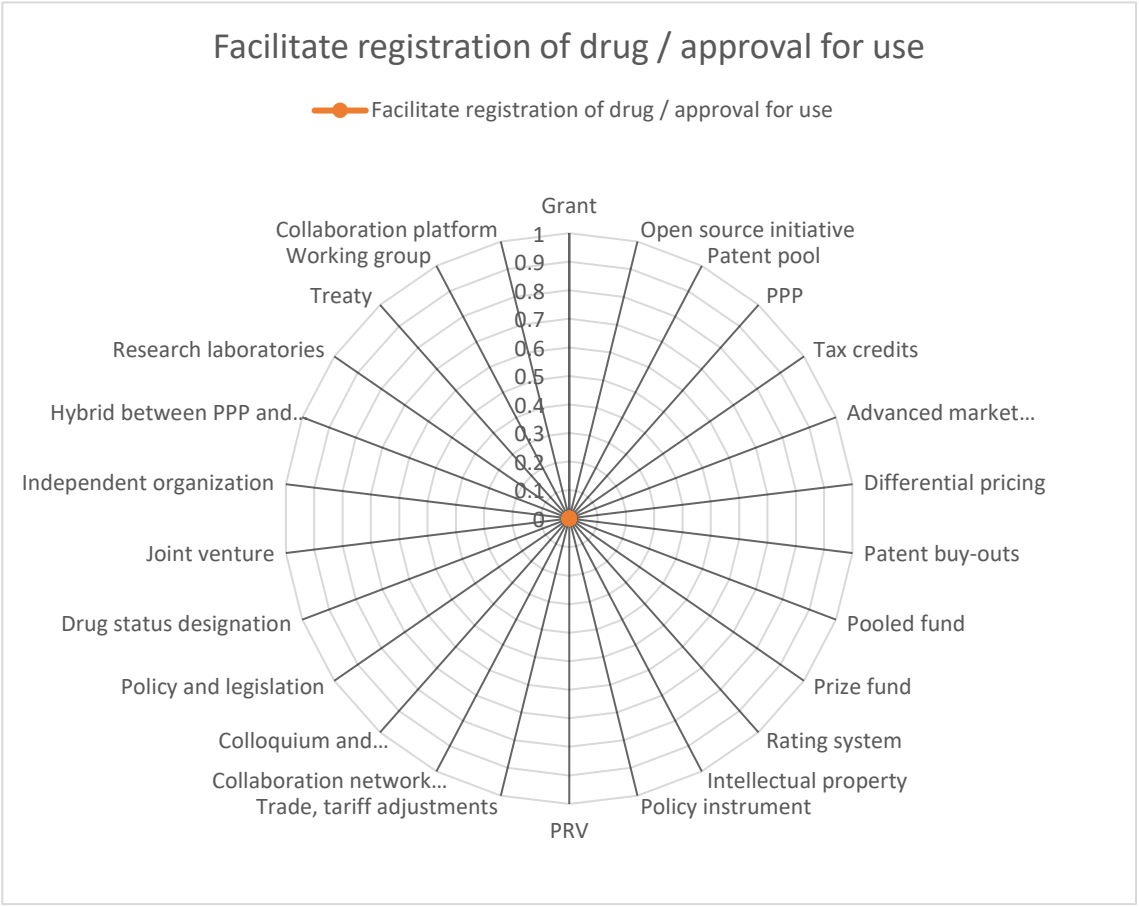


Supplementary material 1 (2 of 2): Hybrid PPP results





Supplementary material 2 (1 of 6): Hybrid PPP results



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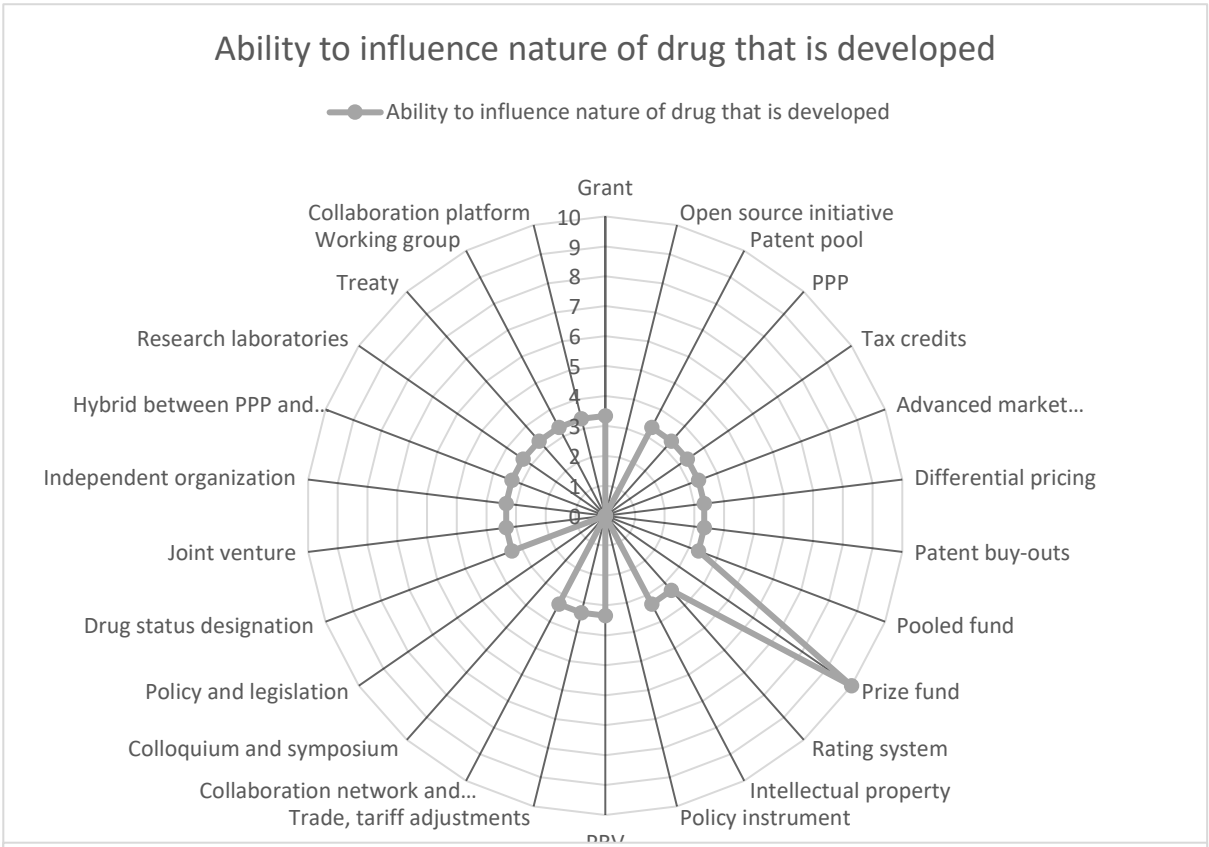

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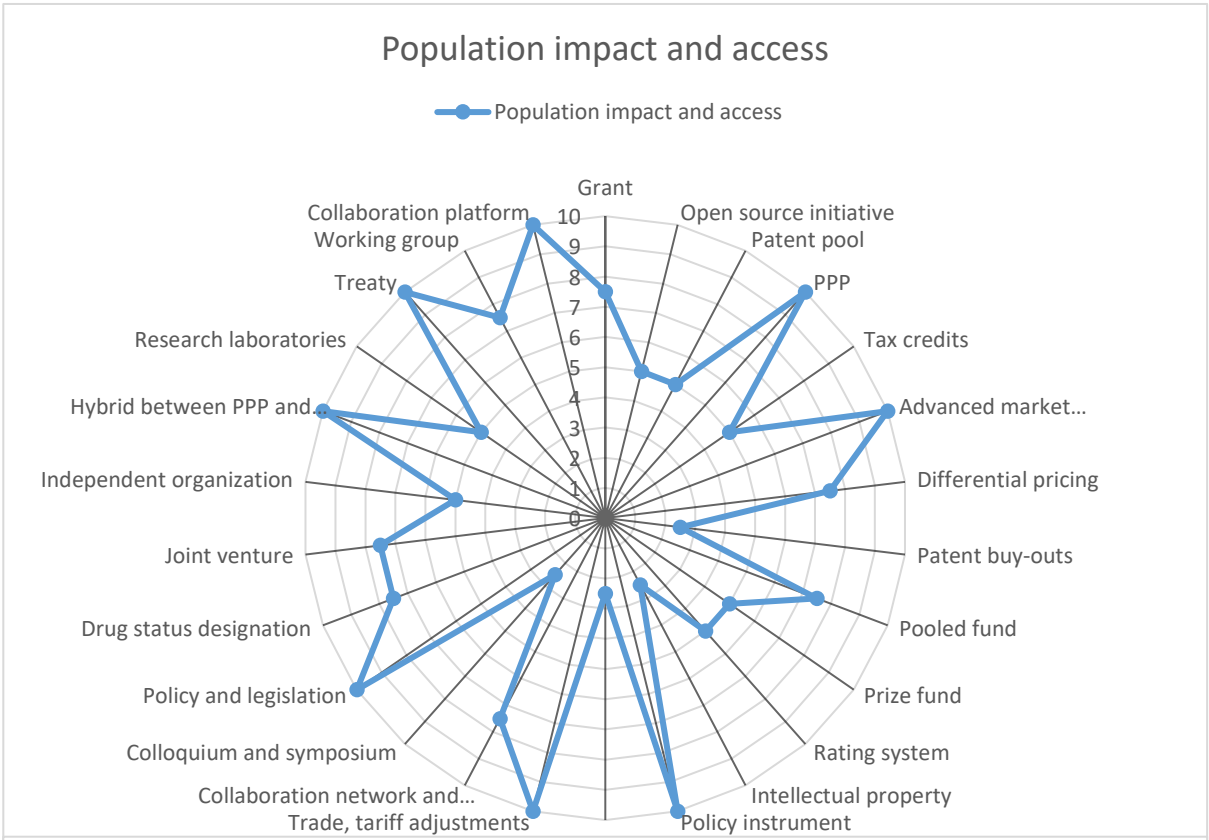

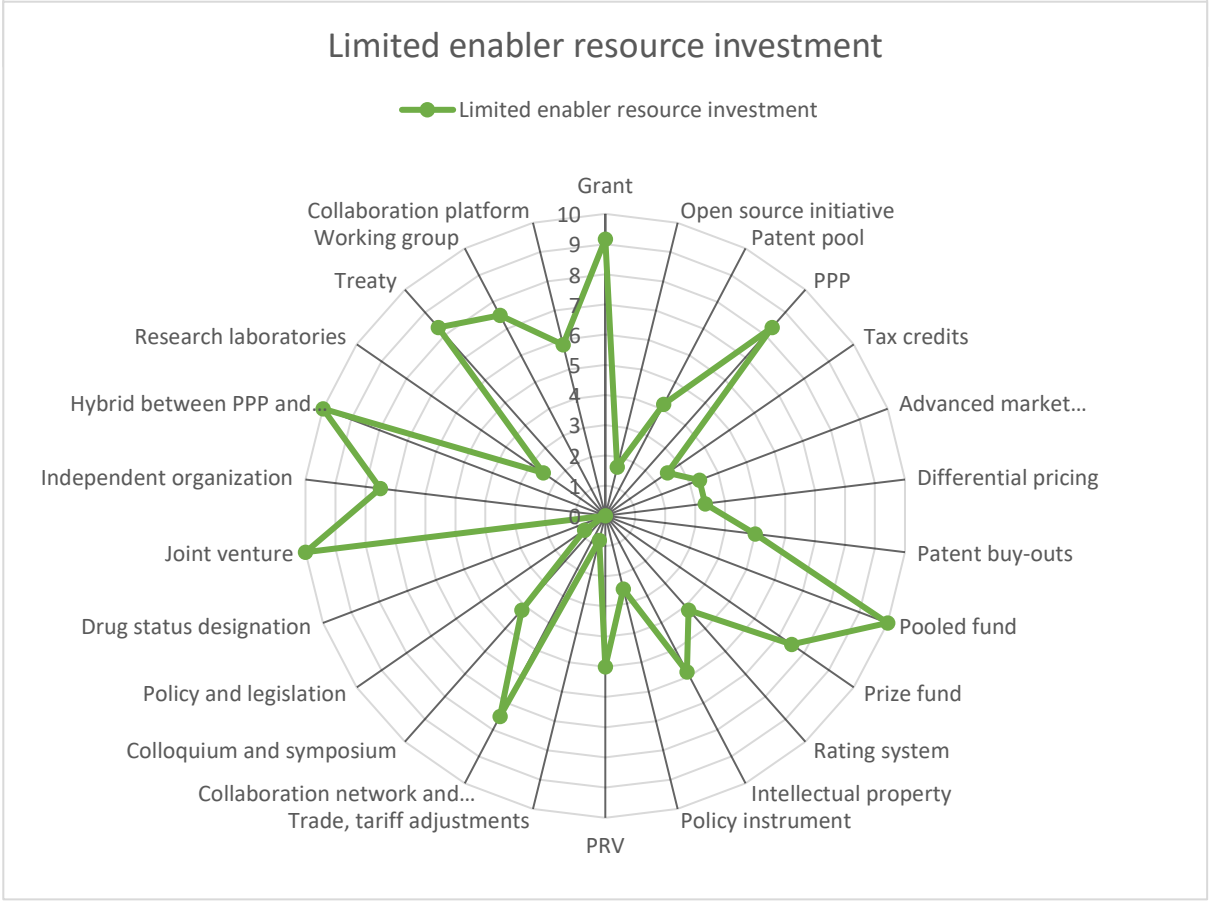

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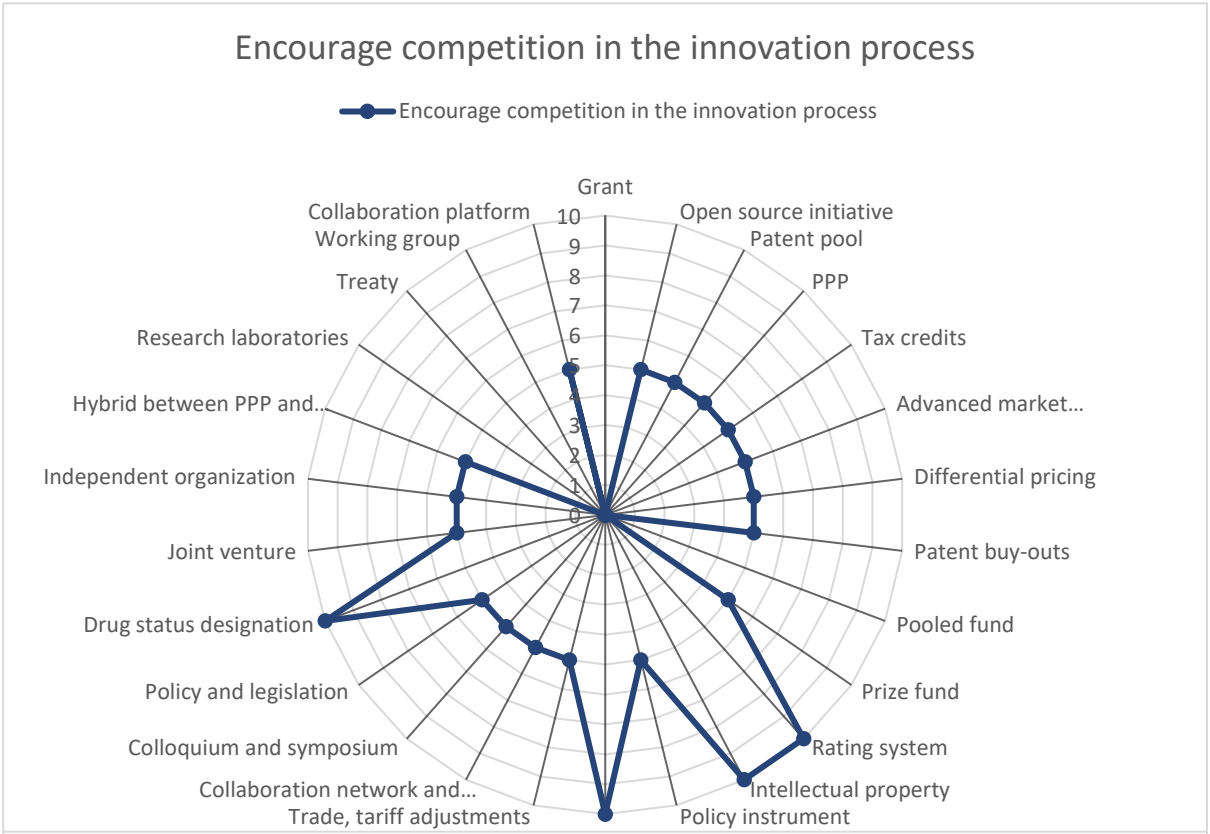

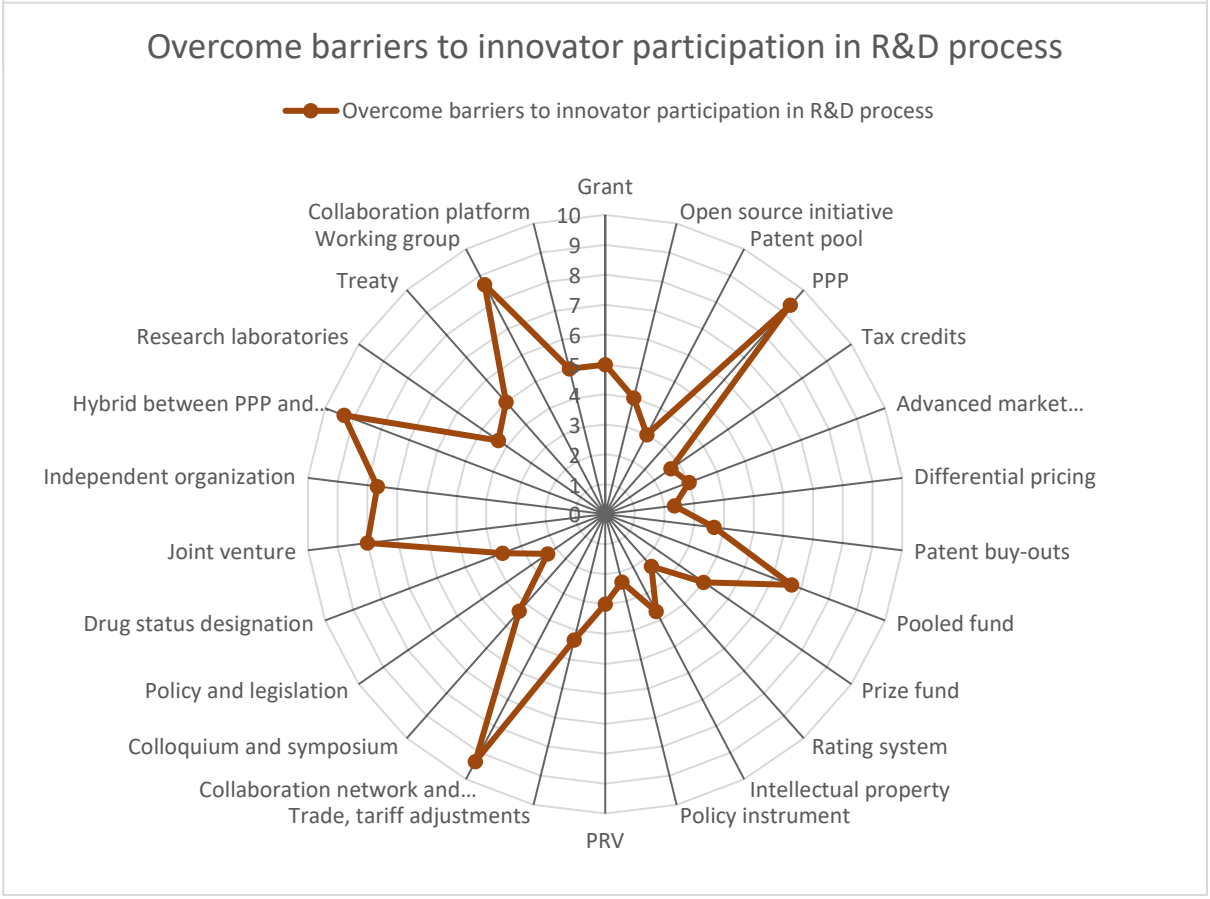

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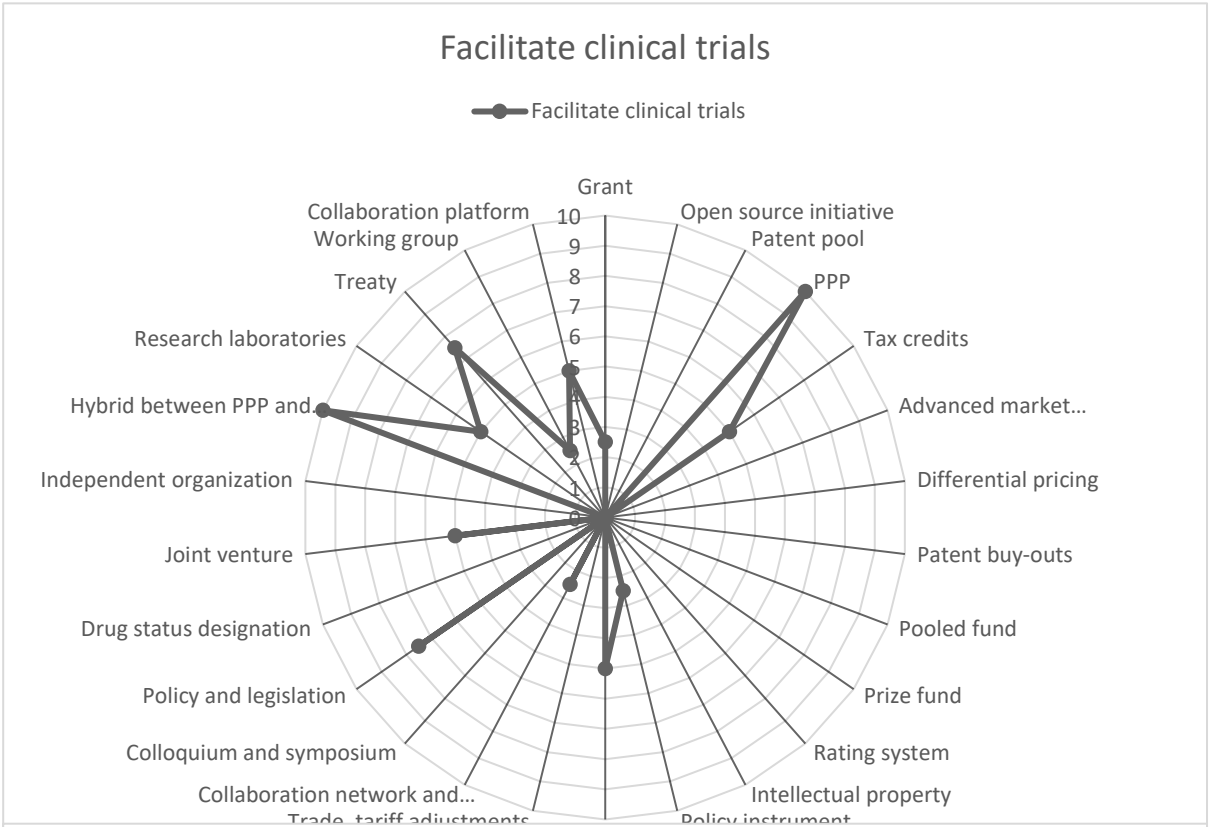
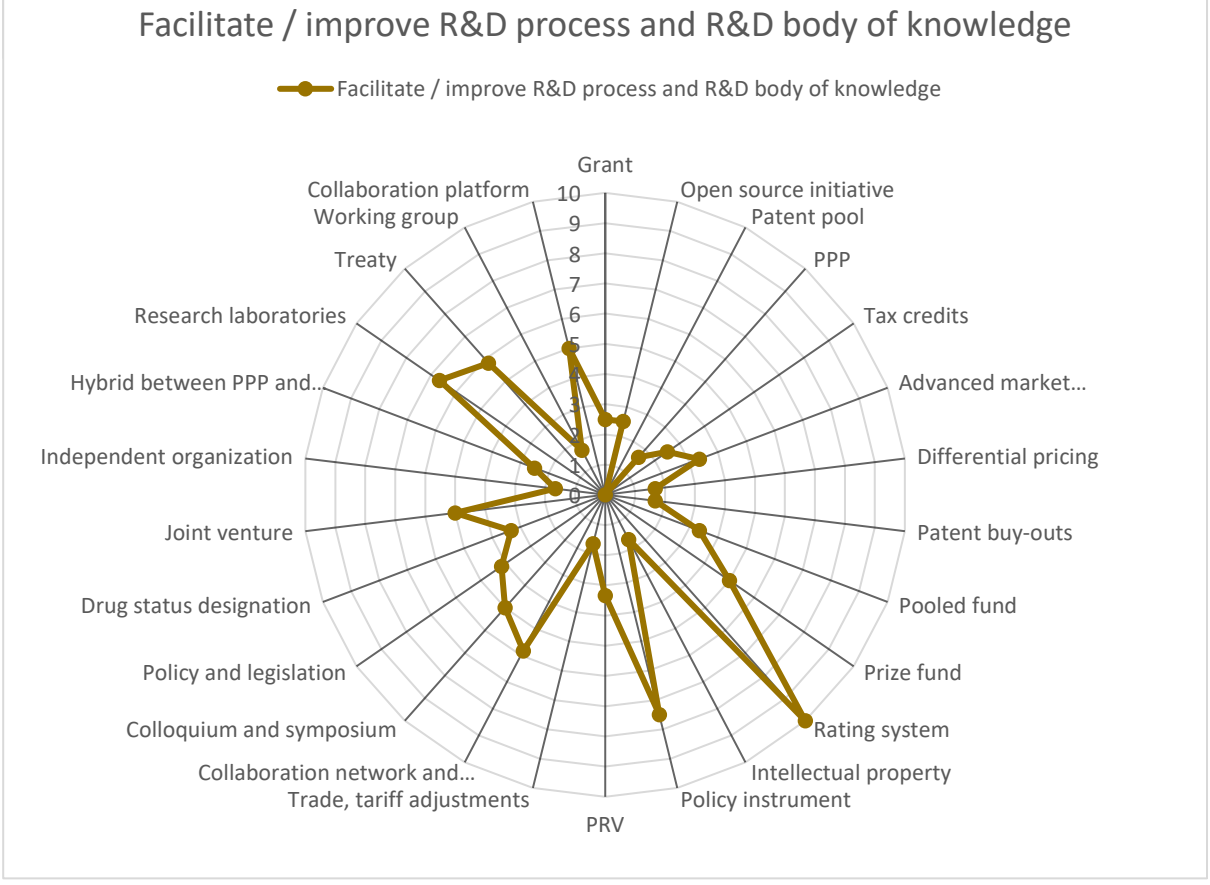
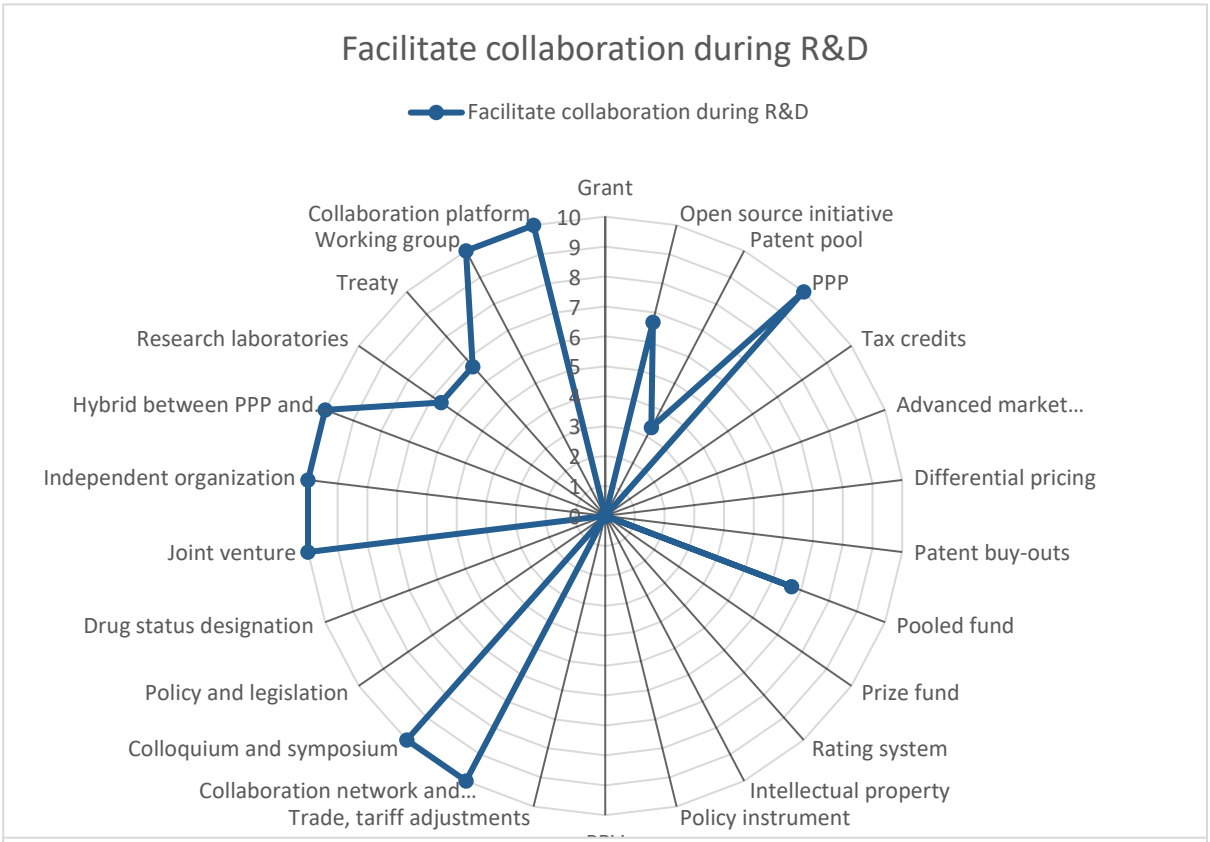
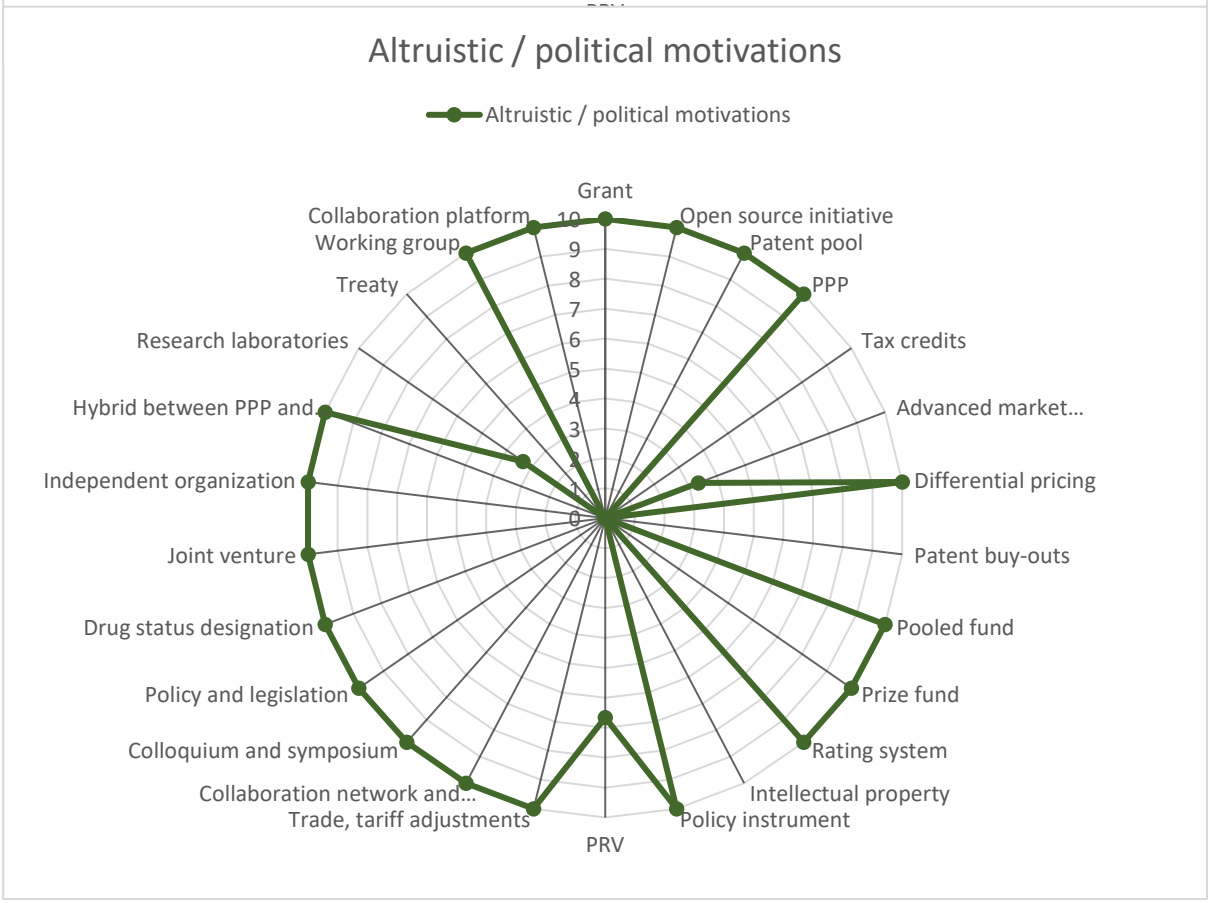


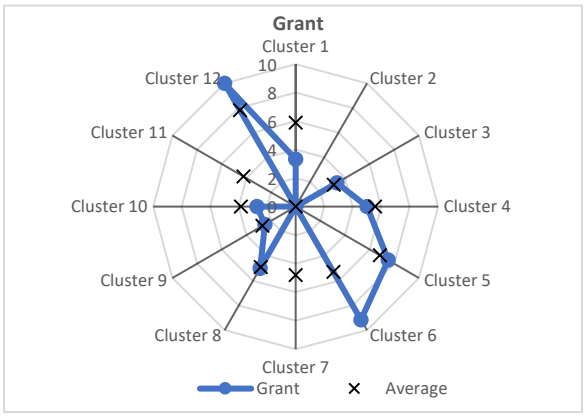


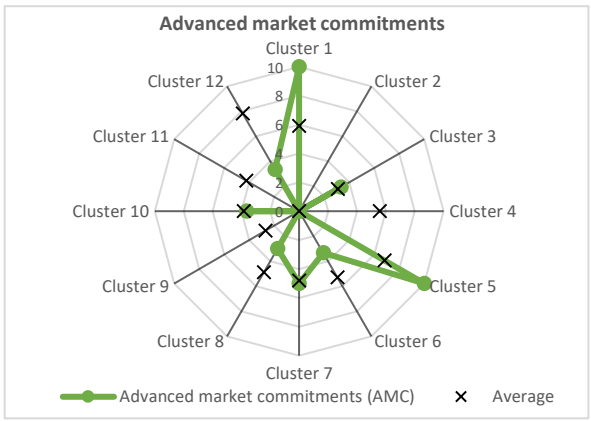
Supplementary material 2 (6 of 6): Hybrid PPP results

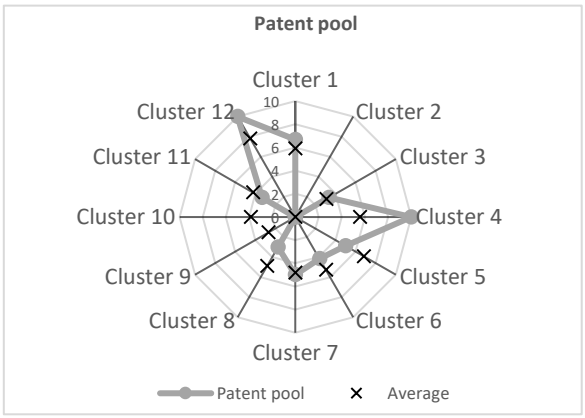


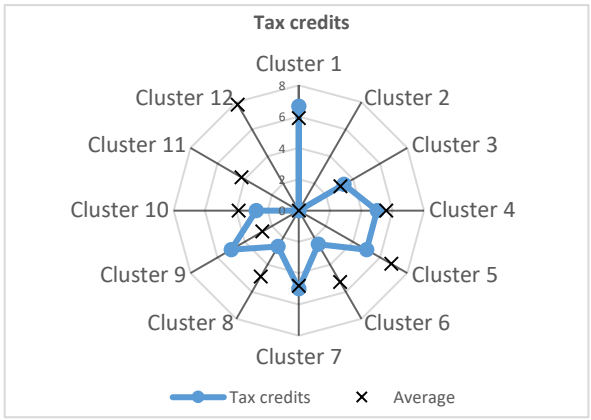


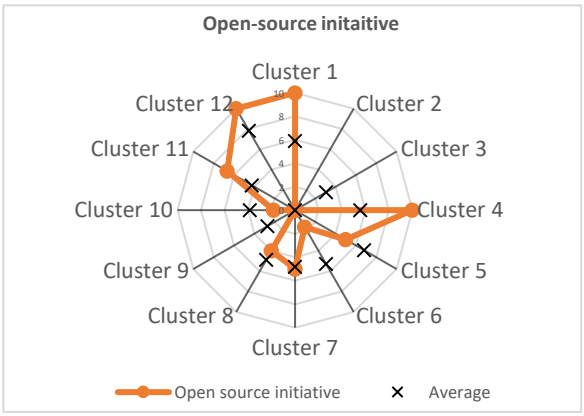
Supplementary material 3 (1 of 4): Hybrid PPP results

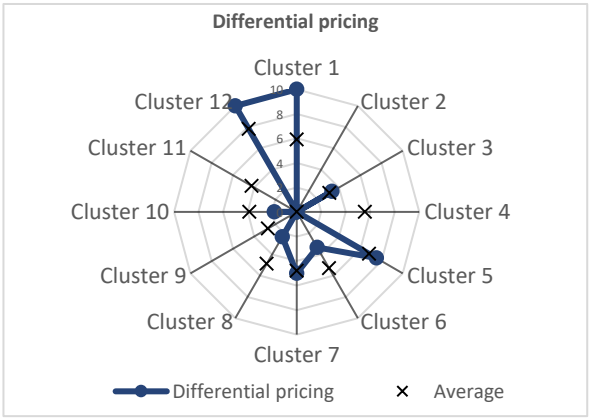


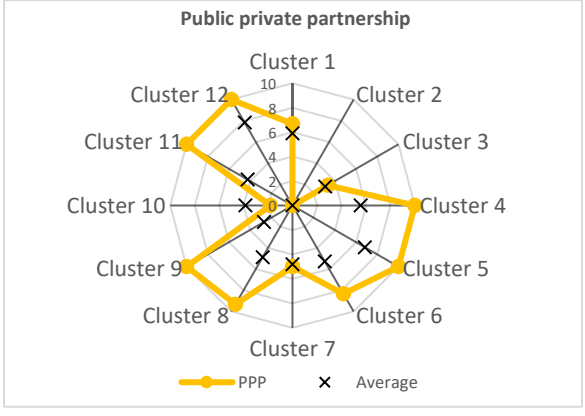


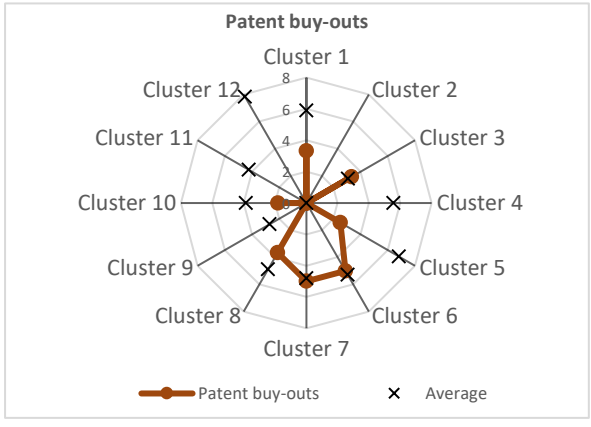




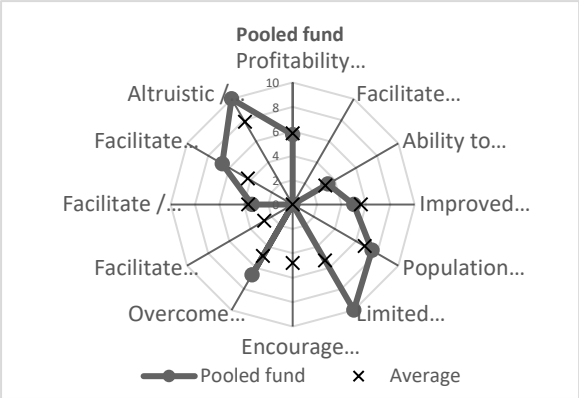


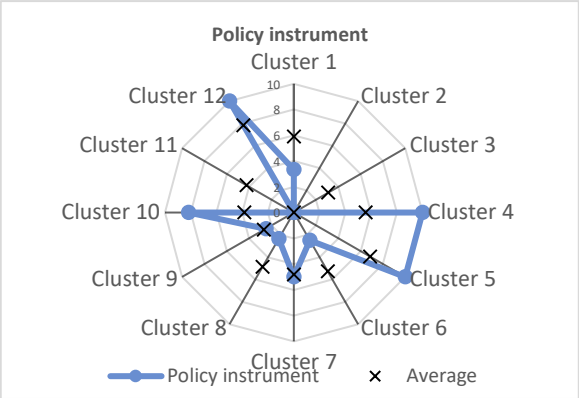


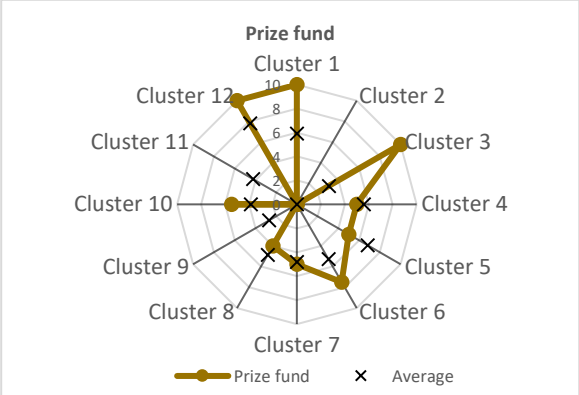


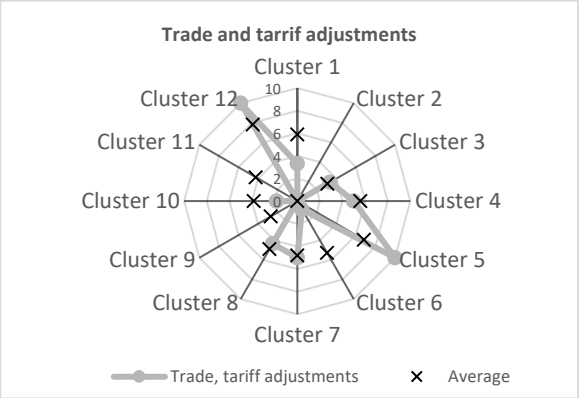


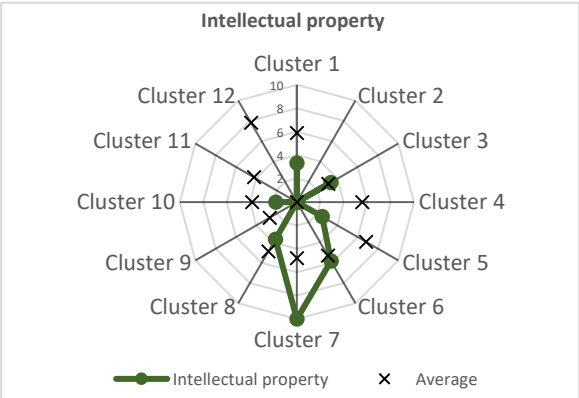
Supplementary material 3 (2 of 4): Hybrid PPP results

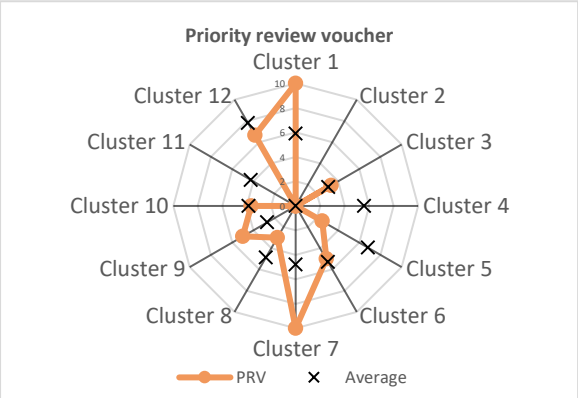


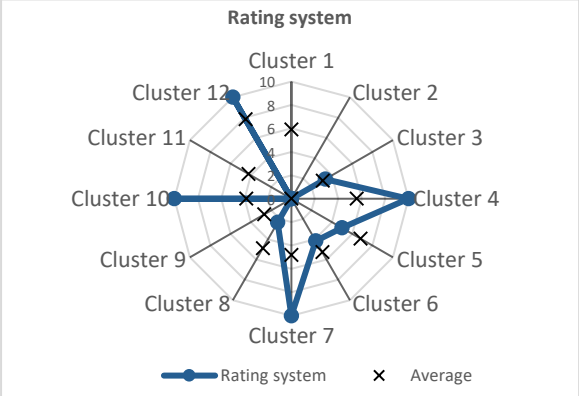


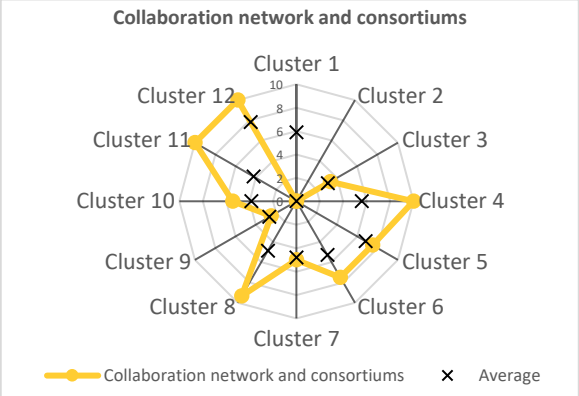




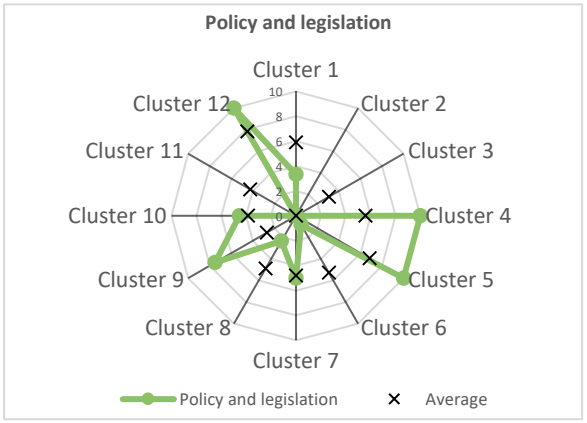


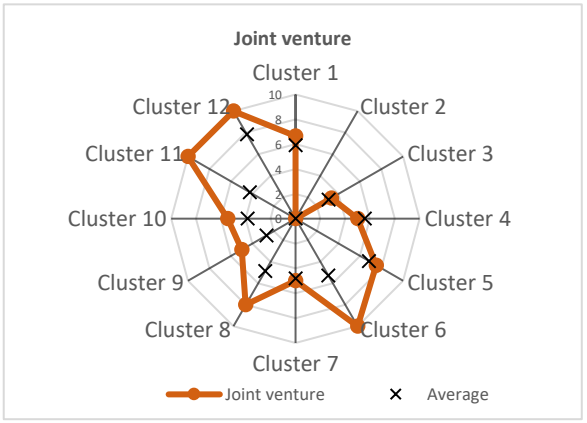


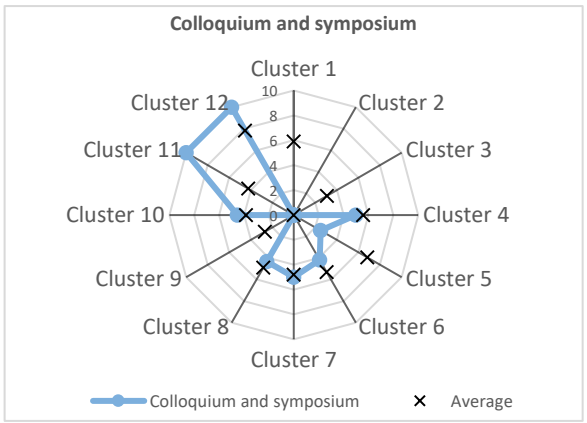


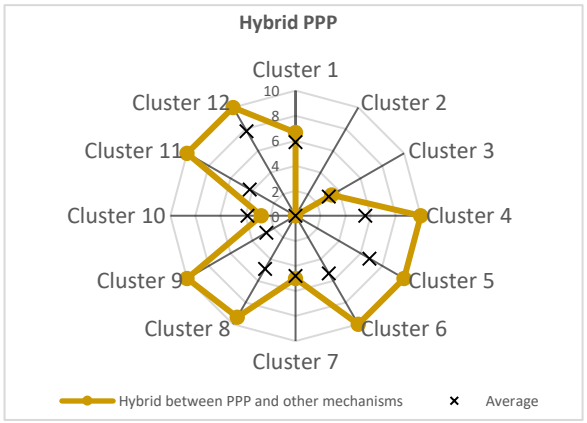


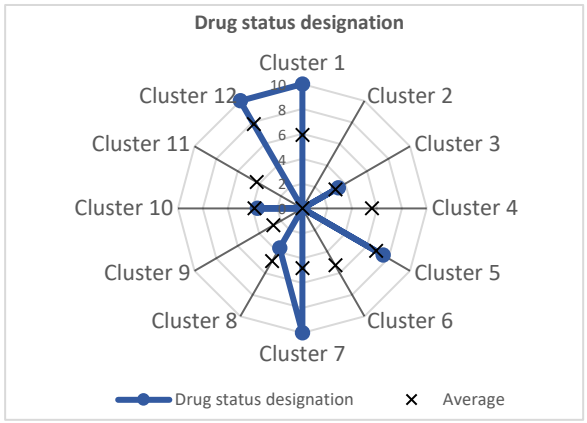
Supplementary material 3 (3 of 4): Hybrid PPP results

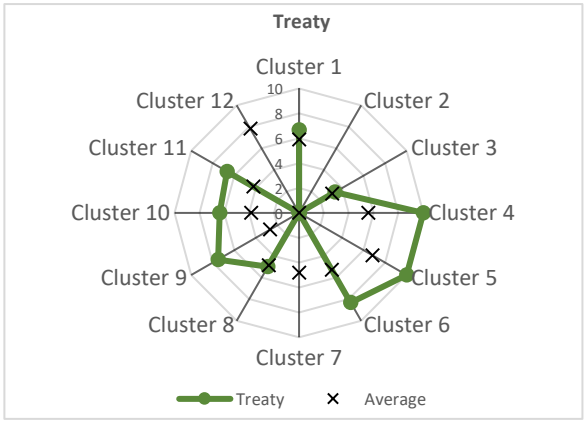


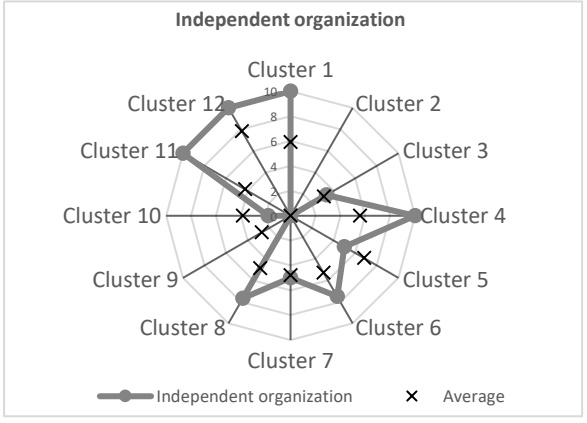


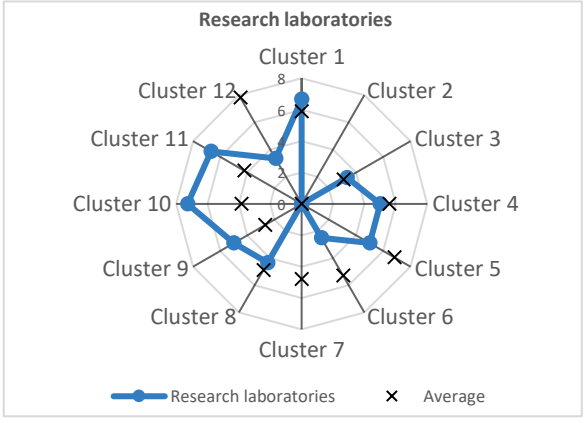




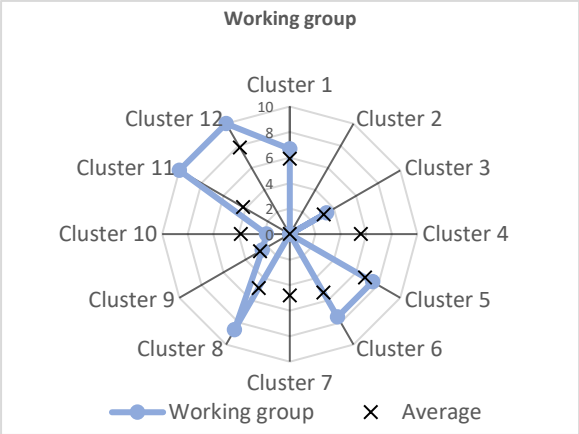


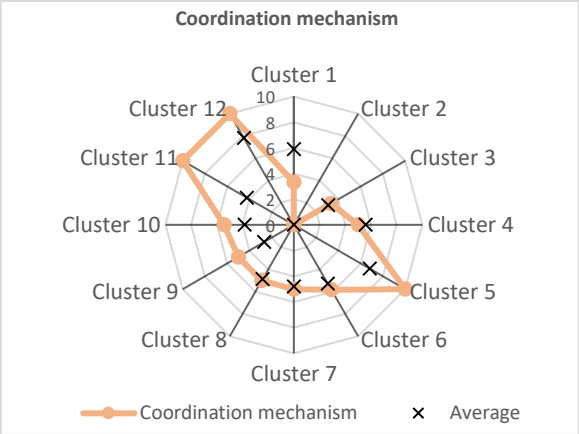




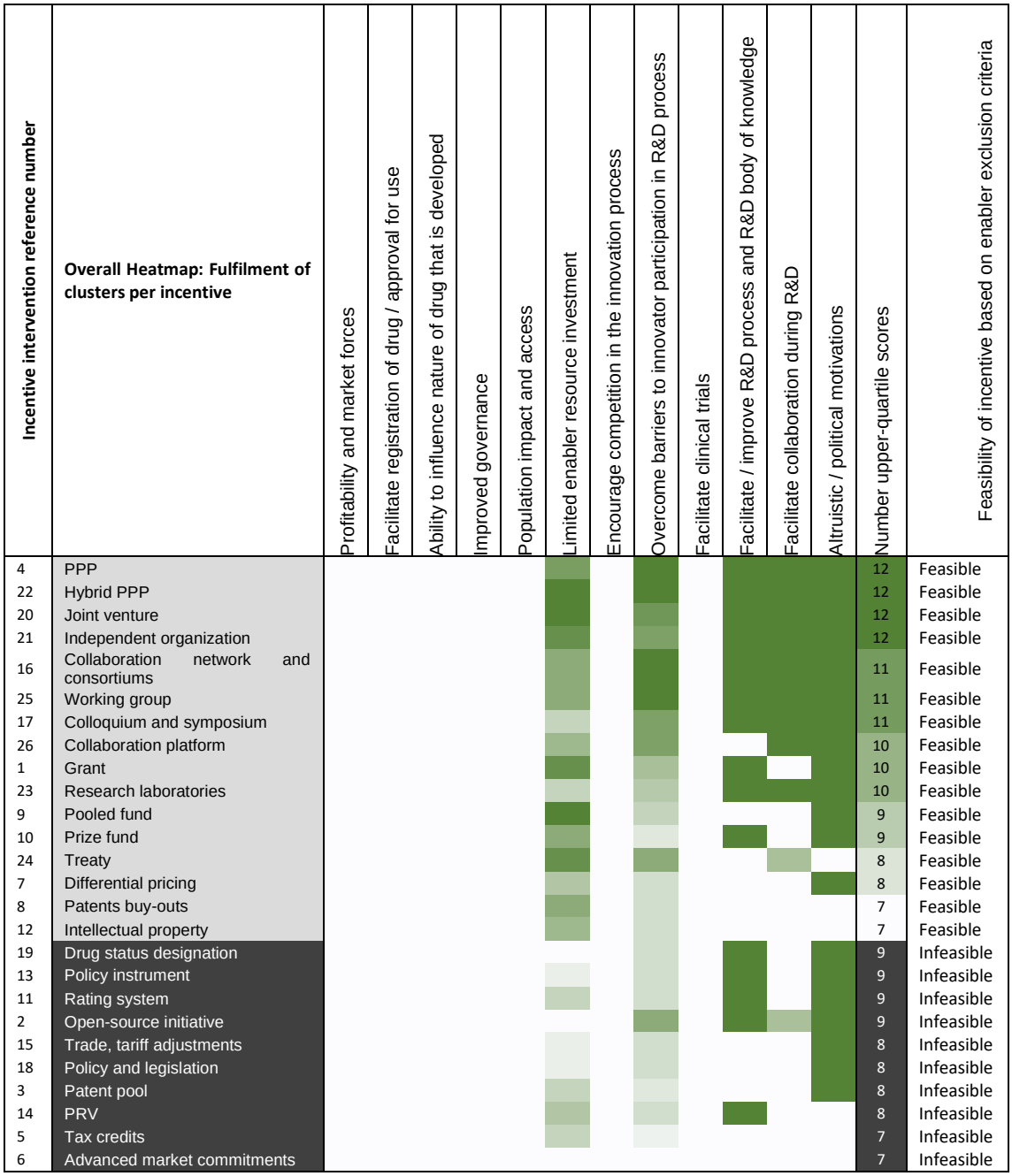


Supplementary material 3 (4 of 4): Hybrid PPP results



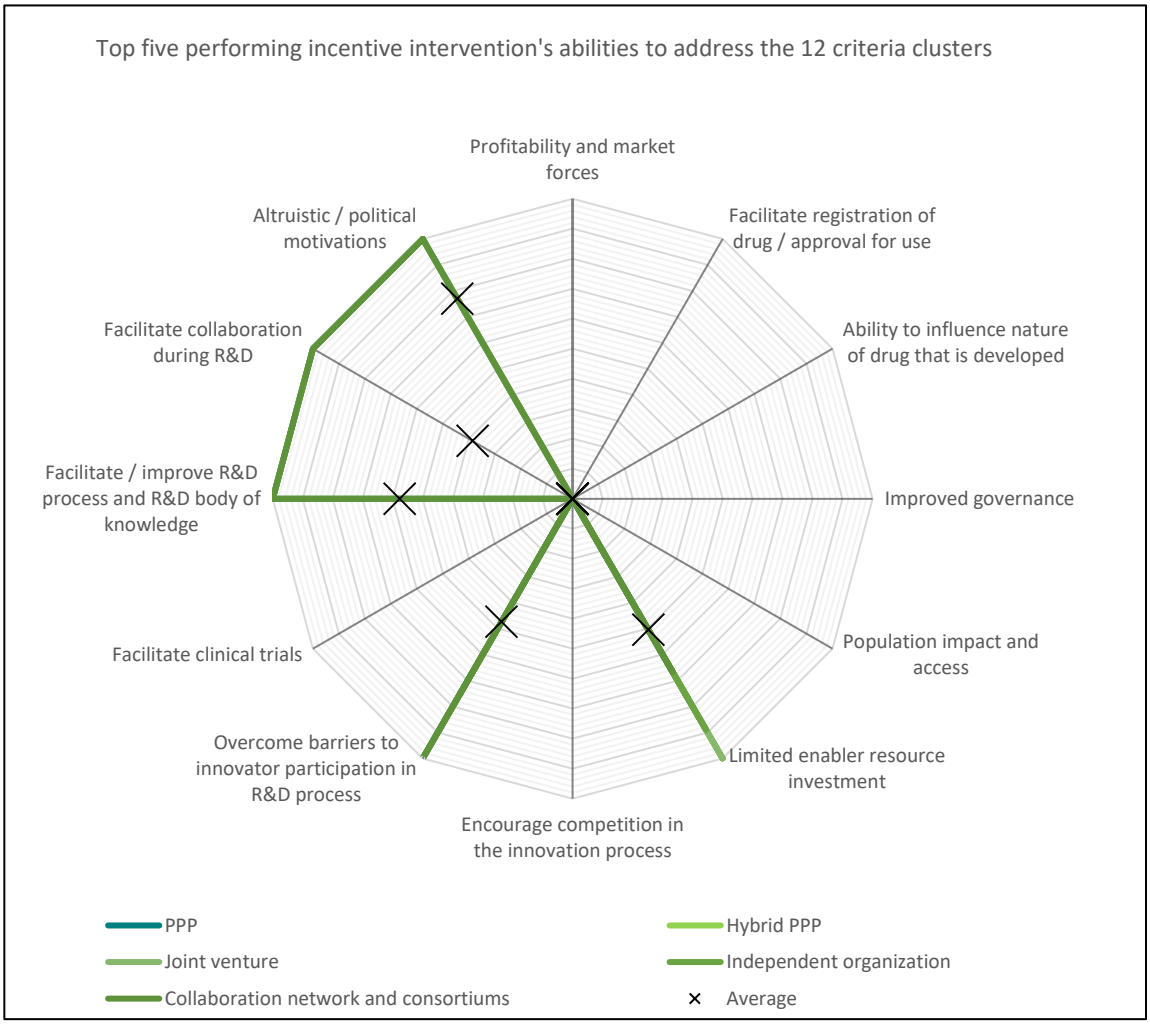


Supplementary material 4 (1 of 2): Hybrid PPP results



Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													12	Feasible
22	Hybrid PPP													12	Feasible
20	Joint venture													12	Feasible
21	Independent organization													12	Feasible
16	Collaboration network and consortiums													11	Feasible
25	Working group													11	Feasible
17	Colloquium and symposium													11	Feasible
26	Collaboration platform													10	Feasible
1	Grant													10	Feasible
23	Research laboratories													10	Feasible
9	Pooled fund													9	Feasible
10	Prize fund													9	Feasible
24	Treaty													8	Feasible
7	Differential pricing													8	Feasible
8	Patents buy-outs													7	Feasible
12	Intellectual property													7	Feasible
19	Drug status designation													9	Infeasible
13	Policy instrument													9	Infeasible
11	Rating system													9	Infeasible
2	Open-source initiative													9	Infeasible
15	Trade, tariff adjustments													8	Infeasible
18	Policy and legislation													8	Infeasible
3	Patent pool													8	Infeasible
14	PRV													8	Infeasible
5	Tax credits													7	Infeasible
6	Advanced market commitments													7	Infeasible

Supplementary material 4 (2 of 2): Hybrid PPP results



Appendix O: PPP case study results

This appendix includes:

(xv) Domain 1: PPP results
(xvi) Background logic 1AB: PPP results
(xvii) Domain 2: PPP results
(xviii) Background logic 2: PPP results
(xix) Domain 3: PPP results
(xx) Background logic 3: PPP results
(xxi) Domain 4: PPP results
(xxii) Background logic 4: PPP results
(xxiii) Background logic 5: PPP results
(xxiv) Domain 5: PPP results
(xxv) Supplementary page 1: PPP results
(xxvi) Supplementary page 2: PPP results
(xxvii) Supplementary page 3: PPP results
(xxviii) Supplementary page 4: PPP results

Domain 1 system demarcation: PPP results

DOMAIN 1: SYSTEM DEMARCATION						System evaluation	
	System elements	2	1	0	Aspect to address	Measure [0|1|2]	Sourced from section
Disease setting and affected population							
1	Country economic status	Low-Income	Low-to high-middle	High-Income	Non-incentive-based solutions (I)	1	Chapter 3.6.2
2	Country-wide burden of the diseases	> 35 000 DALYs (per 100 000)	DALYS > 0	0 DALYS	8. Overall Impact	2	Chapter 3.6.2
3	Burden fully characterized	< 40% of population within 5% of health facility	40% - 60% of population within 5% of health facility	> 60% of population within 5% of health facility	Non-incentive-based solutions (I)	1	Chapter 3.4.1.1 &3.6.2
4	Physicians per 1000 population	¡ 1 per 1 000	1 - 2 physicians per 1 000 population	¿ 2 physicians per 1 000 population	Non-incentive-based solutions (I)	1	SME 4
Existing drug characteristics							
5	The existence of medicine to treat the condition	No drugs	Inadequate number of drugs available	Sufficient number of drugs, including generic versions	8. Overall Impact	1	Chapter 3.6
6	Quality of existing drugs	May lead to death or no-effect at all	Effective to some extent	Treats effectively, trivial side-effects	Non-incentive-based solutions (II)	1	Chapter 3.6
7	Existence of breakthrough drugs	Breakthrough drugs does not exist	Insufficient breakthrough drugs	Sufficient number of breakthrough drugs	8. Overall Impact	1	Chapter 2.1.2
8	Availability of drugs for the desired population	Does not exist, no supply of drugs	Irregular supply of drugs	Exists and adequate supply of drugs	Non-incentive-based solutions (II)	1	Chapter 2.2.5
9	Access of current drugs to desired population	No access to drugs	Insufficient consumer access	All consumers have access (minimum travelling, no waiting)	4. Access	1	Chapter 2.2.5
10	Affordability of current drugs to the desired population	Mostly out-of-pocket & no third party/ public subsidy	Some out-of-pocket & some third party/ public subsidy	No out-of-pocket & third party/ public subsidy	Non-incentive-based solutions (II)	2	Chapter 2.2.5
11	Appropriateness of drugs to the desired population	Inappropriate language & wrong diagnosis	Insufficient language and diagnosis	Appropriate language & right diagnosis	Non-incentive-based solutions (II)	1	Chapter 2.2.5
12	Acceptability of drugs to the desired population	Unacceptable; Disregards culture, stigmas, values and norms	Unacceptable	Acceptable (Respects culture, stigmas, values and norms)	Non-incentive-based solutions (II)	1	Chapter 2.2.5
13	Mass drug administration	No mass drug administration	Insufficient drug administration	Mass drug administration efforts are implemented	4. Access	1	Chapter 3.6.2
Service delivery							
14	Comprehensiveness of services delivered	The range of health services delivered does not satisfy all health needs	The range of services delivered insufficient in satisfying health needs	The range of health services delivered satisfies all health needs	Non-incentive-based solutions (III)	1	Chapter 2.2.3
15	Continuity of consumers' access to health services	Consumers do not have continuous access to health services	Insufficient continuous access to most health services	Consumers have continuous access to health services	Non-incentive-based solutions (III)	1	Chapter 2.2.3
16	Coordination of service delivery networks	Service delivery networks are not arranged across all levels of care	Service delivery networks are not arranged across all levels of care	Service delivery networks are arranged across all levels of care	Non-incentive-based solutions (III)	1	Chapter 2.2.3
17	Minimize waste of resources in service delivery	Does not attempt to reduce resource waste	Insufficient waste management	Minimizes resource waste	Non-incentive-based solutions (III)	2	Chapter 2.2.3
Consumers, Competitors, and suppliers							
18	Demand size or sales force (relates to disease burden)	No demand	Insufficient demand for the product	Sufficient demand	Non-incentive-based solutions (IV)	0	Chapter 3.4.3 & 3.7.3
19	The role of brand loyalty	Brand loyalty has no influence; or loyal to ineffective drug	Insufficient brand loyalty	Loyal to a drug once proven to work	Non-incentive-based solutions (IV)	1	Chapter 3.7.3
20	Bargaining power of the suppliers (chemical entities)	Resources are rare and extremely costly	Insufficient resource availability	Resources widely available and affordable	Non-incentive-based solutions (V)	1	Chapter 3.4.3
21	Existence of competitors	No competitors	Some competitors	A lot of competition	Non-incentive-based solutions (V)	1	Chapter 3.4.3
22	Existence of barriers to new drug entrants	Large number of barriers to new entrants	Some barriers to new entrants	No barriers to new drug entities	2. Implementation feasibility	2	Chapter 3.4.3
23	Scale of globalization and cooperation among competitors	No cooperation or globalization between competitors	Insufficient coordination	Organizations coordinate on various levels	5. Participation and cooperation	0	Chapter 3.4.3
24	Extent of data sharing and collaboration	No collaboration or sharing of data	Insufficient collaboration and data sharing	Data often shared and good collaboration	5. Participation and cooperation	0	Chapter 3.4.3
Governance and leadership							
25	Political will and contribution to improve R&D for disease	Uninvolved	Insufficient support	Very supportive	Non-incentive-based solutions (VI)	1	Chapter 3.6.2
26	Functioning of domestic policy structures	Unclear or non-existing	Insufficient functioning of domestic policy	Clear, fully operational	6. Governance and leadership	2	Chapter 3.6.2
27	Regulatory exclusivity provisions for R&D in the disease	No exclusivity	Insufficient exclusivity	R&D exclusive	6. Governance and leadership	1	Chapter 3.6.2
28	Regulatory oversight to promote R&D for the disease	No regulatory oversight	Insufficient oversight	Strict regulatory oversight	6. Governance and leadership	1	Chapter 3.6.2
29	Effective national budget allocation	No budget	Insufficient budget	Sufficient budget available	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
30	Regulation of strategic health policy	No regulation of strategic health policy	Insufficient regulation of strategic health policy	Appropriate regulation of strategic health policy	Non-incentive-based solutions (VI)	1	Chapter 2.1.2
31	Resources to deliver health service, are financed by government	Delivery of health services not government financed	Government finance some resources to deliver health services	Government finances resources to deliver health services	6. Governance and leadership	1	Chapter 2.2.3
32	Adequate supply of the health service	Inadequate supply of the health service	Insufficient supply of the health service	Adequate supply of the health service	Non-incentive-based solutions (VI)	2	Chapter 2.2.5
33	Monitoring of the actual health system and system performance	Health system is not monitored	Insufficient monitoring of health system and performance	Health system and performance is monitored	Non-incentive-based solutions (VI)	1	Chapter 2.2.3
Profitability and market forces							
34	Expected market and financial return on investment (potential)	No perceived potential	Insufficient market potential	Sufficient market potential	1. Profitability and market forces	1	Chapter 2.1 & 3.6.2
35	Current investment capital and returns	Annual returns below stock market (of country for given year)	Annual returns similar to stock market (of country for given year)	Annual returns above stock market (of country for given year)	Non-incentive-based solutions (VII)	2	Chapter 3.6.2
36	Stakeholder demand	No demand	Some demand	High demand	Non-incentive-based solutions (VII)	1	Chapter 2.1.2
37	Established marketing and distribution network	Broken or no distribution or marketing networks	Networks are available, but not fully functioning	High functioning of distribution and marketing networks	Non-incentive-based solutions (VII)	1	Chapter 3.4.3
38	Product export potential	Products cannot be exported	Products can be exported to some countries	Products can be exported to all countries	1. Profitability and market forces	1	Chapter 3.4.3 & 3.6.2
39	Priority on health agenda	Not a priority	Insufficient priority	Is a priority on health agenda	6. Governance and leadership	1	Chapter 3.6.2
Research and development process							
40	Perceived clinical trial risk involved in R&D for specific disease	High perceived risk	Moderate perceived risk	Low perceived risk	9. R&D and clinical trials	1	Chapter 2.1.2
41	Consistency and recommendations on choosing clinical trial metrics	No recommendations or consistency provided	Some recommendations, not always consistent	Appropriate recommendations on clinical trial metrics	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
42	Transparency of clinical trial information	Obscure clinical trial information	Most information is transparent, some questionable	Transparent clinical trial information	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
43	Accountability of clinical trial information	Unaccountable clinical trial information	Accountability questionable	Accountable clinical trial information	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
44	Accessibility of clinical trial information	Clinical trial information inaccessible	Some information is accessible	All clinical trial information is accessible	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
45	Registry and monitoring of clinical trials (comply by FDA standards)	Clinical trials not monitored according to FDA standards	Clinical trials monitored according to some FDA standards	Clinical trials monitored according to FDA standards	9. R&D and clinical trials	2	Chapter 2.1.2
46	Globalization status of clinical trials (comply by FDA standards)	Clinical trial methods not globalized	Clinical trial methods somewhat globalized	Clinical trial methods globalized	9. R&D and clinical trials	1	Chapter 2.1.2
47	Clinical trials activation difficulty	Difficult to initiate clinical trials	Some obstacles in activating clinical trials	Clinical trials easily initiated	9. R&D and clinical trials	0	Chapter 2.1.2
48	Quality of clinical trials	Clinical trial quality clearly questionable	Clinical trial quality somewhat questionable	Good clinical trial quality	9. R&D and clinical trials	2	Chapter 2.1.2
49	Clinical trial regulation too costly	Unaffordable clinical trial regulation	Somewhat affordable clinical trial regulation	Affordable clinical trial regulation	9. R&D and clinical trials	0	Chapter 3.6.2
50	The use of innovative clinical trial tools and technology	No innovative tools or technology used in clinical trials	Some innovative tools or technology used in clinical trials	Innovative tools or technology used in clinical trials	Non-incentive-based solutions (VIII)	0	Chapter 2.1.2
51	Struggling to prove efficacy	Cannot prove efficacy	Difficulty in proving efficacy	Efficacy easily proved	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
52	Legal and ethical regulations for clinical trials too difficult	Difficult to comply with legal and ethical regulations	Difficulty in complying with legal and ethical regulations	Legal and ethical regulations easily complied by	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
53	Safety assessments standards	Safety assessment standards not met	Safety assessment standards sometimes met	Safety assessment standards easily met	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
54	Adaptive clinical trials occurrence	Never occurs (drugs do not 'survive' the R&D process)	Often occur	Mostly occur	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
55	Recruitment and retention of participants	Difficult to recruit participants, not easily retained	Participants sometimes difficult to recruit and retain	Participants easily recruited and mostly retained	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
56	Racial differences in participation in clinical trial	No racial differences in clinical trials	Some racial differences in clinical trials	Clinical trials completed on various races	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
57	Relationships between innovators and participants	No or very poor relationship (very little trust)	Relationship mostly professional	Appropriate professional relationship	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
58	Physician participation	Difficult to find physicians willing to participate	Some difficulty in finding participating physicians	Easy to find participating physicians	Non-incentive-based solutions (VIII)	1	Chapter 2.1.2
59	Skilled workforce	Workforce not skilled	Some workforce members not skilled enough	Highly skilled workforce	Non-incentive-based solutions (VIII)	1	Chapter 3.4.3
60	R&D productivity	Cycle times longer than the average (12 - 15 years)	Cycle times average between 12 to 15 years	Cycle times shorter than average (12 - 15 years)	9. R&D and clinical trials	2	Chapter 2.1.3
61	Clinical trial registration	No clinical trials performed are registered	Some clinical trials performed are registered	All clinical trials performed are registered	9. R&D and clinical trials	2	Chapter 2.1.2 & 2.1.3
Manufacturing systems							
62	Existence of manufacturing plants	No manufacturing plants	Inadequate amount of manufacturing plants	Adequate amount of manufacturing plants	Non-incentive-based solutions (IX)	1	Chapter 2.1.2
63	Drug manufacturing adheres to regulatory requirements	Drug manufacturing does not adhere to regulatory requirements	Drug manufacturing adheres to some regulatory requirements	Drug manufacturing adheres to regulatory requirements	Non-incentive-based solutions (IX)	0	Chapter 2.1.2
64	Appropriate technology used for the manufacturing of drugs	Technology not appropriate	Somewhat appropriate	Technology is appropriate	Non-incentive-based solutions (IX)	1	Chapter 3.4.3
Sustainability							
65	Green R&D of drugs	R&D process does not consider carbon footprint	R&D process addresses carbon footprint	Carbon footprint closely monitored and adheres to SDGs	3. Green R&D of drugs	1	Chapter 3.4.3
Health information systems							
66	Health data generation	Health data are not generated and captured	Some health data are not generated and captured	Health data are generated and captured	Non-incentive-based solutions (X)	0	Chapter 2.2.3
67	Communication and use of public health data	Public health data not communicated or used	Some public health data are communicated and used	Public health data are communicated or used	Non-incentive-based solutions (X)	1	Chapter 2.2.3

Background Logic 1AB: PPP results

	BACKGROUND LOGIC 1A&B: CRITERIA MATRIX	1. Profitability and market forces			2. Implementation feasibility and security				3. Green and sustainability			4. Population impact and access				5. Participation and cooperation					6. Governance and leadership							7. Rewards focus						8. Impact on R&D process and clinical trials							
			Improve NPV	Delink revenue from sales volume	Improve product export potential	Minimizes barriers to implementation	Minimize disruptive effects to population	Affordable to implement the incentive	Provide R&D project insurance	Ensure conservation of resources in R&D process	Encourage efficient innovation	Green R&D of drugs	Potential to reduce burden of disease	Encourage R&D of a drug/novel drug	Improve consumer access	Enable mass drug administration	Enables participation of small and medium organization	Encourage large firm participation	Facilitates cooperation and synergy	Platform for coordinating innovators	Allow competition among parallel experiments	Promote equitable health-focused governance	Promote transparency and accountability	Advances the priority of disease on health agenda	Advance proper functioning of domestic policy	Regulatory oversight to promote R&D	Regulatory exclusivity provisions for R&D	Resources to develop drug government financed	Payoff to innovators based on cost-effectiveness	Reward innovation	Financing timed across drug lifecycle	Provide long term R&D financing	Provide sustainable financing	Provide public subsidies for clinical trials	Reduce clinical trial risk involved	Assist in registration and monitor of trials	Globalize clinical trial methods	Reduce clinical trials activation difficulty	Enhance or prompt the quality of clinical trials	Assist in expensive clinical trial regulation	Improves R&D productivity	Enlarge number of clinical trials registered
			2	2	1	2	2	2	2	2	2	1	1	1	2	1	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	2	2	1	2	1	0	2	0	2	2
1	**Grants:** Grants are funds, usually non-repayable, distributed to certain entities. Grant funds are often orchestrated by the government, or non-profit organizations to enhance or meet a demand that cannot be met without financial assistance. Most grants are made available for a specific project, and requires a certain level of compliance and reporting		1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	1	0	1	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0
2	**Open-source initiative:** Open-source refer to a collaborative initiative where parts of a project are made available and known to all, or a certain group of entities. The information can be accessed and sometimes modified by all. The open-source initiatives thus serve as a platform, where the access to these data sets have the ability to benefit all participants.		1	1	0	1	1	1	0	0	0	0	1	0	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1
3	**Patent pool:** Patent pools occur when two or more patent owners agree to 'pool' their patents and to offer licensing terms to one another or to third parties. Patent pools, usually have pre-defined licencing terms in place for the licensees to pay fees (royalties) to the patent owners.		1	1	1	0	0	1	0	0	0	0	1	1	1	0	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
4	**Public-private partnership:** Public-private partnerships is any arrangement between one or more public and private entities. PPPs are created to achieve a public health objective or to develop a health-related product that enhances the public good.		1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	1	0	0	1	1	1	1	0	1	1	1	0	1	0	1
5	**Tax credits:** Tax credits apply to current expenditures and is a specified deductible percentage on the total tax liability of the company. Tax credits are independent from corporate income tax and can be carried forward to offset future tax liabilities.		1	0	0	1	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0
6	**Advanced market commitments:** Advanced market commitments are legally binding pre-order contracts that are made between funders, and pharmaceutical developers. The sponsors of AMCs thus guarantee future purchase of drugs that are currently in development stages, where the developers agree to supply a set amount of their completed product at a set price to the given sponsors.		1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
7	**Differential pricing:** Differential pricing is when people with different backgrounds or regions, are required to pay different prices for the same product. The difference in pricing is usually based on geographical, external environmental or on economic reasons.		1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
8	**Patent buyouts:** IP rights can be purchased by donors. Thus, the patent holding organization is compensated for with a monetary amount in exchange for the IP laws of the R&D of the drug or vaccine.		1	0	0	0	0	0	1	0	0	0	1	1	0	0	1	1	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
9	**Pooled fund:** When many organizations or investors have an aggregated purpose for investment, then the sum of their investments is a pooled fund.		0	1	0	1	0	1	1	1	1	0	1	1	1	1	1	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0
10	**Prize fund:** Prizes are large monetary rewards provided, mostly by governments or donor organization, for when a pharmaceutical organization successfully delivers an innovation subscribed to a certain set of criteria. Prizes are often awarded in for incremental milestones met by the pharmaceutical organizations.		1	1	0	1	0	1	0	1	1	0	1	1	1	0	1	0	0	0	1	0	1	1	0	0	0	0	0	1	1	1	0	0	0	0	0	1	0	1	0	0	1
11	**Rating system:** Pharmaceutical organizations are rated according to a certain set of criteria. The organizations are either rated on a scale, or in comparison with one another and their ability to meet the specified criteria set.		0	0	0	0	0	1	0	1	1	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0
12	**Intellectual property and market exclusivity:** Intellectual property refers to the right that the innovator receives when a new innovation is developed. When the pharmaceutical innovator is awarded exclusivity over an innovation. The exclusivity refers to the exclusive rights that innovators are awarded regarding the marketing of newly approved drugs.		1	0	1	0	0	1	1	0	0	0	1	1	0	0	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
13	**Policy instrument:** Policy instruments refer to any intervention made by the government or public authorities, with the intention to achieve outcomes that adhere to the objectives of public policy. Instruments can also include altering and enforcing domestic policies.		0	0	1	1	1	1	0	1	1	1	1	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0	1
14	**Priority review voucher:** Law under which companies that receive FDA approval for a drug or vaccine satisfying certain criteria, are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choice.		1	1	0	1	0	1	0	0	0	0	1	1	0	0	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0
15	**Trade, tariff adjustments:** Adjustments made to the trading or the taxes and required costs associated with trading of specified manufactured drugs.		1	0	1	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	1	0	1	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
16	**Collaboration and consortiums:** A collaboration network refer to a variety of entities, with a heterogeneous background and geographical origin. The entities collaborate to achieve a common goal or objective. Consortiums are very similar with two or more entities coming together, to complete a common activity to achieve a goal.		0	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	0	1	0	1	1	0	1	1	1	0	1	1	1	0
17	**Colloquium and symposium:** An academic conference or seminar held, focussing on one topic.		0	0	0	0	0	1	0	0	1	0	1	0	0	0	1	1	1	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0
18	**Policy and legislation:** Legislation include laws constructed by governments; whereas policies must adhere to the law and is practical objectives and principles to guide decisions and actions within the pharmaceutical industry.		0	0	1	1	1	0	0	0	1	1	1	0	1	1	1	1	0	0	0	1	1	0	1	1	0	1	0	0	0	0	0	0	0	1	0	1	1	1	1	0	0	1
19	**Drug status designation:** Provides an exclusive status to the drugs that treats certain sets of diseases. The exclusivity then leads to certain advantages, or rewards for innovating pharmaceutical companies.		1	1	1	1	0	0	1	0	0	0	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
20	**Joint venture:** Joint ventures are business arrangements in which two or more parties agree to pool together their resources, with the aim of accomplishing a specific task or activity. In contrast with partnerships, joint ventures have an end date affiliated to it.		1	0	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	1
21	**Independent organization:** Independent organizations does not require the approval of a government agency for decision-making and financial planning.		1	1	0	1	0	0	0	0	0	0	1	1	1	0	1	1	1	1	0	1	1	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0	0
22	**Hybrid public-private partnership:** This sub-category involves all the incentive interventions that are formed by a PPP and involve another incentive strategy discussed in this research. For each intervention, the type of incentive strategies involved in the intervention is stated before the definition of the intervention is provided.		1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	0	1	0	1
23	**Research laboratories:** Research laboratories are scientifically orientated facilities equipped with equipment to complete experiments aimed at R&D of drugs.		1	0	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	1	1	0	1
24	**Treaty:** Formal agreement between two or more political authorities, subject to international law.		1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	1	1	1	1	1	0	1	0	0	0	0	0	1	0	0	1	0	1	1	0	1
25	**Working Group:** Similar to a collaboration network, a working group is a group of individuals or entities working (studying and reporting back) on a specific goal and making recommendations on its findings.		1	0	1	1	0	1	1	0	0	0	1	1	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0
26	**Coordination mechanism and platform:** Initiatives to coordinate R&D investments and activities. Operate to clarify priorities, increase transparency, and diversify stakeholders.		0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1

Domain 2 Enabler profile: PPP results

DOMAIN 2: ENABLER INQUIRY FORM				
OBJECTIVES			**INTERNAL CAPABILITIES**	
1	**Goal of the incentive strategy? (Inclusion)**		**1**	**Available funding. (Exclusion)**
	Improve the state of the R&D pipeline	2		Limited to an amount 0
	Enable organizations to innovate easier	2		Full capacity 0
	Gain market exclusivity over an innovation	0		No capacity 2
	Advance the R&D field	2	**2**	**Tranches to innovators? (Inclusion)**
	Deliver affordable and accessible treatment	2		Beginning once-off 0
	Convey an important message	2		End once-off 0
	Fulfil corporate social responsibility	2		Once output is provided 0
	Increase bandwidth and network	1		Incrementally, based on output 0
	De-risk R&D process	2		Incrementally, based on timing 0
	Political obligations	0		Incrementally, as innovator requires 0
2	**Which innovators are targeted? (Inclusion)**		**3**	**Ability to influence policy? (Inclusion)**
	Large pharmaceutical organizations (private)	2		Clinical trial regulation policies 0
	SMEs (private)	2		Market authorization policies 0
	Governmental institutions	1		Market exclusivity policies 0
	Independent scientists	2		Pricing policies 1
	Academic institutions	2		Tax credit policies 0
	NGO organizations	2		National/international intellectual property policies 0
	Everyone	1		National policies and legislation 1
3	**Intention for the consumers? (Exclusion)**			International trade law 0
	Provide drug	2		**Access and expertise? (Inclusion)**
	Multi-purpose drug	2	**4**	Access to key data 2
	Play a role in improved access	2		Access to compounds 2
	Implement mass drug administrations	0		Access to intellectual property 2
	Deliver regime treatment	2		Technology expertise and access 2
4	**Desired relationship with innovators? (Inclusion)**			R&D expertise 2
	Once-off occasion	0		
	Limited to a number of years	0		
	Milestone related	1		
	Engage at given time instances	1		
	Collaborate and build a partnership	2		
5	**Role and Responsibility willing to play? (Exclusion)**			
	Fund R&D	0		
	Partially fund R&D	0		
	Facilitate collaboration between innovators	2		
	Collaborate with innovator	1		
	Facilitate in regulatory process	0		
	Provide market exclusivity	0		
	Adjust policies and regulations	0		
	Provide market certainty	0		

Background Logic 1AB: PPP results

Background Logic 2: Enabler Matrix	1. Goal of the incentive strategy										2. Which innovators are targeted?							3. Intention for the patients?					4. Desired relationship with innovator?					5. Role & responsibility willing to play?								1. Available funding?			2. Funding timing?			3. Ability to influence /provide guidance in policies?						4. Access to aspects?				
	Improve the state of the R&D pipeline	Enable organizations to innovate easier	Gain market exclusivity over an innovation	Advance the R&D field & body of knowledge	Deliver affordable and accessible treatment	Convey an important message	Fulfil corporate social responsibility	Increase bandwidth and network	De-risk R&D process	Political obligations	Large pharmaceutical organizations(private)	SMEs (private)	Governmental institutions	Independent scientists	Academic institutions	NGO organizations	Everyone	Provide drug/novel drug	Multi-purpose drug	Play a role in improved access	Deliver regime treatment	Implement mass drug administrations	Once-off occasion	Limited to a number of years	Milestone related	Engage at given time instances	Collaborate and build a partnership	Fund R&D	Partially fund	Facilitate collaboration between innovators	Collaborate with innovator	Facilitate in regulatory process	Provide market exclusivity	Adjust policies and regulations	Provide market certainty	Limited to an amount	Full capacity	No capacity	Beginning once-off	End once-off	Once output provided	Incrementally, based on output	Incrementally, based on timing	Incrementally, as innovator requires	Clinical trial regulation policies	Market authorization policy	Market exclusivity policies	Pricing policies	Tax credit policies	National policies and legislations	National/International intellectual property policies	International trade law	Access to key data	Access to compounds	Access to intellectual property	Technology expertise and access	R&D expertise
Push interventions	2	2	0	2	2	2	2	1	2	0	2	2	1	2	2	2	1	2	2	2	2	0	0	0	1	1	2	0	0	2	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	1	0	1	0	0	2	2	2	2	2
1 Grant	1	0	0	1	0	0	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
2 Open-source initiative	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
3 Patent Pool	1	0	1	0	1	0	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0
4 PPP	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5 Tax credits	1	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0
Outcome-based pull strategies																																																									
6 Advanced market commitments	1	0	0	0	0	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0
7 Differential pricing	1	0	0	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
8 Patent buyouts	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	0	0	1	0	1	1	1	1	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
9 Pooled fund	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
10 Prize fund	1	1	0	1	0	0	1	0	1	0	0	1	1	1	0	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
11 Rating system	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lego-regulatory pull strategies																																																									
12 Intellectual property and market exclusivity	1	0	1	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	0	1	1	0	0	0	1	0	0	0	0	1	0	0	0	1	1	0	0	0	0
13 Policy instrument	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
14 Priority review voucher	1	0	0	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	1	1	0	0	0	1	0	0	0	1	0
15 Trade, tariff adjustments	1	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	0	0
Hybrid strategies																																																									
16 Collaboration network and consortiums	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	1	1	0	1	1	
17 Colloquium and symposium	0	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	1	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
18 Policy and legislation	0	0	1	0	1	0	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	1	1	1	1	0	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
19 Drug status designation	1	0	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	0	0	0	1	1	0	1	1	1	0	1	0	0	0	0
20 Joint venture	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	1	1	1	1	1	
21 Independent organization	0	0	0	1	0	0	1	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	0	1	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	1	1	0	1	1	
22 Hybrid PPP	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
23 Research laboratories	1	1	0	1	0	0	1	0	0	1	0	1	1	1	1	1	0	1	1	0	1	0	0	1	0	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
24 Treaty	1	1	1	0	1	0	0	1	0	1	0	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	1	1	1	1	1	1	1	1	0	1	
25 Working Group	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1		
26 Coordination mechanism*	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	

Domain 3 Innovator matrix: PPP results

DOMAIN 3: INNOVATOR INQUIRY FORM					
OBJECTIVES			**INTERNAL CAPABILITIES**		
1	**Reason for performing R&D for the disease?**		**1**	**Nature of innovator stakeholder?**	
	Profit maximization	0		Small to medium organization (includes start-up)	2
	Corporate social responsibility	2		Large pharmaceutical organization	2
	Not for profit	1		Not-for-profit organization	2
	Profit improvement	1		Governmental institution	2
	Political obligations	1		Academic institution	2
2	**Focus area of R&D and intention for patients?**			Independent scientist (no organization linked)	0
	R&D of drug	2	**2**	**Capacity to provide own funding?**	
	R&D of multi-purpose drug	2		No capacity	0
	Play a role in improved access	1		Limited to an amount	1
	Drug repurposing	2		Full capacity	0
	Deliver regime treatment	2	**3**	**R&D limitations?**	
3	**Require from the enabler?**			Don't have research laboratory	2
	Fund all R&D costs	1		Don't have adequate equipment	2
	Partially fund R&D	1		Lack of information (knowledge) on disease	2
	Collaboration with enabler	2		Cumbersome nature of clinical trial regulations	1
	Adjust policies and regulations	0		Shortage of finances	2
	Facilitate regulatory process	0		Policies or regulatory limitations	0
	Provide market exclusivity	0		No market certainty	0
	Provide market certainty	0	**4**	**Authorization standards adhered to?**	
	Provide a collaboration platform	2		None	0
	Provide risk insurance or security	1		Accredited authorisation organization	2
	Improve export potential	0			
4	**Preference or required funding timing?**				
	Beginning once-off	0			
	End once-off	0			
	Incrementally based on output	0			
	Incrementally based on timing	0			
	Incrementally as required	0			
	Once output provided	0			
	Don't require any funding	0			

Background Logic 3 Innovator matrix: PPP results

		1. Reason for performing R&D for the disease?	Profit maximization	Corporate or social responsibility	Not for profit	Profit improvement	Political obligations	2. Focus area of R&D and intention for patients?	R&D of drugs / novel drugs	Develop regime treatment	R&D a multi-purpose drug/vaccine	Play a role in improved access	Drug repurposing	3. Require from enabler / incentive intervention	Cover all R&D costs	Partly cover R&D costs	Collaboration with enabler	To adjust policies and regulations	To facilitate in the regulatory process	To provide market certainty	To provide market exclusivity	Collaboration platform	Risk insurance or security	Improve export potential	4. Preference or required funding timing?	Beginning once-off	End once-off	Incrementally based on output	Incrementally based on timing	Incrementally as required / incrementally	Once output provided	Do not require any funding	1. Nature of organization?	Large pharmaceutical organizations (private)	Small-and medium enterprise (private)	NGO	Governmental institution	Academic Institution	Scientist (no company)	2. Capacity to provide own funding?	No capacity	Limited to an amount	Full capacity	3. R&D limitations?	Don't have research laboratory	Don't have adequate equipment	Lack of information (knowledge) on disease	Cumbersome nature of clinical trial regulations	Shortage of finances	Policies or regulation limitations	No market certainty	4. Which Authorization standards adhered to?	None	Accredited authorisation organization
Push interventions			0	2	1	1	1		2	2	2	1	2		1	1	2	0	0	0	0	2	1	0		0	0	0	0	0	0	0		2	2	2	2	2	0		0	1	0		2	2	2	1	2	0	0		0	2
1	Grant		0	1	1	1	1		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		1	0	1	1	0	0	0		0	1	1	1	1	1		1	1	1		0	0	0	0	1	0	0		0	1
2	Open-source initiative		0	1	1	1	1		0	0	0	0	1		0	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	0		0	0	1	1	0	0	0		1	1
3	Patent Pool		0	1	1	1	0		1	1	1	1	1		0	0	0	0	0	0	1	1	0	1		0	0	0	0	1	0	1		1	1	1	1	0	0		0	0	0		0	0	0	0	0	0	0		0	1
4	PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
5	Tax credits		1	0	0	1	0		1	1	1	0	1		0	1	0	1	0	0	0	0	0	0		0	0	0	1	0	1	1		1	1	0	1	1	0		0	0	0		0	0	0	0	0	0	0		0	0
Outcome-based pull incentives																																																										
6	Advanced market commitments		1	1	0	1	1		1	1	1	1	1		0	0	0	0	0	1	0	0	1	0		0	1	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		0	1
7	Differential pricing		0	1	1	1	1		1	1	1	1	1		0	1	0	1	0	0	0	0	0	1		0	0	0	0	0	1	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	0		0	0
8	Patent buyouts		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	1	1	0	1	0		0	1	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	0	0		0	1
9	Pooled fund		0	1	1	0	1		1	1	1	1	1		1	1	0	0	0	0	0	1	1	0		1	1	1	1	1	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		1	1
10	Prize fund		1	1	1	1	0		1	1	1	1	1		1	1	0	0	0	0	0	0	0	0		0	1	1	0	0	1	0		0	1	1	1	1	1		1	1	0		0	0	0	0	1	0	0		0	1
11	Rating system		0	1	1	0	1		1	1	1	1	0		0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	1		1	1	1	1	1	0		0	0	1		0	0	0	0	0	0	0		1	1
Lego-regulatory pull strategies																																																										
12	Intellectual property and market exclusivity		1	0	0	1	0		1	1	1	0	0		0	1	0	0	0	0	1	0	1	1		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		0	1
13	Policy instrument		0	1	1	0	1		0	0	0	1	0		0	0	0	1	1	0	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	0	1		0	0	0	0	0	1	0		1	1
14	Priority review voucher		1	0	1	1	0		1	1	1	0	0		0	1	0	0	1	0	0	0	0	0		0	0	0	0	0	1	1		1	1	1	1	1	1		0	0	1		0	0	0	1	0	1	0		1	1
15	Trade, tariff adjustments		1	1	1	1	1		1	1	1	1	0		0	1	0	1	0	1	1	0	1	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		0	0	0	0	1	1	0		1	1
Hybrid strategies																																																										
16	Collaboration network and consortiums		0	1	1	0	1		1	1	1	1	1		1	1	1	0	0	0	0	1	1	1		0	0	1	1	1	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
17	Colloquium and symposium		0	1	1	0	0		0	0	0	0	0		0	0	1	0	1	0	0	1	0	0		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	1	1	0	0	0		1	1
18	Policy and legislation		0	1	1	0	1		0	1	0	1	1		0	0	0	1	1	1	1	0	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		0	0	1		0	0	0	0	0	1	0		1	1
19	Drug status designation		1	1	1	1	0		1	1	1	1	1		0	1	0	1	0	1	0	0	1	1		0	0	0	0	0	0	1		1	1	1	1	0	0		0	0	1		0	0	0	0	0	0	1		1	1
20	Joint venture		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		0	1	1		1	1	1	1	1	0	0		1	1
21	Independent organization		1	1	1	1	0		1	1	1	1	1		1	0	1	0	1	1	0	1	0	0		1	1	1	1	1	0	1		1	1	1	0	0	1		0	0	1		1	1	1	1	0	0	0		1	1
22	Hybrid PPP		0	1	1	1	1		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	1	1		1	1
23	Research laboratories		1	1	0	1	1		1	1	1	0	1		0	0	1	0	0	0	0	0	0	0		0	0	0	0	0	0	1		0	1	1	1	1	1		0	0	1		1	1	0	0	0	0	0		1	1
24	Treaty		0	0	0	1	1		1	1	1	1	1		1	1	0	1	1	1	1	1	1	1		1	1	0	1	0	0	1		0	0	0	1	0	0		1	1	1		0	0	1	1	1	1	0		1	1
25	Working Group		0	1	1	1	1		1	1	1	1	1		1	1	1	0	0	1	0	1	1	1		1	0	1	1	1	0	1		0	1	1	1	1	1		1	1	1		1	1	1	1	1	0	1		1	1
26	Coordination mechanism		1	1	1	0	1		1	1	1	1	1		0	1	1	0	0	0	0	1	0	1		0	0	0	0	0	0	1		1	1	1	1	1	1		1	1	1		1	1	1	1	1	0	0		1	1

Domain 4 Consumer profile: PPP results

DOMAIN 4: CONSUMER REQUIREMENTS		
END CONSUMER (patient)		
1	**Socio-economic inequalities**	
	Require differential pricing	1
	Must eliminate all financial risk	0
2	**Contextual treatment criteria**	
	Accommodates contextual treatment criteria	2
PROCUREMENT: PUBLIC / PRIVATE (FOR-/ NOT FOR PROFIT)		
3	**Affordability**	
	Require differential pricing	0
4	**End-price profit margins**	
	Any profit margins allowed	0
	Restricted profit margins	0
	No profit	0
5	**Availability and accessibility**	
	IP regulation allows procurement of drugs to target area	1
	Existing drugs not allowed in target area	0
	Drug status designation required	0

BACKGROUND LOGIC 4: CONSUMER MATRIX	END-CONSUMER				PROCURERS (PUBLIC / PRIVATE)							
	1. Socio-economic inequalities	Require differential pricing	Must eliminate all financial risk	**2. Contextual treatment criteria**	Addresses contextual treatment criteria	**3. Affordability**	Require differential pricing	**4. End-price profit margins**	Any profit margins allowed	Restricted profit margins	No profit	**5. Availability and accessibility**	IP regulation allows procurement of drugs to target area	Existing drugs not allowed in target area	Drug status designation required
Push intervention		1	0		2		0		0	0	0		1	0	0
1 Grant		0	0		1		0		0	0	0		0	0	0
2 Open-source initiative		0	0		1		0		0	1	1		1	0	0
3 Patent pool		0	0		1		0		0	0	0		1	1	0
4 PPP		1	1		1		1		0	1	0		1	0	1
5 Tax credits		0	0		1		0		0	1	0		0	0	1
Outcome-based pull strategies															
6 Advanced market commitments		0	0		1		0		1	1	0		0	1	0
7 Differential pricing		1	1		0		1		0	1	0		0	0	0
8 Patent buy-outs		0	0		1		0		1	1	0		1	1	0
9 Pooled fund		0	0		1		0		0	0	0		0	0	0
10 Prize fund		0	0		1		0		0	0	0		0	0	0
11 Rating system		0	0		1		0		0	0	1		0	1	1
Lego-regulatory pull strategies															
12 Intellectual property		0	0		1		0		1	1	0		1	1	0
13 Policy instrument		1	1		1		1		1	1	1		1	1	1
14 PRV		0	0		1		0		0	1	0		0	0	0
15 Trade, tariff adjustments		1	1		0		1		1	1	1		1	1	1
Hybrid strategies															
16 Collaboration network and consortiums		0	0		1		0		0	0	1		0	0	0
17 Colloquium and symposium		0	0		1		0		0	0	1		0	0	0
18 Policy and legislation		0	0		1		0		1	1	1		1	1	0
19 Drug status designation		1	1		1		1		0	0	1		1	1	1
20 Joint venture		0	1		1		0		0	1	1		1	1	0
21 Independent organization		0	1		1		0		1	0	1		0	1	0
22 Hybrid between PPP and other mechanisms		1	1		1		1		1	1	1		1	1	1
23 Research laboratories		0	0		0		0		1	0	1		0	0	0
24 Treaty		1	0		0		1		0	1	1		1	1	0
25 Working group		0	0		1		0		0	1	1		0	1	0
26 Coordination mechanism		0	0		1		0		0	1	1		0	1	0

Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	BL	1			1	3		2	2	2	3		2	3	2	2	2	2		1	3	3	4	1		2	2	4	4	4		1	2	3		2	3		3	2	1	4	3		1	1	1	1
	Cluster 1: Profitability and market forces	**Delink revenue from sales volume**	**Incentive improves product export potential**	Improve product export potential (Incentive ability)	Improve export potential (Innovator require)	**Incentive allows market exclusivity over an innovation**	Gain market exclusivity over an innovation (Enabler goal)	Provide market exclusivity (Enabler ability)	Market exclusivity policies (Enabler ability to alter)	Provide market exclusivity (Innovator require)	**Incentive provides market certainty**	Provide market certainty (Enabler role)	Provide market certainty (Innovator require)	**Incentive involves/requires national/international intellectual property policies (Enabler ability)**	**Incentive involves/requires tax credit policies (Enabler ability)**	**Incentive involves/requires pricing policies (Enabler ability)**	**Incentive involves/requires international trade law (Enabler ability)**	**Incentive improves NPV of stakeholders**	Improve NPV of stakeholders	Profit improvement (Innovator goal)	**Profit maximization (Innovator goal)**	**Any profit margins allowed (Consumer require)**	**Minimizes barriers to implementation (implementation of incentive)**		**Cluster 2Facilitate registration of drug / approval for use**	**Incentive involves/requires market authorization policies (Enabler ability)**	**Incentive involves/requires national policies and legislations (Enabler ability)**	**Existing drugs not allowed in target area (Consumer availability)**	**Drug status designation required (Consumer availability)**	**IP regulation allows procurement of drugs to target area (Consumer availability)**		**Cluster 3: Ability to influence nature of drug that is developed**	**Incentive encourage R&D of a drug/intervention**	Encourage R&D of a drug/intervention (Incentive ability)	Provide drug (Enabler goal)	R&D of drug (Innovator goal)	**Incentives stimulates multi-purpose drug R&D**	Multi-purpose drug (Enable goal)	R&D of multi-purpose drug (Innovator goal)	**Incentive allows the delivery of regime treatment**	Deliver regime treatment (Innovator goal)	Deliver regime treatment (Enabler goal)	**Payoff to innovators based on cost-effectiveness**	**Contextual treatment criteria can be addressed by incentive (Consumer requirements)**	**Incentive allows drug repurposing (Innovator goal)**		**Cluster 4: Improved governance**	**Promote equitable health-focused governance (Incentive ability)**	**Promote transparency and accountability (Incentive ability)**	**Advances the priority of disease on health agenda (Incentive ability)**	**Advance proper functioning of domestic policy (Incentive ability)**
	8	2	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	2	2	1	0	0	2		**2**	0	1	0	0	1		**12**	2	1	2	2	2	2	2	2	2	2	2	2		**7**	2	2	1	2
Push mechanisms																																																
Grant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0			0	0	0	0	0			1	1	1	1	1	1	1	1	1	0	1	1			0	1	1	0
Open-source initiative		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1			0	0	0	0	1			0	0	0	0	0	0	0	0	0	0	1	1			1	1	1	1
Patent pool		1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0			0	0	1	0	1			1	1	1	1	1	1	1	1	1	0	1	1			1	1	0	0
PPP		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1			1	1	0	1	1			1	1	1	1	1	1	1	1	1	0	1	1			1	1	1	1
Tax credits		0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	0	1			0	0	0	1	0			1	1	1	1	1	1	1	1	1	0	1	1			0	1	1	0
Outcome-based pull strategies																																															
Advanced market commitments (AMC)		1	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1			0	0	1	0	0			1	1	1	1	1	1	1	1	1	0	1	1			0	0	1	0
Differential pricing		1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1	1			0	0	0	0	0			1	1	1	1	1	1	1	1	1	0	0	1			0	0	1	0
Patent buy-outs		0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	1			1	0	1	0	1			1	1	1	1	1	1	1	1	1	0	1	0			0	0	1	0
Pooled fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1			0	0	0	0	0			1	1	1	1	1	1	1	1	1	0	1	1			0	1	1	0
Prize fund		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1			0	0	0	0	0			1	1	1	1	1	1	1	1	1	1	1	1			0	1	1	0
Rating system		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	1	1	0			1	1	1	1	1	1	1	1	1	0	1	0			1	1	1	1
Lego-regulatory pull strategies																																															
Intellectual property		0	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0	1			0	0	1	0	1			1	1	1	1	1	1	1	1	1	0	1	0			0	0	1	0
Policy instrument		0	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	1	1	1			1	1	1	1	1			0	0	0	0	0	0	0	0	0	0	1	0			1	1	0	1
PRV		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1			1	1	0	0	0			1	1	1	1	1	1	1	1	1	0	1	0			0	0	1	0
Trade, tariff adjustments		0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0			1	1	1	1	1			1	1	1	1	1	1	1	1	1	0	0	0			1	0	1	1
Hybrid strategies																																															
Collaboration network and consortiums		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	0	0	0			1	1	1	1	1	1	1	1	1	0	1	1			1	1	1	0
Colloquium and symposium		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0	0	0	0			0	0	0	0	0	0	0	0	0	0	1	0			0	1	1	1
Policy and legislation		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1			1	1	1	0	1			0	0	0	0	0	0	0	1	1	0	1	1			1	1	0	1
Drug status designation		1	1	1	1	0	0	0	0	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1			1	1	1	1	1			1	1	1	1	1	1	1	1	1	0	1	1			0	0	1	0
Joint venture		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	0	1	1	1	0	0	1			0	0	1	0	1			1	1	1	1	1	1	1	1	1	0	1	1			0	1	1	0
Independent organization		1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1	1	1	1	1	1			0	0	1	0	0			1	1	1	1	1	1	1	1	1	0	1	1			1	1	1	0
Hybrid between PPP and other mechanisms		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1			1	1	0	1	1			1	1	1	1	1	1	1	1	1	0	1	1			1	1	1	1
Research laboratories		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1			0	0	0	0	0			1	1	1	1	1	1	1	1	1	0	0	1			0	1	1	0
Treaty		0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1			1	1	0	1	1			1	1	1	1	1	1	1	1	1	0	0	1			1	1	1	1
Working group		0	1	1	1	0	0	0	0	0	1	1	1	0	0	0	0	0	1	1	1	0	0	1			0	0	1	0	0			1	1	1	1	1	1	1	1	1	0	1	1			0	0	1	0
Coordination mechanism		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1			0	0	1	0	0			1	1	1	1	1	1	1	1	1	0	1	1			0	1	1	0
			1	2	3		1	2	1	1		4	4	2	4			1	1		2	3		2	3		2	3		2	3		2	3	2	3	2	2	2	2			1	2	3	1	1	2	

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 5: Population impact and access	Incentive improves consumer access	Improve consumer access (Incentive ability)	Play a role in improved access (Enabler goal)	Play a role in improved access (Innovator goal)	Incentive enables mass drug administration	Enable mass drug administration (Incentive ability)	Implement mass drug administrations (Enabler goal)	Incentive aims to reduce burden of disease in area	Incentive aims to minimize disruptive effects to	Incentive allows for differential pricing (Consumer	Incentive allows differential pricing (End-consumer	Incentive allows differential pricing (Procurer	Deliver affordable and accessible treatment (Enabler	Incentive eliminates all financial risk (Consumer	Cluster 6: Limited enabler resource investment	Affordable to implement the incentive	Incentive allows resources to develop drugs to be	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be in the	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be at the end,	Incentive allows payoff to innovator to be	Incentive allows payoff to innovator to be incrementally,	Incentive allows payoff to innovator to be incrementally,	Incentive does not require enabler funding (Enabler no	Incentive does not require enabler funding (Enabler has	Innovator does not require any funding from enabler, or	Incentive requires/allows the enabler to partially fund	Incentive requires/allows the enabler to partially fund	Incentive requires/ allows innovator to partially fund	Incentive payout to innovator is a once-off occasion	Incentive payout to innovator occurs once output is	Incentive allows innovator payouts to be limited to a	Incentive allows innovator payouts to be milestone	Incentive allows enabler to engage with innovator at	Incentive allows enabler funding to be limited to an	Cluster 7: Encourage competition in the innovation	Incentive encourages large firm participation	Incentive encourages large firm participation	Incentive allows large pharmaceutical organization	Incentive aimed at incentivising large pharmaceutical	Incentive allows competition among parallel	Incentive enlarges the number of clinical trials	Incentive targets all organizations to participate
	9	2	2	2	1	1	1	0	1	2	1	1	0	2	0	8	2	1	0	0	0	0	0	0	0	0	0	2	2	0	1	0	1	0	0	1	1	0	7	2	2	2	2	2	2	1
Push mechanisms																																														
Grant		1	1	1	1	1	1	1	1	0	0	0	0	0	0		1	1	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	1	1	0	1		0	0	0	0	0	0	0
Open-source initiative		0	0	0	0	0	0	0	1	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0		1	1	1	1	0	1	0
Patent pool		1	1	1	1	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0	0		1	1	1	1	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1		1	1	1	1	0	1	1
Tax credits		0	0	0	0	1	1	1	1	0	0	0	0	0	0		0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	0	1	0		1	1	1	1	0	0	0
Outcome-based pull strategies																																														
Advanced market commitments (AMC)		1	1	1	1	1	1	1	1	1	0	0	0	0	0		1	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	1	1	0	0	0		1	1	1	1	0	0	1
Differential pricing		1	1	1	1	1	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	0	0	0		1	1	1	1	0	0	1
Patent buy-outs		0	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1		1	1	1	1	0	0	1
Pooled fund		1	1	1	1	1	1	1	1	0	0	0	0	0	0		1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	1		0	0	0	0	0	0	1
Prize fund		1	1	1	1	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	0		0	0	0	0	1	1	1
Rating system		1	1	1	1	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	1	0	1	0		1	1	1	1	1	0	1
Lego-regulatory pull strategies																																													
Intellectual property		0	0	0	0	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	1	0		1	1	1	1	1	0	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1		1	1	1	1	0	1	1
PRV		0	0	0	0	0	0	0	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	1	0		1	1	1	1	1	0	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	0	1		1	1	1	1	0	0	1
Hybrid strategies																																													
Collaboration network and consortiums		1	1	1	1	1	1	1	1	0	0	0	0	1	0		1	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	0	1	0			1	1	1	1	0	0	1
Colloquium and symposium		0	0	0	0	0	0	0	1	0	0	0	0	0	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	1	0	0		1	1	1	1	0	0	1
Policy and legislation		1	1	1	1	1	1	1	1	1	0	0	0	1	0		0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1		1	1	1	1	0	1	1
Drug status designation		1	1	1	1	1	1	1	1	0	1	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0		1	1	1	1	1	0	1
Joint venture		1	1	1	1	1	1	1	1	0	0	0	0	0	1		1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	1	1		1	1	1	1	0	1	0
Independent organization		1	1	1	1	0	0	0	1	0	0	0	0	0	1		0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	1		1	1	1	1	0	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1		1	1	1	1	0	1	0
Research laboratories		0	0	0	0	0	0	0	1	1	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0		0	0	0	0	0	1	0
Treaty		1	1	1	1	1	1	1	1	1	1	1	1	1	0		1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	1	1	1	1	0		0	0	0	0	0	1	0
Working group		1	1	1	1	1	1	1	1	0	0	0	0	1	0		1	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0		0	0	0	0	0	0	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	1		1	1	1	1	0	1	1

Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	**Cluster 8: Overcome barriers to innovator participation in R&D process**	**Incentive allows small and medium organizations to be incentivized**	Incentive enables participation of small and medium organizations	Incentive enables participation of small and medium organizations (Enabler target)	Incentive enables participation of small and medium organizations (Innovator identity)	**Incentive allows governmental institutions to be incentivized**	Incentive allows governmental institutions to be incentivized (Enabler target)	Incentive allows governmental institutions to be incentivized (Innovator identity)	**Incentive allows independent scientists to be incentivized**	Incentive allows independent scientists to be incentivized (Enabler target)	Incentive allows independent scientists to be incentivized (Innovator identity)	**Incentive allows academic institutions to be incentivized**	Incentive allows academic institutions to be incentivized (Enabler target)	Incentive allows academic institutions to be incentivized (Innovator identity)	**Incentive allows NGO organizations to be incentivized**	Incentive allows NGO organizations to be incentivized (Enabler target)	Incentive allows NGO organizations to be incentivized (Innovator identity)	**Incentive financing is timed across drug lifecycle**	**Incentive provides long term R&D financing**	**Incentive provides sustainable financing for innovator**	**Incentive provides R&D project insurance**	Incentive provides R&D project insurance	Incentive provides risk insurance or security (Innovator requirement)	**Incentive de-risks the R&D process**	**Incentive requires/allows enabler to fund R&D**	Incentive allows enabler to fund R&D (Enabler goal)	Incentive requires enabler to fund all R&D costs (Innovator requirement)	**Incentive allows enabler to fully fund R&D (Enabler full capacity)**	Incentive allows enabler to fully fund R&D (Enabler full capacity)
			1	2	3		2	3		2	3		2	3		2	3	1	1	1		1	2	2		2	3		2
	38	2	2	2	2	2	1	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	1	2	1	0	1	0	0
Push mechanisms																													
Grant		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	1
Open-source initiative		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Patent pool		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tax credits		1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Outcome-based pull strategies																													
Advanced market commitments (AMC)		1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1
Differential pricing		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Patent buy-outs		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1
Pooled fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0
Prize fund		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	1	1	1	1	0	0
Rating system		1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Lego-regulatory pull strategies																													
Intellectual property		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	1	1
Policy instrument		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1
PRV		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Trade, tariff adjustments		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1
Hybrid strategies																													
Collaboration network and consortiums		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
Colloquium and symposium		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Policy and legislation		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	1	1
Drug status designation		1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	1	1	0	0	0	0	1	1
Joint venture		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1
Independent organization		1	1	1	1	0	0	0	0	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Research laboratories		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	1	1
Treaty		0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	1	1	1
Working group		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Incentive requires enabler to completely fund R&D (Innovator no ability)	**Incentive requires enabler to partially fund R&D (Innovator ability)**	Incentive requires enabler to partially fund R&D (Innovator requirement)	Incentive requires enabler to partially fund R&D (Innovator ability)	**Incentive allows funding to be incremental, as innovator requires**	Incentive allows funding to be incremental, as innovator requires (Enabler ability)	Incentive allows funding to be incremental, as innovator requires (Innovator requirement)	**Incentive allows funding to be incremental, based on timing**	Incentive allows funding to be incremental, based on timing (Enabler ability)	Incentive allows funding to be incremental, based on timing (Innovator requiirement)	**Incentive does not provide any funding (Innovator has full capacity to provide own funding)**	**Incentive allows enabler to increase bandwidth and network (Enabler goal)**	**Incentive utilizes enabler's ability to influence intellectual property (Enabler ability)**	**Incentive requires/ utilizes enabler's access to key data**	Incentive utilizes enabler's access to key data (Enabler ability)	Incentive provides innovator with information (knowledge) on disease (Innovator requirement)	**Incentive utilizes enabler's access to compounds (Enabler ability)**	**Incentive requires/ utilizes enabler technology expertise and access**	Incentive requires/ utilizes enabler technology expertise and access	Incentive provides innovator access to adequate equiptment (Innovator requirement)	Incentive provides innovator with access to research laboratory (innovator requirement)	**Incentive requires/ utilizes enablers R&D expertise**	Incentive requires/ utilizes enablers R&D expertise	Incentive aids innovator with cumbersome nature of clinical trial regulations (innovator requirement)	**Incentive addresses innovator's policy or regulatory limitations (innovator requirement)**	**Incentive provides innovator with market certainty (innovator requirement)**	**Innovator does not adhere to any authorization standards (innovator nature)**	**Innovator has accredited authorisation organization (innovator nature)**	**Incentive rewards innovation**
	3		3	3		2	3		2	3	3	2	2		2	3	2		2	3	3		2	3	3	3	3	3	1
	0	2	2	1	0	0	0	0	0	0	0	1	2	2	2	2	2	2	2	2	2	2	2	1	0	0	0	2	2
Push mechanisms																													
Grant	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Open-source initiative	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	1	0
Patent pool	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1
PPP	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0
Tax credits	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Outcome-based pull strategies																													
Advanced market commitments (AMC)	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1
Differential pricing	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Patent buy-outs	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1
Pooled fund	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Prize fund	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1
Rating system	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Lego-regulatory pull strategies																													
Intellectual property	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
Policy instrument	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
PRV	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1
Trade, tariff adjustments	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1
Hybrid strategies																													
Collaboration network and consortiums	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Colloquium and symposium	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	1	1	1	0	0	1	1	0
Policy and legislation	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0
Drug status designation	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Joint venture	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Independent organization	0	0	0	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1
Hybrid between PPP and other mechanisms	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Research laboratories	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	0
Treaty	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0	1	1	0
Working group	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0
Coordination mechanism	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0

Background Logic 5: PPP

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 9: Facilitate clinical trials	Incentive allows provision of public subsidies for clinical trials	Incentive reduces clinical trial risk involved	Incentive assist in registration and monitor of trials	Incentive globalizes clinical trial methods	Incentive reduces clinical trial activation difficulty	Incentive enhances or prompt the quality of clinical trials	Incentive aids in clinical trial regulation	Clinical trial regulation policies (Enablers ability to influence)
		1	1	1	1	1	1	1	2
	8	2	1	2	1	0	2	0	0
Push mechanisms									
Grant		0	0	0	0	1	0	0	0
Open-source initiative		0	1	1	1	0	0	0	0
Patent pool		0	0	0	0	0	0	0	0
PPP		1	0	1	1	1	0	1	1
Tax credits		1	0	0	0	0	0	0	1
Outcome-based pull strategies									
Advanced market commitments (AMC)		0	0	0	0	0	0	0	0
Differential pricing		0	0	0	0	0	0	0	0
Patent buy-outs		0	0	0	0	0	0	0	0
Pooled fund		0	1	0	0	0	0	0	0
Prize fund		0	0	0	1	0	1	0	0
Rating system		0	0	0	0	0	1	0	0
Lego-regulatory pull strategies									
Intellectual property		0	0	0	0	0	0	0	0
Policy instrument		0	0	1	1	0	1	1	1
PRV		0	0	0	0	1	0	1	1
Trade, tariff adjustments		0	0	0	0	0	0	0	0
Hybrid strategies									
Collaboration network and consortiums		0	1	1	1	0	1	1	0
Colloquium and symposium		0	0	0	1	0	1	0	0
Policy and legislation		1	0	1	1	1	1	0	1
Drug status designation		0	0	0	0	0	0	0	1
Joint venture		0	1	0	1	1	1	1	0
Independent organization		0	0	0	0	0	1	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	0	1	1
Research laboratories		0	0	1	1	1	1	1	0
Treaty		1	0	0	1	0	1	1	1
Working group		0	0	0	1	1	0	0	0
Coordination mechanism		0	1	1	1	1	1	1	0

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 10: Facilitate / improve R&D process and R&D body of knowledge	Incentive aims to/ allows improvement of R&D productivity	Incentive provides regulatory oversight to promote R&D	Incentive provides regulatory exclusivity provisions for R&D	Incentive encourages efficient innovation	Incentive ensures the conservation of resources in R&D process	Incentive requires/ allows green R&D of drugs	Incentive enables organizations to innovate easier (Enabler goal)	Incentive advances the R&D field & body of knowledge (Enabler goal)	Incentive can improve the state of the R&D pipeline (Enabler goal)
		1	1	1	1	1	1	2	2	2
	15	2	1	1	2	2	1	2	2	2
Push mechanisms										
Grant		0	1	0	0	0	0	0	1	1
Open-source initiative		1	0	0	0	0	0	1	1	1
Patent pool		0	0	0	0	0	0	0	0	1
PPP		0	0	0	0	0	0	0	1	1
Tax credits		0	1	1	0	0	0	0	0	1
Outcome-based pull strategies										
Advanced market commitments (AMC)		0	0	0	1	1	0	0	0	1
Differential pricing		0	0	1	0	0	0	0	0	1
Patent buy-outs		0	0	1	0	0	0	0	0	1
Pooled fund		0	0	0	1	1	0	1	0	1
Prize fund		0	0	0	1	1	0	1	1	1
Rating system		1	1	1	1	1	1	0	1	0
Lego-regulatory pull strategies										
Intellectual property		0	0	1	0	0	0	0	0	1
Policy instrument		0	1	0	1	1	1	0	1	0
PRV		0	0	1	0	0	0	0	1	1
Trade, tariff adjustments		0	0	1	0	0	0	0	0	1
Hybrid strategies										
Collaboration network and consortiums		1	0	0	1	1	0	1	1	1
Colloquium and symposium		1	1	0	1	0	0	1	1	0
Policy and legislation		0	1	0	1	0	1	0	0	0
Drug status designation		0	0	1	0	0	0	0	1	1
Joint venture		0	0	0	1	1	0	1	1	1
Independent organization		0	0	0	0	0	0	0	1	0
Hybrid between PPP and other mechanisms		0	1	0	0	0	0	1	1	1
Research laboratories		0	0	0	1	1	1	1	1	1
Treaty		0	1	0	1	1	1	1	0	1
Working group		0	0	0	0	0	0	1	1	1
Coordination mechanism		0	0	0	1	1	1	1	0	0

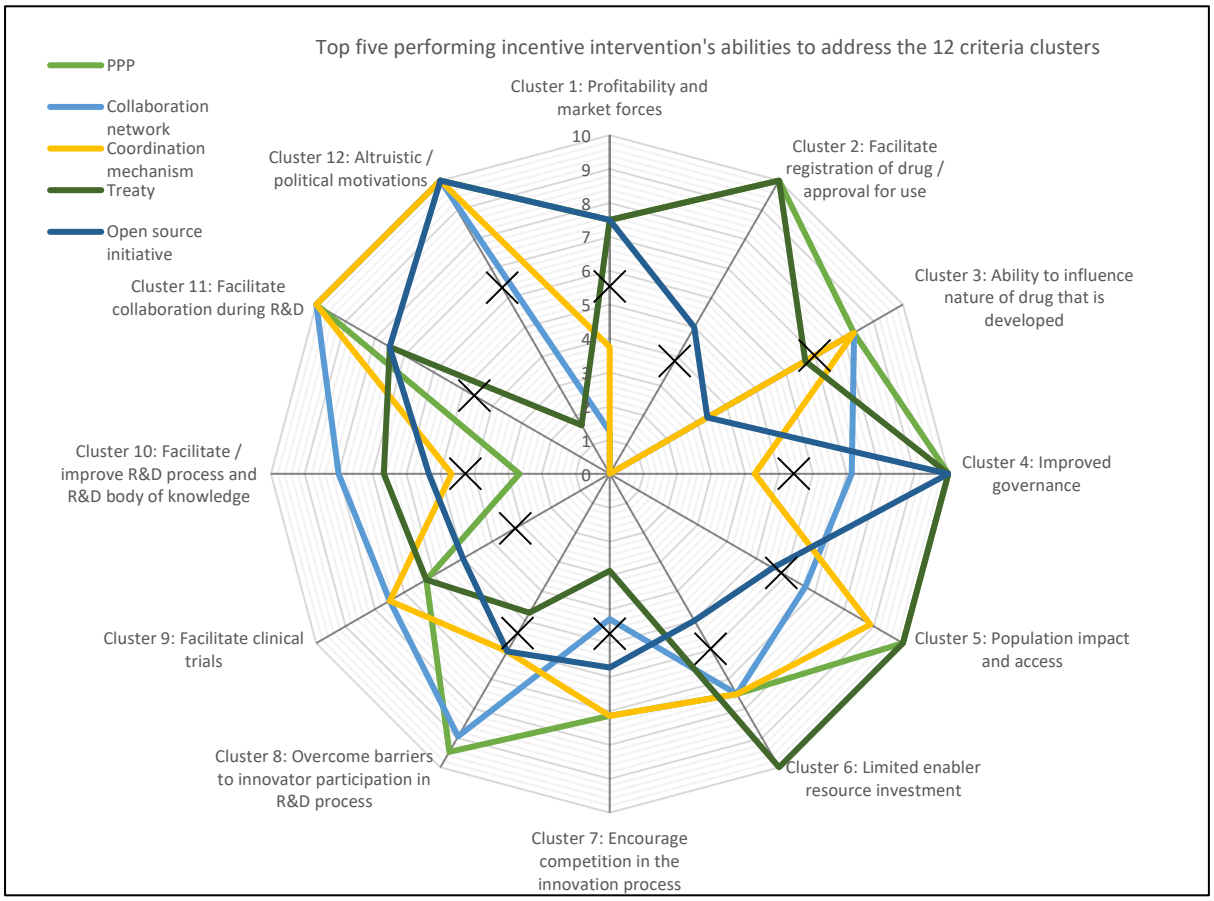
BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 11: Facilitate collaboration during R&D	Incentive facilitates cooperation and synergy between all stakeholders	Facilitates cooperation and synergy between all stakeholders	Incentive facilitates collaboration between innovators (Enabler goal)	Incentive allows enabler to collaborate and build a partnership/s (Enabler goal)	Incentive allows enabler to collaborate with innovator	Incentive allows enabler to collaborate with innovator (Enabler goal)	Incentive allows innovator to collaborate with enabler (Innovator requirement)	Incentive provides a platform for coordinating innovators	Incentive provides a platform for coordinating innovators	Incentive provides a collaboration platform (Innovator requirement)	Incentive allows/ requires enabler to facilitate in regulatory process	Incentive allows/ requires enabler to facilitate in regulatory process (Enabler ability)	Incentive allows/ requires enabler to facilitate innovator in regulatory process (Innovator requirement)	Incentive requires enabler to adjust policies and regulations	Enabler has ability to adjust policies and regulations	Innovator requires enabler to adjust policies and regulations (should be allowed by incentive)
			1	2	2		2	3		1	3		2	3		2	3
	8	2	2	2	2	2	1	2	2	2	2	0	0	0	0	0	0
Push mechanisms																	
Grant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Open-source initiative		1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0
Patent pool		0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1
Tax credits		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Outcome-based pull strategies																	
Advanced market commitments (AMC)		0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Differential pricing		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Patent buy-outs		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pooled fund		1	1	0	1	0	0	0	1	1	1	0	0	0	0	0	0
Prize fund		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rating system		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lego-regulatory pull strategies																	
Intellectual property		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Policy instrument		0	0	0	1	0	0	0	0	0	0	1	1	1	1	1	1
PRV		0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0
Trade, tariff adjustments		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Hybrid strategies																	
Collaboration network and consortiums		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Colloquium and symposium		1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0
Policy and legislation		0	0	0	1	0	0	0	0	0	0	1	1	1	1	1	1
Drug status designation		0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Joint venture		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Independent organization		1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0
Hybrid between PPP and other mechanisms		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Research laboratories		1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
Treaty		1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1
Working group		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0

BACKGROUND LOGIC 5: CRITERIA CLUSTER SCORING	Cluster 12: Altruistic / political motivations	Incentive convey an important message (Enabler goal)	Incentive allows corporate social responsibility to be fulfilled	Incentive allows enabler to fulfil corporate social responsibility (Enabler goal)	Incentive allows innovator to fulfil corporate social responsibility (Innovator goal)	Incentive allows enabler to fulfil political obligations	Incentive allows enabler to fulfil political obligations (Enabler goal)	Incentive allows innovator to fulfil political obligations (innovator goal)	Incentive allows not for profit R&D (Innovator goal)	Incentive allows not for profit/ restricted profit margins for drug procurers	Incentive enables/ allows restricted profit margins for drug procurers	Incentive enables no profit margins for drug procurers
		2		2	3		2	3	3		4	4
	6	2	2	2	2	1	0	1	1	0	0	0
Push mechanisms												
Grant		0	1	1	1	1	1	1	1	0	0	0
Open-source initiative		1	1	1	1	1	1	1	1	1	1	1
Patent pool		0	1	1	1	0	0	0	1	0	0	0
PPP		1	1	1	1	1	1	1	1	1	1	0
Tax credits		0	0	0	0	0	0	0	0	1	1	0
Outcome-based pull strategies												
Advanced market commitments (AMC)		0	1	1	1	1	1	1	0	1	1	0
Differential pricing		1	1	1	1	1	1	1	1	1	1	0
Patent buy-outs		0	0	0	0	0	0	0	0	1	1	0
Pooled fund		0	1	1	1	1	1	1	1	0	0	0
Prize fund		0	1	1	1	0	0	0	1	0	0	0
Rating system		1	1	1	1	1	1	1	1	0	0	1
Lego-regulatory pull strategies												
Intellectual property		0	0	0	0	0	0	0	0	1	1	0
Policy instrument		0	1	1	1	1	1	1	1	1	1	1
PRV		1	0	0	0	0	0	0	1	1	1	0
Trade, tariff adjustments		0	1	1	1	1	1	1	1	1	1	1
Hybrid strategies												
Collaboration network and consortiums		1	1	1	1	1	1	1	1	0	0	1
Colloquium and symposium		1	1	1	1	0	0	0	1	0	0	1
Policy and legislation		0	1	1	1	1	1	1	1	1	1	1
Drug status designation		1	1	1	1	0	0	0	1	0	0	1
Joint venture		0	1	1	1	1	1	1	1	1	1	1
Independent organization		0	1	1	1	0	0	0	1	0	0	1
Hybrid between PPP and other mechanisms		0	1	1	1	1	1	1	1	1	1	1
Research laboratories		0	1	1	1	1	1	1	0	0	0	1
Treaty		0	0	0	0	1	1	1	0	1	1	1
Working group		1	1	1	1	1	1	1	1	1	1	1
Coordination mechanism		1	1	1	1	1	1	1	1	1	1	1

Domain 5 solution set (1 of 2): PPP results

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													11	Feasible
16	Collaboration network													7	Feasible
26	Coordination mechanism													8	Feasible
24	Treaty													7	Feasible
2	Open-source initiative													4	Feasible
21	Independent organization													4	Feasible
25	Working group													5	Feasible
17	Colloquium and symposium													2	Feasible
23	Research laboratories													2	Feasible
22	Hybrid PPP													9	Infeasible
20	Joint venture													4	Infeasible
10	Prize fund													5	Infeasible
18	Policy and legislation													5	Infeasible
11	Rating system													4	Infeasible
19	Drug status designation													4	Infeasible
7	Differential pricing													2	Infeasible
9	Pooled fund													2	Infeasible
13	Policy instrument													5	Infeasible
15	Trade, tariff adjustments													2	Infeasible
6	Advanced market commitments													2	Infeasible
14	PRV													3	Infeasible
12	Intellectual property													2	Infeasible
5	Tax credits													1	Infeasible
1	Grant													1	Infeasible
8	Patents buy-outs													0	Infeasible
3	Patent pool													1	Infeasible

Domain 5 solution set (2 of 2): PPP results



Non-incentive-based interventions (1 of 8): PPP results

1. Country economic status		*For further reference*	
Meaning	The World Bank categorizes countries based on a national income per person measure.	(Jalava and Pohjola, 2002; The World Bank, 2018; Błazejowski *et al.*, 2019)	1
Relevance	The income status of a country does not indicate that the health and availability of adequate drugs are not possible for the country. It can, however, indicate the difficulty of the necessary structures and resources available to easily alleviate the health circumstances within that country.		
Intervention considerations	This attribute is dependent on a significant number of factors including: (i)human resources; (ii) natural resources; (iii) capital formation; (iv) technological development; (v) social and political factors; (vi) imports and exports; and (vii) the stewardship of country finances.		

2. Burden fully characterized		*For further reference*	
Meaning	The affected patients are diagnosed, being monitored and documented properly.	(Olmsted et al., 2006; RAND Corporation, 2007; Novak et al., 2013)	1
Relevance	Once the burden of a disease is fully characterized, consumer demand can be estimated. Consumer demand will have an influence on how profitable the perceived market is. Fully characterizing the burden also assists in the planning, distribution and implementation of control strategies.		
Intervention considerations	Diagnostic tools and technology, availability and access there of		
	Diagnostic intervention and intervention strategies		
	Availability of health facilities (option is to consider mobile health facilities)		
	Educate populations on disease side-effects, risks, and necessity of health interventions		
	Capture burden characterization data		

3. Physicians per 1000 population		*For further reference*	
Meaning	The number of physicians available per capita / 1000 of people	(Al-Shamsi, 2017)	1
Relevance	The higher the availability of physicians in a country, the higher the likelihood that the population will have access to adequate care.		
Intervention considerations	Recruit international medical graduates		
	Modify postgraduate majors to allow physicians to enter the practice in areas of need		
	Shorten the preparatory under-graduate medical education years and introduce modern methods of teaching.		

4. Quality of existing drugs		*For further reference*	
Meaning	Drugs should not pose significant health risks to patients and should be effective in treating the disease.	(van Olmen et al., 2010); (Dorlo et al., 2012); (Rauscher, Walkowiak and Djara, 2018); (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	1
Relevance	Patients depend on drugs for disease mitigation. If quality is not up-to-standard, then disease burden might increase or might not decrease.		
Intervention considerations	Repeat final clinical trial stages to monitor effects of medicine in a controlled environment		
	Remove drugs from market		
	Improve monitoring of ADR		
	Pharmacovigilance		
	Quality control of current manufacturing procedures		
	Enforce international clinical trial and manufacturing practices and regulations		

5. Availability of drugs for the desired population		*For further reference*	
Meaning	Drugs are available in the right quantities, on the right time for patients to access.	(Jackson, 2018) ; (Niëns and Brouwer, 2013), (Holt, Gillam and Ngondi, 2012)	1
Relevance	If drugs are adequate but not available, then patients might not be effectively treated. Possible resistance to medicines.		
Intervention considerations	Supply chain management		
	Distribution networks		
	Inventory management at health facilities		
	Replenishment systems at health facilities		
	Burden characterization assists in inventory planning		

Non-incentive-based interventions (2 of 8): PPP results

6. Affordability of current drugs to desired population		*For further reference*	
Meaning	The population can afford to buy/ acquire the drugs needed to mitigate the disease that they have.	(Leisinger et al., 2012)	2
Relevance	If the drugs are developed and available, but not affordable, then disease burden will still not decrease.		
Intervention considerations	Corporate social responsibilities of innovating organizations should include to offer affordable drugs		
	Collaborate with other health delivery entities to form partnerships		
	Manufacture drugs nationally, instead of importing		

7. Appropriateness of drugs to the desired population		*For further reference*	
Meaning	Drugs must target the disease intended for. Intervention must be understandably explained and not interfere with culture.	(Jackson, 2018), (Hotez, 2008)	1
Relevance	If drugs are not appropriate, then patients won't use it or, if they use it, improvements in disease burden will not be made.		
Intervention considerations	Screen culture and explore possible cultural and ethical issues		
	Improve diagnostics of patients		
	Communication in understandable language for population group		
	Survey to understand the feelings of patients		

8. Acceptability of drugs to the desired population		*For further reference*	
Meaning	Drugs are not acceptable because of cultural values norms or stigmas.	(Jackson, 2018) ; (Institute of Medicine & Committee on Quality of Health Care in America, 2001)	1
Relevance	If patients do not accept drugs, then intervention strategies go to waste.		
Intervention considerations	Educate people to reduce stigmas.		
	Educate people to understand potential of drugs.		
	Respect and honour the norms and values of the patient group.		

9. Comprehensiveness of services delivered		*For further reference*	
Meaning	Service delivery is sustainable and in the appropriate doses. Care focuses on empowering patients (e.g. to prevent being infected again), and not only providing medicine.	(Global Forum for Health Research, 2004), (WHO, 2010)	1
Relevance	If health service is not comprehensive, then patients might not take precaution measures. Or patients might feel neglected and lose trust in the system.		
Intervention considerations	Education of prevention measures.		
	Address root-cause of disease (e.g. water and sanitation)		
	Investigate the needs of the affected population group		
	Address social needs of patients		
	Repeat prevention or mass drug administration interventions, if deemed necessary.		

10 Continuity of patients' access to health services [Check in Case study 1 Appendix]		*For further reference*	
Meaning	For health interventions where once-off treatment is not adequate, follow-up treatments must be scheduled and adhered to.	(Jackson, 2018, (Holt, Gillam and Ngondi, 2012, Stevens, 2004)	1
Relevance	If follow-up treatments are not provided, then patient health might not improve as desired.		
Intervention considerations	Scheduling of follow-up interventions		
	Mobile health facilities		
	Track patient health records and data		
	Monitor and track patients		

11. Coordination of service delivery networks		*For further reference*	
Meaning	Service delivery is done in an organized, timely, professional and appropriate manner.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001; WHO, 2010a; Rauscher et al., 2018)	1
Relevance	If service delivery is not coordinated properly, then some patients might be overlooked for treatment, not have access, or might miss the opportunity to meet with health care workers (if not properly communicated)		
Intervention considerations	Communication services		
	Scheduling of health workers		
	Monitor service delivery per area		
	Monitor drug distribution or mass drug administrations per region.		

Non-incentive-based interventions (3 of 8): PPP results

12. Minimize waste of resources in service delivery		*For further reference*	
Meaning	Any resource that is not used or used in an effective or efficient manner, leads to waste and possible financial losses.	(Priya, Nandini and Selvamani, 2012)	2
Relevance	Given that most waste is preventable, resources could be used in a more effective manner.		
Intervention considerations	Monitor service delivery to identify and address waste.		
	Coordinate service delivery actions		
	Waste management		

13. Demand size or sales force (relates to disease burden)		*For further reference*	
Meaning	The size of the burdened population, and patients who needs medicines, or intervention strategies.	(Novak et al., 2013; RAND Corporation, 2007)	0
Relevance	By determining the size of the burdened population, service delivery and intervention strategies can be planned more accurately. Also, service delivery waste can be reduced.		
Intervention considerations	Characterization of the burden of disease		
	Diagnostic interventions		
	Target repurposing		
	The size of the burdened population, and patients who needs medicines, or intervention strategies.		

14. The role of brand loyalty		*For further reference*	
Meaning	Brand loyalty of consumers to certain brands / drugs means that consumers buy certain drugs, based on previous experience, or perceived value. (relevant to other brands).	(Griffiths, 2008; Panchal *et al.*, 2012)	1
Relevance	If a product does not have brand loyalty, it might have the necessary characteristics to mitigate disease, but patients are not using it as a result of not 'trusting' the drug.		
Intervention considerations	Awareness amongst physicians of the value of the drug		
	Build trust in the communities		
	Well planned market strategies		

15. Bargaining power of the suppliers (chemical entities)		*For further reference*	
Meaning	The ability of suppliers to influence the prizing of the entities that they offer the pharmaceutical innovators and manufacturers.	(Whiteside, 2016)	1
Relevance	The stronger the bargaining power of the suppliers; the higher the prizes of resources, and the higher the total cost of drug interventions.		
Intervention considerations	Research alternative suppliers.		
	Support local suppliers.		
	Consider importing of goods.		
	Ensure quality of suppliers, if weak bargaining power.		

16. Existence of competitors		*For further reference*	
Meaning	Competitors refer to other pharmaceutical innovators completing R&D in the same field, thus, targeting the same disease.	(Thakor and Lo, 2018; (Whiteside, 2016)	1
Relevance	Strong competition exists because of intellectual property rights that are gained for new chemical entities innovated.		
Intervention considerations	Explore and compare for similar drugs being marketed as different products.		
	Competition is not always a bad thing (speeds up discovery)		
	Collaboration and open innovation		

17. Political will and contribution to improve R&D for disease		*For further reference*	
Meaning	The effort and contribution that the government of a country is willing to make towards R&D of diseases.	(Brinkerhoff, 2003; (Emmanuel and Emmanuel, 1996; World Health Organization, 2018)	1
Relevance	Governments should be obligated to make significant efforts to reduce disease burden within a country		
Intervention considerations	Enforce SDGs		
	Ministry of Health audit		
	Policy reform		
	Political accountability systems		

Non-incentive-based interventions (4 of 8): PPP results

18. Effective national budget allocation		*For further reference*	
Meaning	The financial plan of a country should include planning and financial allocations to the health and health care of citizens.	(World Health Organization, 2018; Emmanuel and Emmanuel, 1996; Becker, 2015)	1
Relevance	The health care of a country is the responsibility of its government. Without budget allocation, health care advancement is less likely.		
Intervention considerations	Implement SDGs		
	Policy reform		
	Strategic resource allocation options		
	Global health governance		

19. Regulation of strategic health policy		*For further reference*	
Meaning	The goals, visions, priorities and budgetary decisions of a country needs to be regulated, to be in line with health needs.	(Liang and Mackey, 2012; World Health Organization, 2018; Nagpal, Sinclair and Garner, 2013)	1
Relevance	If the strategic plans and actions to undertake and achieve are not taken, then the health of the country will lack improvement.		
Intervention considerations	Global health governance		
	Strategic political interventions		
	Domestic, private, and global policy interventions		

20. Adequate supply of the health service		*For further reference*	
Meaning	The health service should be fully sufficient, suitable or fit for the target population.	(Jacobs et al., 2012; RAND Corporation, 2007; Manjit Kaur; Sarah Hall, 2002)	2
Relevance	If health intervention is supplied but not sufficient then the impact of the intervention might not reach its goals.		
Intervention considerations	Strategic service delivery		
	Burden characterization		
	Health supply management		

21. Monitoring of the actual health system and system performance		*For further reference*	
Meaning	The observation and measurement of health system performance.	(WHO, 2010a; International Federation *et al.*, 2015; Jones *et al.*, 2015; Newman *et al.*, 2016)	1
Relevance	By observing and measuring performance of the health system, problems can be located faster and more easily.		
Intervention considerations	Information systems and data handling		
	Pharmacovigilance		
	Reporting networks		
	Personnel training		
	Accountability networks and schedules		

22. Current investment capital and returns		*For further reference*	
Meaning	ROI is one of the major drivers for the innovation of drugs.	(Vischer et al., 2017; Bates et al., 2015; Ho, Zarrinpar and Chow, 2016; Payne et al., 2015)	2
Relevance	This factor refers to the current ROI being profitable or not, if not then more investment in a similar research area is not likely.		
Intervention considerations	Financial analysis		
	Cost analysis of activities		
	Reduce indirect and operational costs		

23. Stakeholder demand		*For further reference*	
Meaning	Stakeholder demand refer to whether the public desires, and needs the product being developed.	(Thakor and Lo, 2018; Whiteside, 2016)	1
Relevance	The higher the demand for the products being delivered, the greater the perceived potential ROI.		
Intervention considerations	Target market analysis		
	Marketing strategies		
	Inform governments and the public that require this drug.		
	Pricing of the product		

Non-incentive-based interventions (5 of 8): PPP results

24. Established marketing and distribution network		*For further reference*	
Meaning	The marketing and distribution of drugs are important, to inform patients, and provide access and availability.	(Ravn, 2012; Radulescu, 2012)	1
Relevance	Distribution adds to effective service delivery; and marketing creates and enlarges the market demand.		
Intervention considerations	Marketing strategies		
	Effective distribution networks		
	Supply chain management		
	Coordination of service delivery, inventory management and distribution services		

25. Consistency and recommendations on choosing metrics for clinical trials		*For further reference*	
Meaning	Clinical trials are the most timeous procedure of drug R&D, using the correct metrics are essential in innovation productivity.	(Gupta et al., 2016; Moatti et al., 2016; Mayo et al., 2017; Clifton, Kohrt and Peoples, 2015; Zhou et al., 2015)	0
Relevance	Guidelines and regulations should be followed to advance in clinical trial phases. If not consistent then clinical trials might be trivial.		
Intervention considerations	Structured regulations and policy recommendations		
	Standardized clinical trial metrics		
	Market authorization regulation		
	Capture data of clinical trial methods and metric outputs		

26. Transparency of clinical trial information		*For further reference*	
Meaning	Clinical trial information is openly available, reliable and does not entail any suspicious information.	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	0
Relevance	Transparent clinical trial information assures that products being developed adhere to safety, efficacy and regulatory requirements.		
Intervention considerations	Annual, and unannounced firm audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

27. Accountability of clinical trial information		*For further reference*	
Meaning	Clinical trial information should be trustworthy	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	1
Relevance	There should be clear accountability for the information of clinical trials.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

28. Accessibility of clinical trial information		*For further reference*	
Meaning	The clinical trial information should be made available (within the market exclusivity agreements)	(Shaw and Ross, 2015) (Campa, Ryan and Menter, 2016) (Tsourounis et al., 2015) (Šolić et al., 2017) (Li et al., 2016)	1
Relevance	Secrecy on critical clinical trial information not allowed, especially if it alters the safety and efficacy of the drugs.		
Intervention considerations	Annual, and unannounced organization audits		
	Ethical conduct		
	Education on misconduct and legal consequences		
	Adhere to international clinical trial authority agency regulations		

29. The use of innovative clinical trial tools and technology		*For further reference*	
Meaning	Advanced tools and technologies exist for performing clinical trials.	(McKinsey&Company, 2017)	0
Relevance	Modern technology and tools assist in clinical trial and drug discovery processes and might enhance the R&D process.		
Intervention considerations	Research on tools and technology available		
	Reliability of current tools and technology used in clinical trials		
	Break-even of getting new equipment, tools and technologies		
	Cost-benefit analysis of getting new equipment, tools and technologies		

Non-incentive-based interventions (6 of 8): PPP results

30. Struggling to prove efficacy		*For further reference*	
Meaning	The ability of pharmaceutical innovators to prove that the drug fulfils the intended result.	(PhRMA, 2016)	1
Relevance	Drugs should target the intended disease and be effective in treating the patients.	(Hay et al., 2014)	
Intervention considerations	Clinical trial information quality	(von Ranke, Fierro and Antunes, 2016) (Ho, Zarrinpar and Chow, 2016)	
	Clinical trial design		
	Tools, technology and equipment used for clinical trials		
	Adhere to international regulation standards		

31. Legal and ethical regulations for clinical trials too difficult		*For further reference*	
Meaning	Extensive laws and regulations exist for the development of drugs.	(Califf and Sugarman, 2015), (Salas, 2017), (Tsukamoto et al., 2016), (Cheng and Xie, 2017), (Tsourounis et al., 2015)	1
Relevance	A lot of difficulty is experienced in bridging legal and ethical barriers in drug R&D.		
Intervention considerations	Collaborate with bigger pharmaceutical organizations		
	Availability of third parties to adhere to regulations and laws		
	Complete annual audits		
	Ensure data transparency, accuracy and accountability		

32. Safety assessments standards		*For further reference*	
Meaning	Safety assessment standards should be adhered to, to quantify and measure risks involved in the drug being developed.	(Singh and Loke, 2012)	1
Relevance	Drugs that does not adhere to safety standards might pose a health risk to patients.	(PhRMA, 2016)	
Intervention considerations	Health authority standards and regulations	(Hay et al., 2014)	
	Clinical trial practices and designs		
	Randomized controlled trials		
	Global health governance		

33. Adaptive clinical trials occurrence		*For further reference*	
Meaning	Clinical trials that involves observing participant outcomes and adjusting drug parameters in accordance.	(Gokhale and Gokhale, 2016)	1
Relevance	Without adaptive clinical trials, important observations cannot be made; and drug safety not improved to the extent necessary.	(Baylor College of Medicine, 2009)	
Intervention considerations	Amount of participants part of adaptive clinical trials	(Hay et al., 2014)	
	Procedures of adaptive clinical trials		
	Data capturing		
	Health authority standards and regulations		

34. Recruitment and retention of participants		*For further reference*	
Meaning	Clinical trials require participants to perform drug safety and adequacy tests.	(Kurt et al., 2017) (Hammer, Eckardt and Barton-Burke, 2016) (Jennings et al., 2015), (Thacker, T., Wegele, A.R., Pirio Richardson, 2016)	1
Relevance	Effort should be done to recruit the right number of participants for clinical trial tests		
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Ensure safety of participants		
	Build trustworthy relationships with participants		

35. Racial differences in participation in clinical trial		*For further reference*	
Meaning	A variety of ethnicity groups, races and both genders' response on the drugs needs to be tested	(Kurt, Semler, et al., 2017)	1
Relevance	Given that drugs can be used by anyone, tests should be performed on various people to test for any difference in reactions or dosage requirements.	(Baylor College of Medicine, 2009)	
Intervention considerations	Marketing strategies		
	Incentivize participants		
	Build trustworthy relationships with participants		

Non-incentive-based interventions (7 of 8): PPP results

36. Relationships between innovators and participants		*For further reference*	
Meaning	Innovators should strive to have a professional, and trustworthy relationship with participants	(Kurt, Semler, et al., 2017) (Tsukamoto et al., 2016) (Califf and Sugarman, 2015) (Salas, 2017)	1
Relevance	If the relationship between innovators and participants is not appropriate; then participants might not agree to complete more trials.		
Intervention considerations	Build trust with participants, by following standard clinical trial procedures		
	Adhere to safety and regulation standards		
	Monitor participants closely		
	Capture data		

37. Physician participation		*For further reference*	
Meaning	Qualified medical practitioners should be present in clinical trial tests on humans.	(Baylor College of Medicine, 2009)	1
Relevance	Qualified physicians will be able to monitor the health and wellbeing of patients in clinical trials, as well as respond if ADR occur.		
Intervention considerations	Incentivize physicians to participate		
	Provide proper training to physicians		
	Adhere to correct clinical trial procedures		

38. Skilled workforce		*For further reference*	
Meaning	Workforce, part of drug R&D process should be skilled to adequately perform tasks.	(Institute of Medicine & Committee on Quality of Health Care in America, 2001), International Labour Office, 2010)	1
Relevance	If workforce is not skilled, preventable problems in the R&D process might arise.		
Intervention considerations	Train workforce (workshops, training programs)		
	Encourage mentorship in work environment		
	Ethical conduct		

39. Existence of manufacturing plants		*For further reference*	
Meaning	Manufacturing plants exists to perform adequate drug manufacturing.	(World Health Organization, 2016), (WHO, 2011)	1
Relevance	If no manufacturing plants exists, then producing drugs on large scale might be difficult.		
Intervention considerations	Encourage/ Incentivize SME drug manufacturers		
	Consider international manufacturing organizations		

40. Drug manufacturing adheres to regulatory requirements		*For further reference*	
Meaning	Drug manufacturing should adhere to regulatory requirements to ensure safety.	(Koeberle and Schiemenz, 2017) (Burnham et al., 2015), (Wechsler, 2015)	0
Relevance	Unregulated manufacturing practices poses potential risks to the drugs.		
Intervention considerations	Audit Manufacturing organizations		
	Global manufacturing practices		
	Comply to cGMPs (Current good manufacturing practices)		
	Unannounced visits by regulatory authorities to manufacturing facilities		

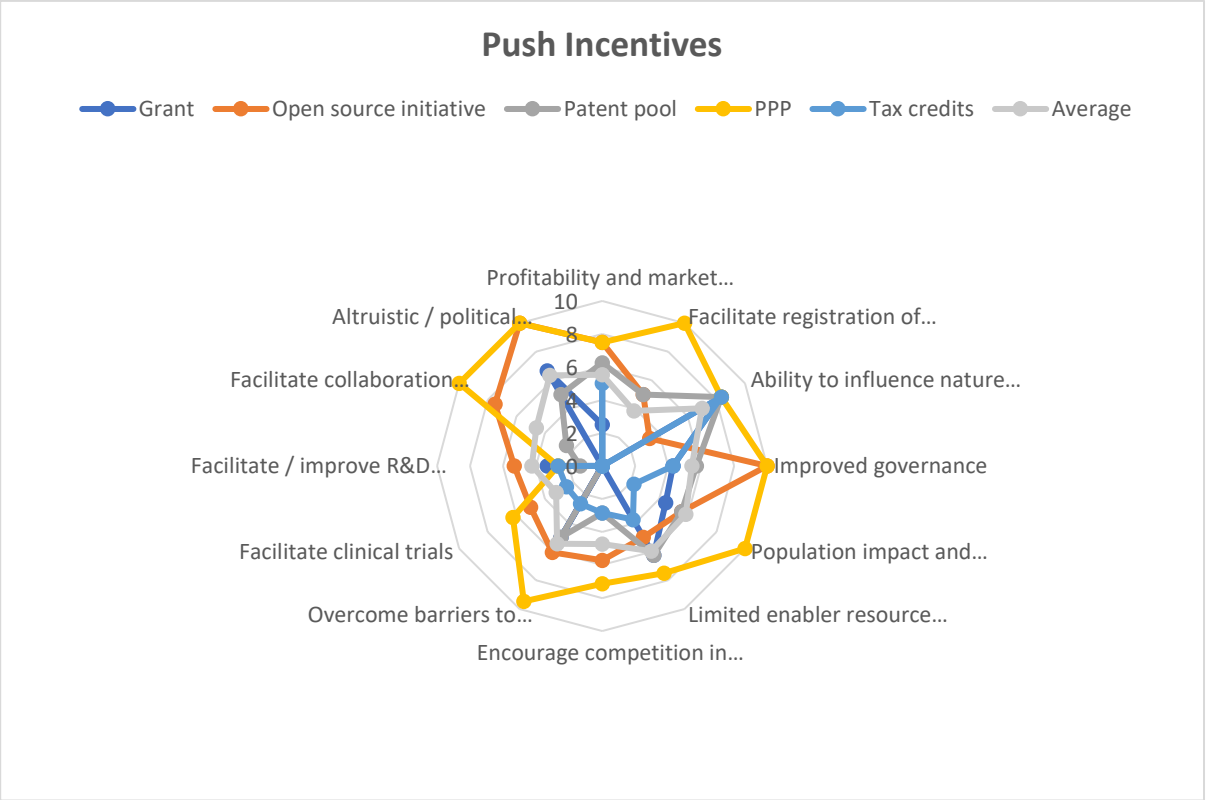
41. Appropriate technology used for the manufacturing of drugs		*For further reference*	
Meaning	A lot of technologies are available to manufacture drugs, some are advised by regulatory agencies.	(World Health Organization, 2011)	1
Relevance	Appropriate technology might improve the safety, productivity and quality of the drugs being manufactured.		
Intervention considerations	Comply to cGMPs		
	Research technology that is available		
	Complete cost-benefit analysis to ensure new technologies are strategic choices		
	Ensure compliance of all regulations and policies		

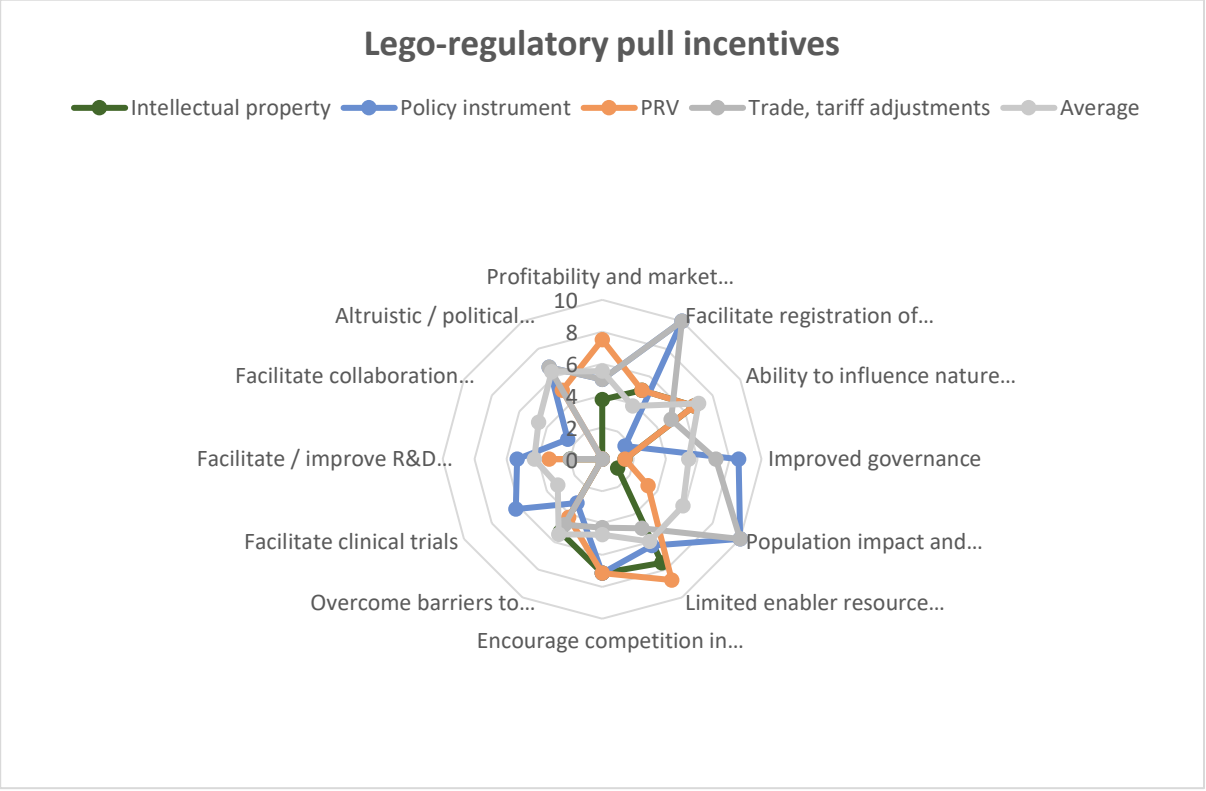
42. Health data generation		*For further reference*	
Meaning	To generate information on the drug R&D process that are of high quality, reliable and thorough.	(Raheja, Dubey and Chawda, 2017) (Fatt and Ramadas, 2018)	0
Relevance	High quality R&D information is required for regulatory agencies and can be used as reference for proving safety and efficacy.		
Intervention considerations	Use adequate health information system		
	Ensure all data is captured accurately		
	Ensure backups of health data		
	Ensure safety of, and the network security of the stored health data		

Non-incentive-based interventions (8 of 8): PPP results

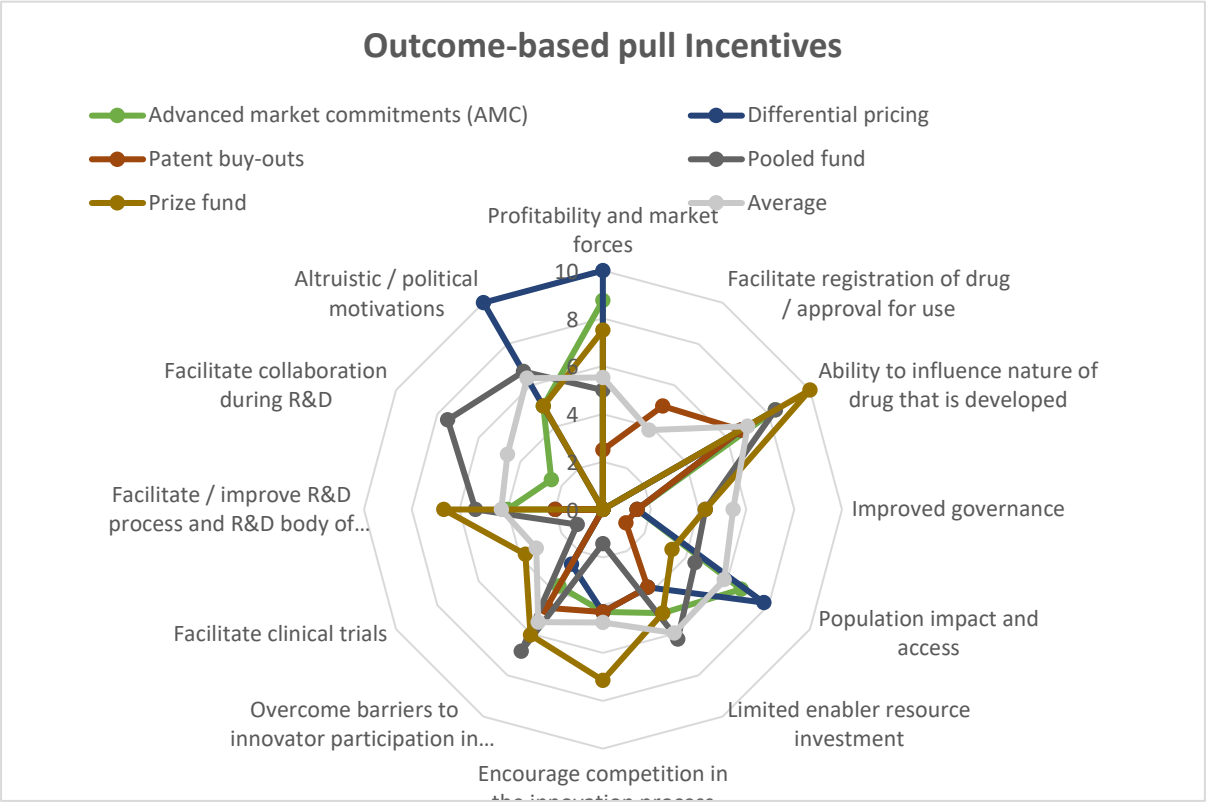
43. Communication and use of public health data		*For further reference*	
Meaning	Analysing, synthesising and validating health data	(WHO, 2010a)	1
Relevance	By evaluating health data, important measures can be implemented to satisfy growing needs, or gaps within the health system.		
Intervention considerations	Establish national sets of indicators with targets and accurate reporting which will inform health sector reviews and improve the planning of future interventions		
	Assess the health systems performance, to determine the success of current interventions		
	Adjust health system operation, based on accurate data.		
	Communicate health statistics to the public for awareness.		

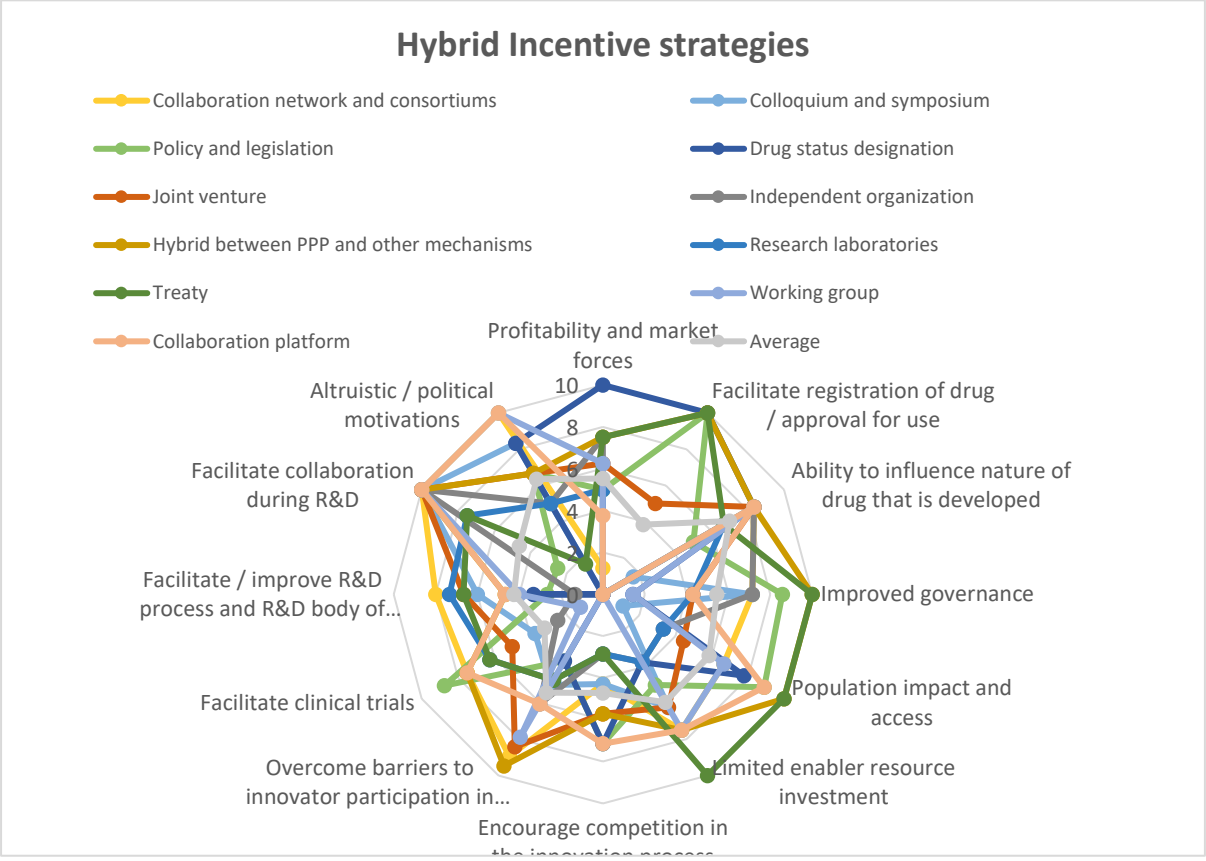
Supplementary material 1 (1 of 2): PPP results



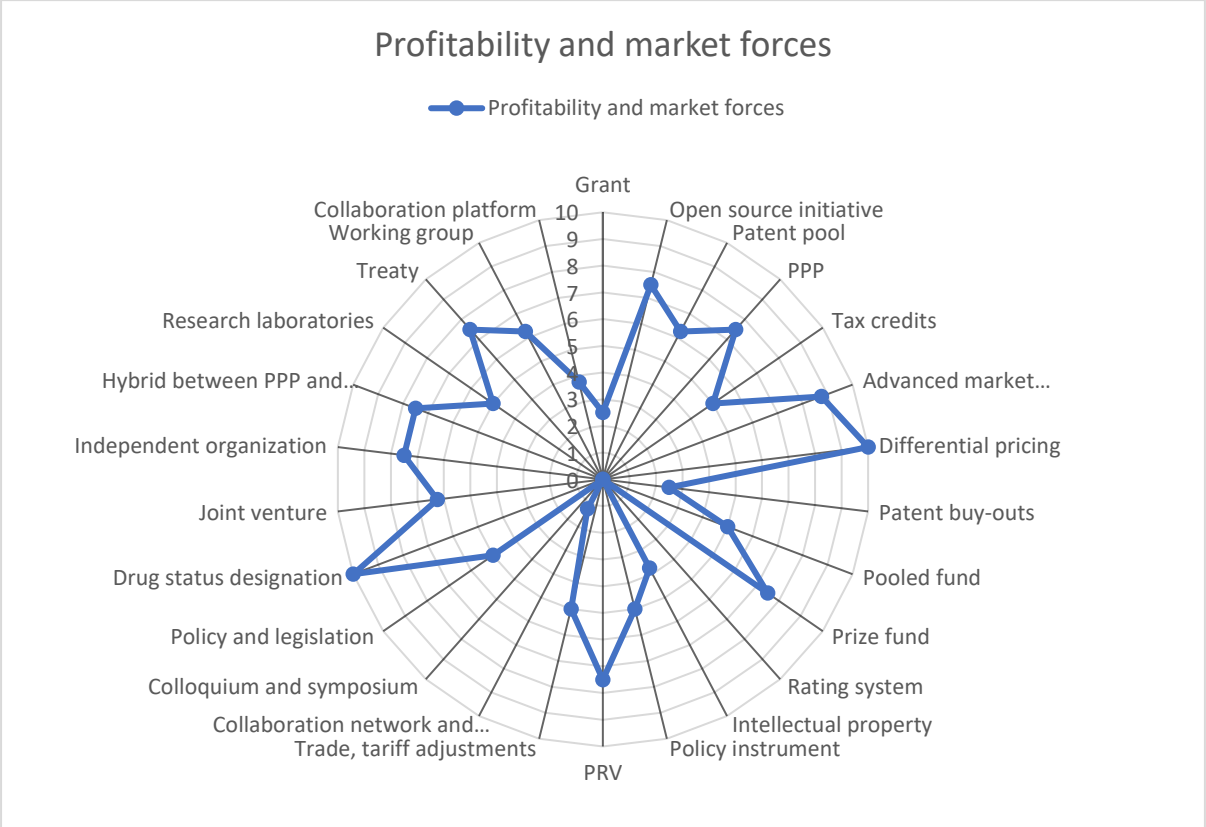


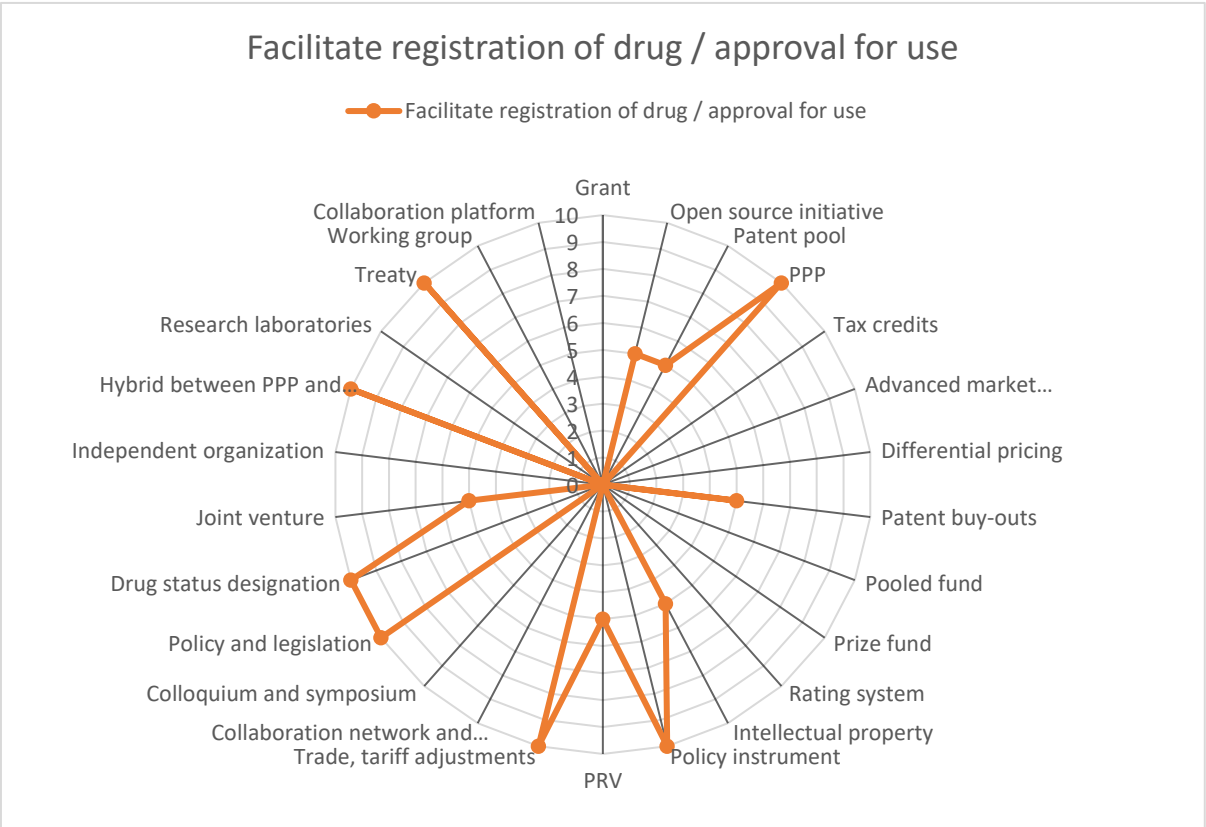
Supplementary material 1 (2 of 2): PPP results





Supplementary material 2 (1 of 6): PPP results





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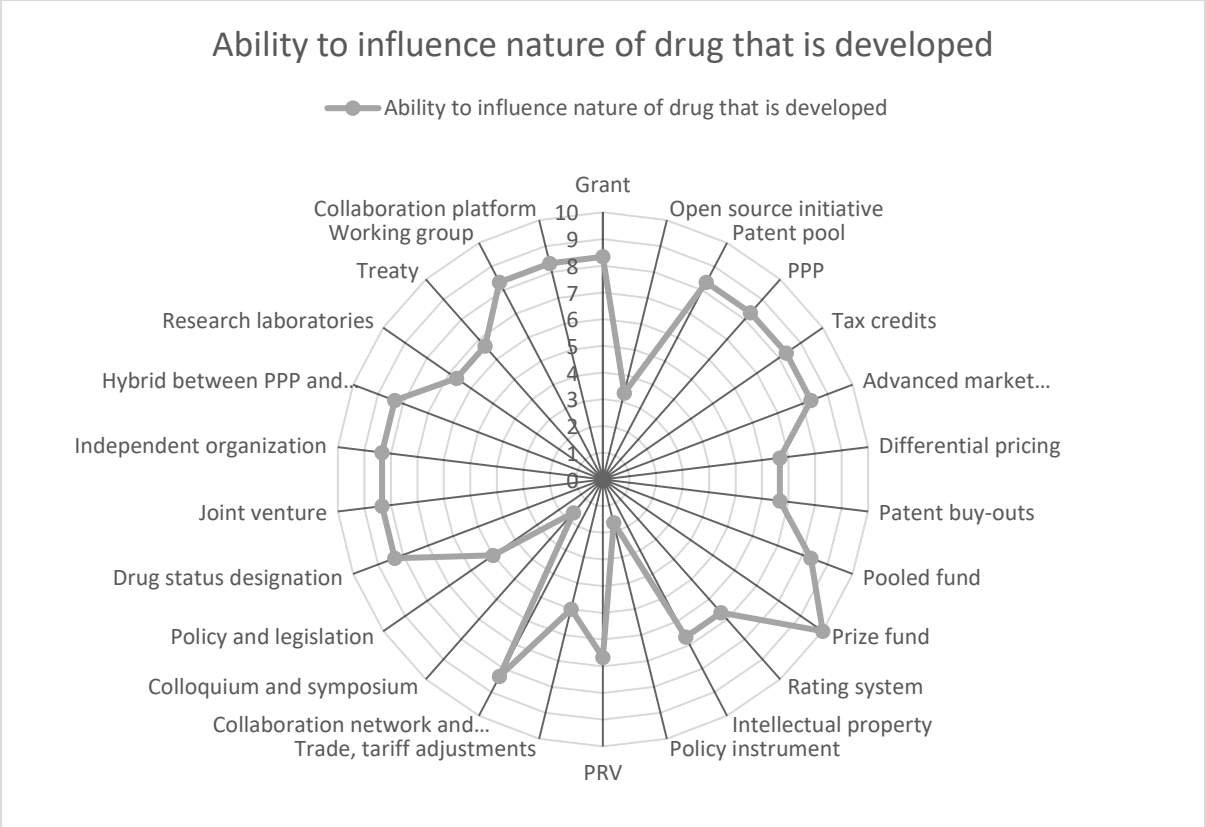

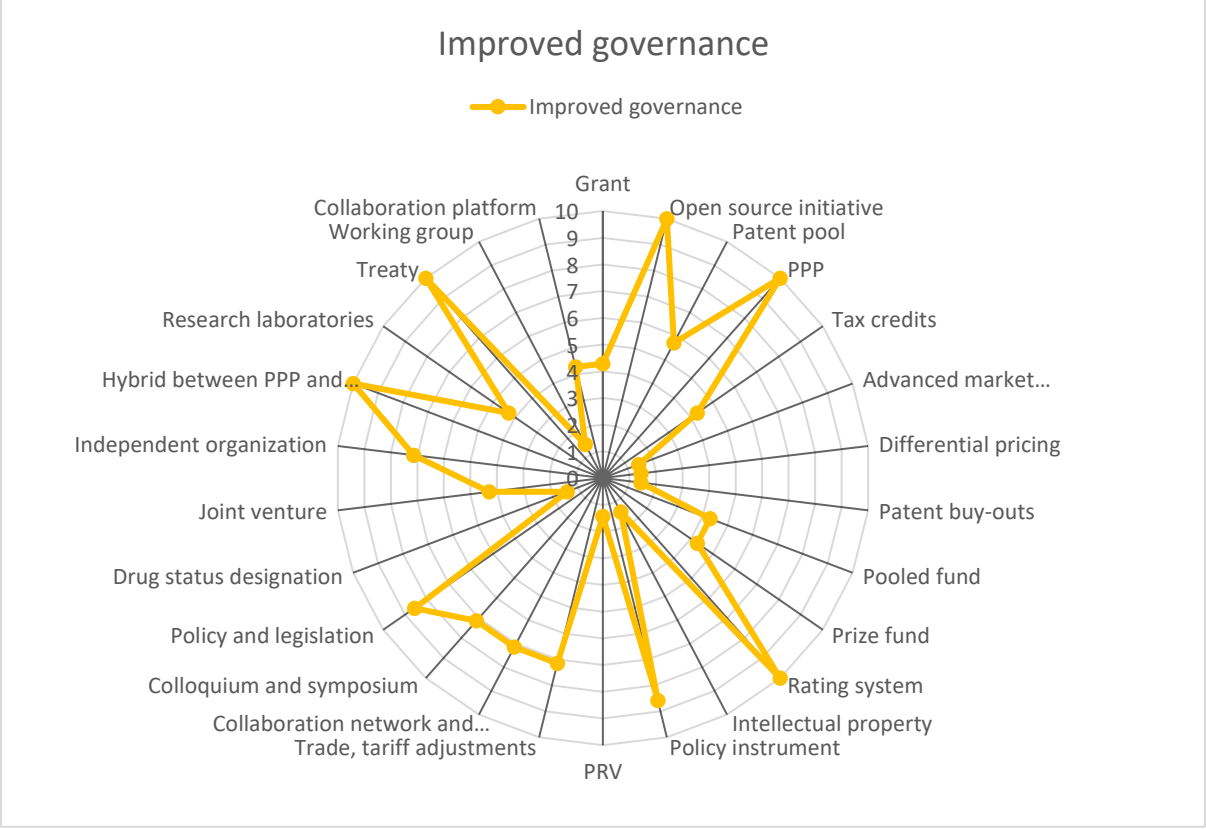

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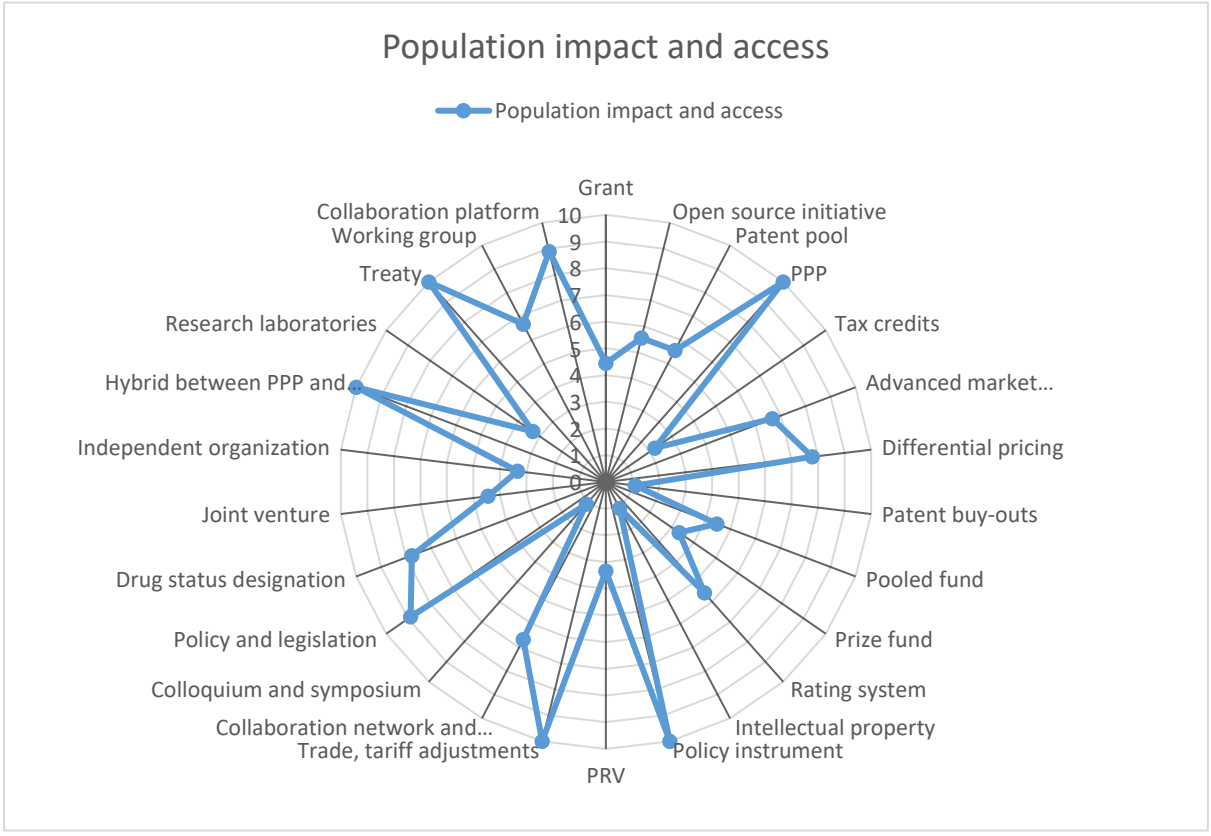

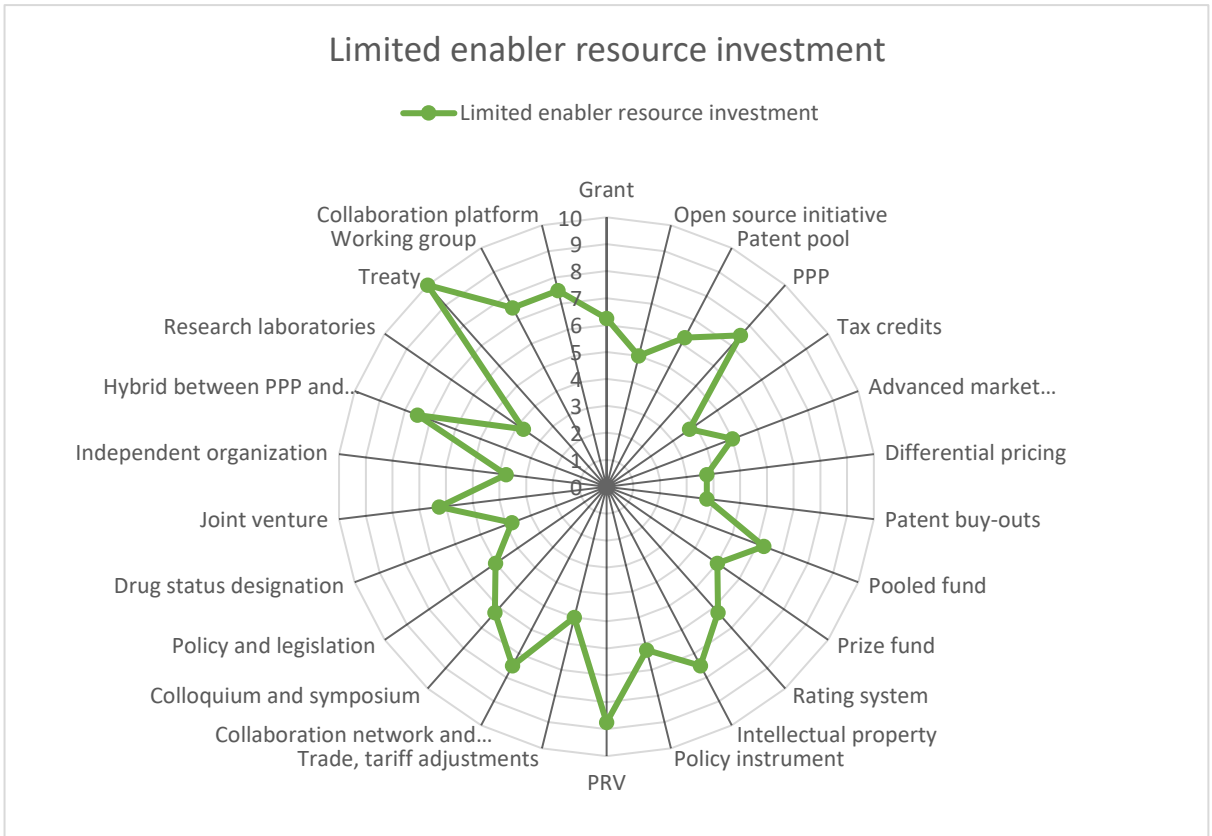

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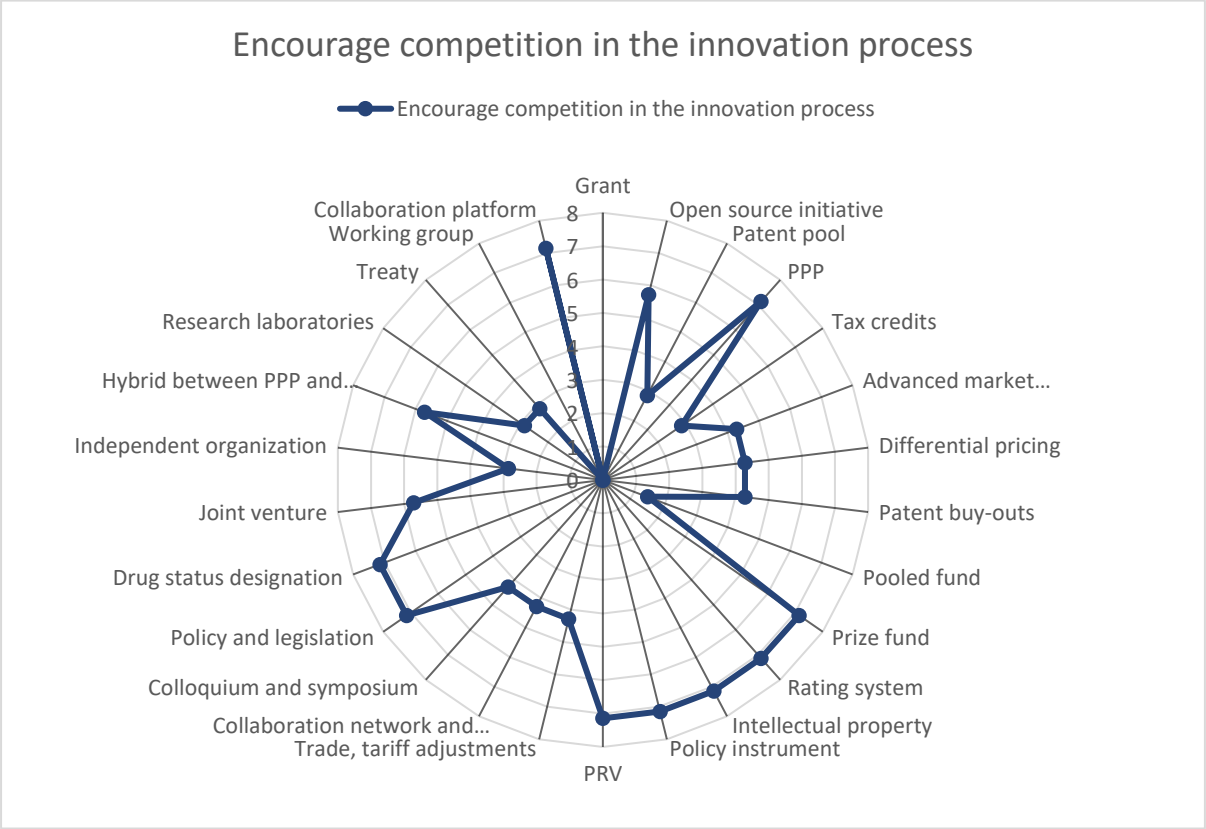

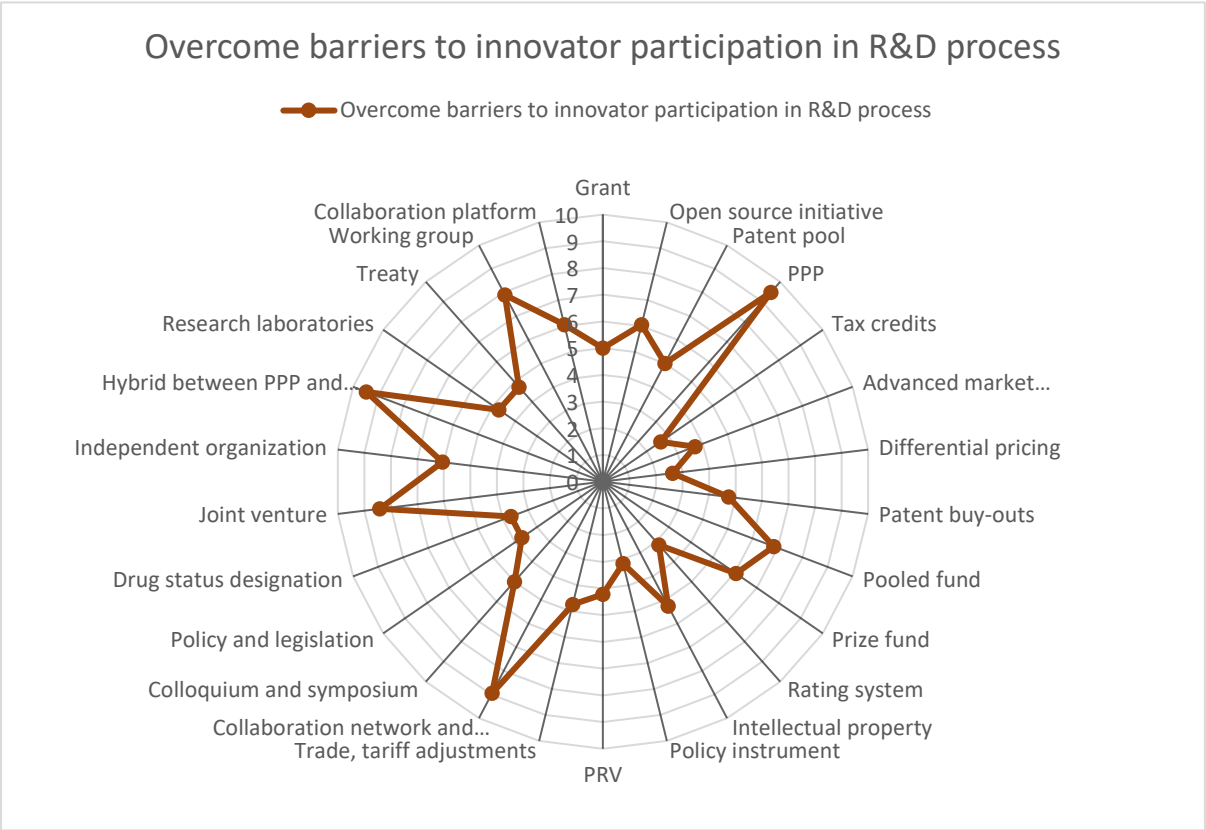

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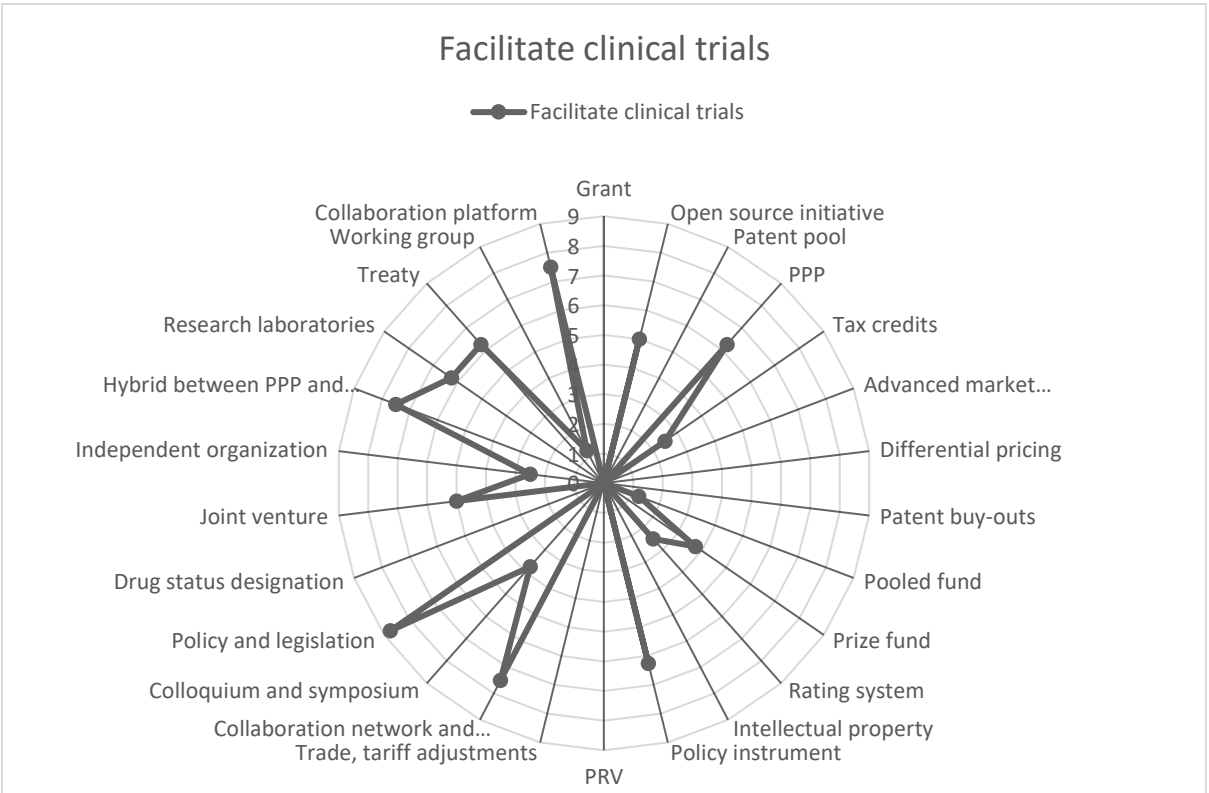

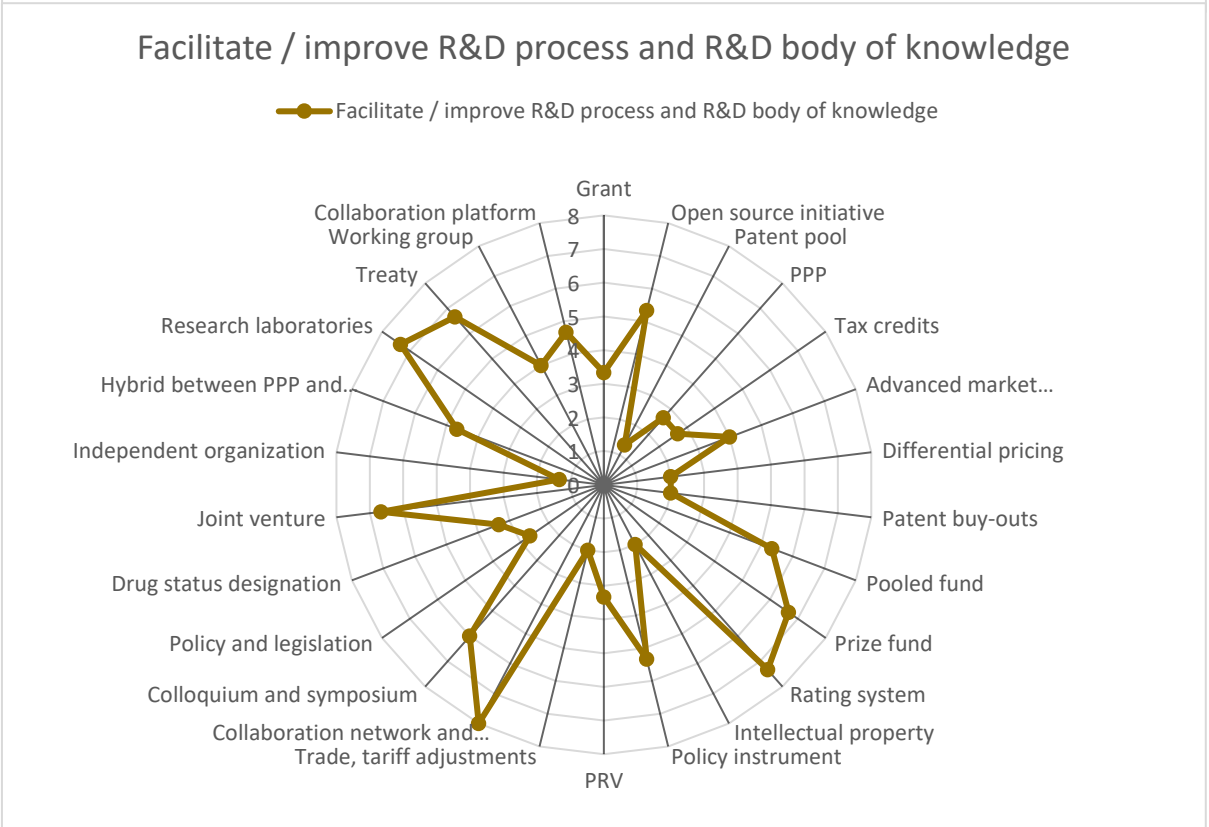

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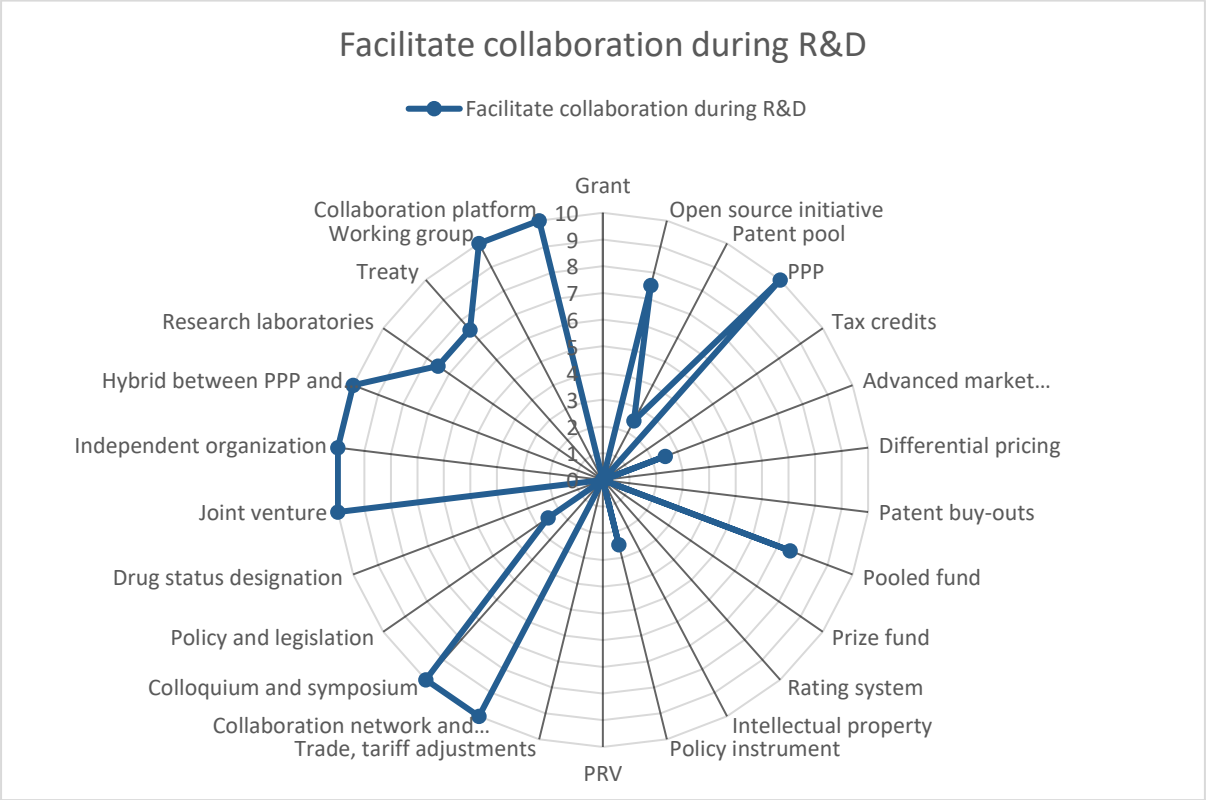

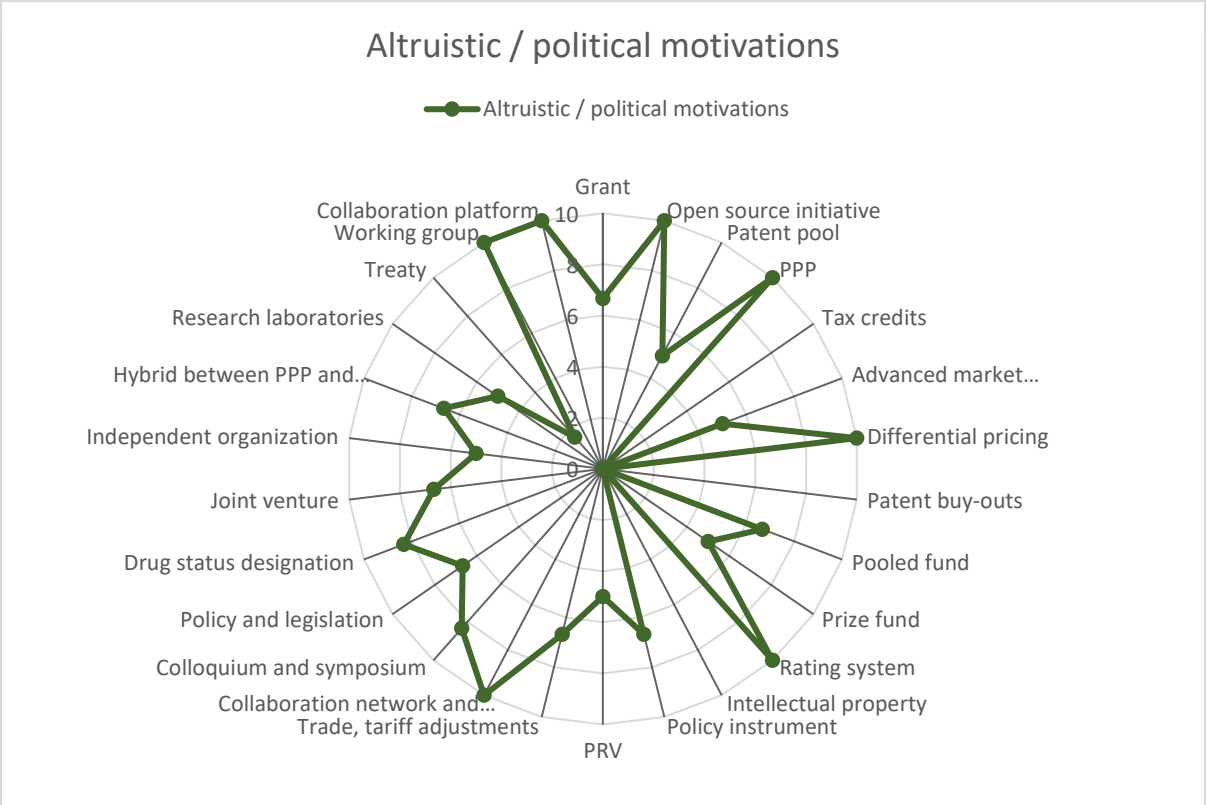

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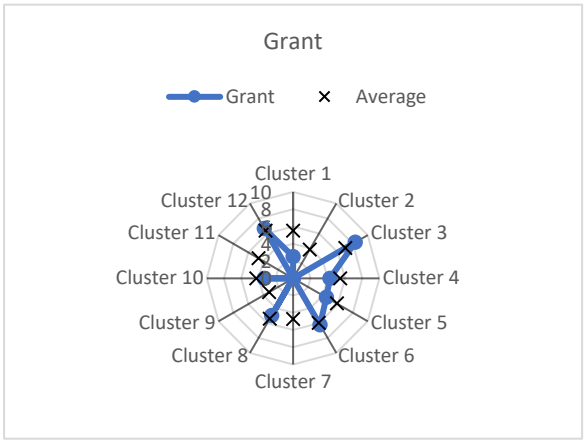
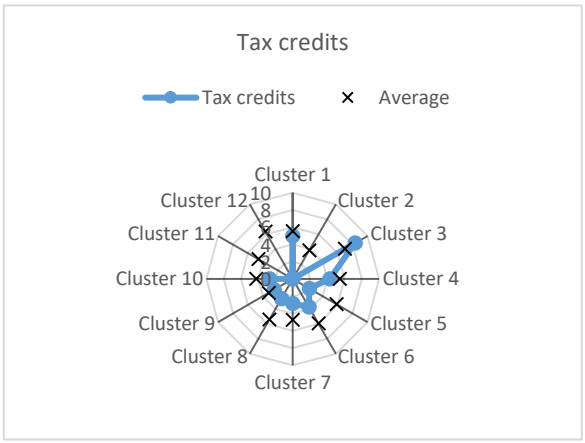
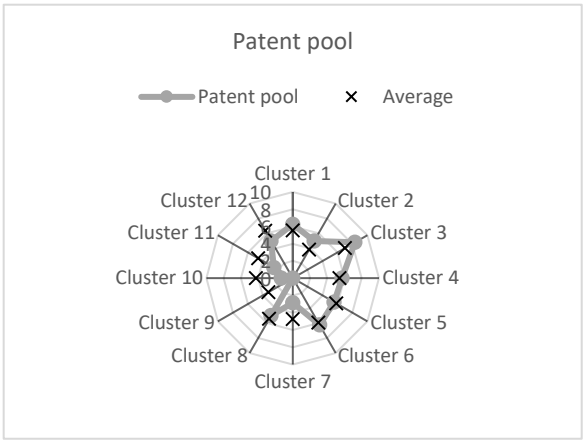
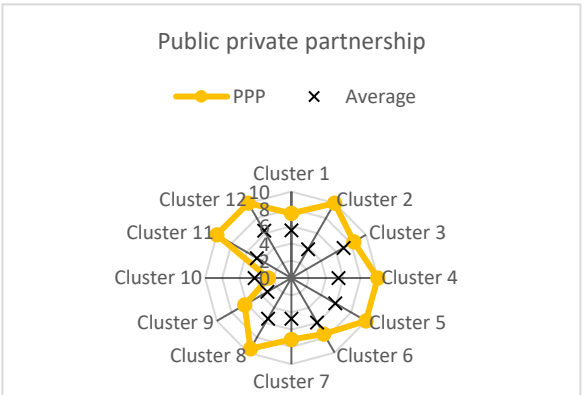
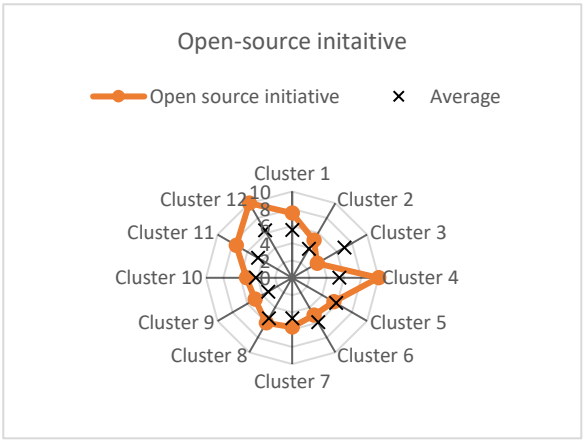
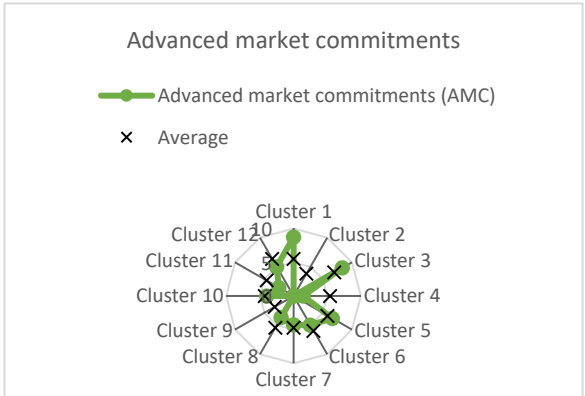


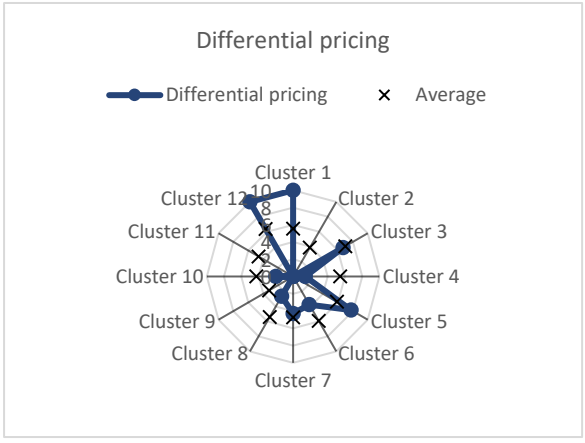


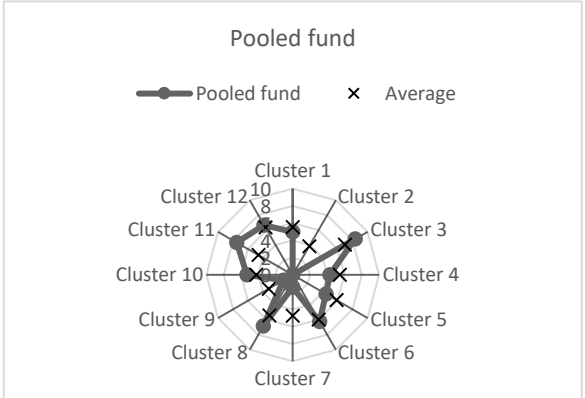




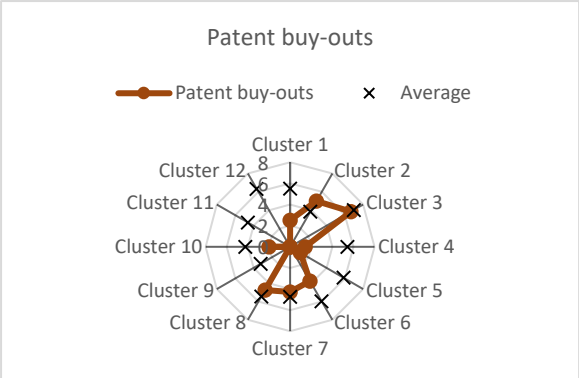


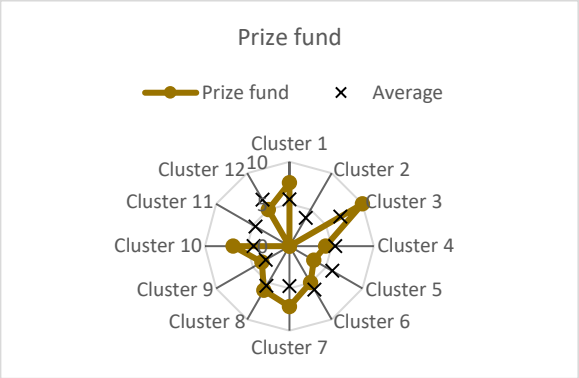


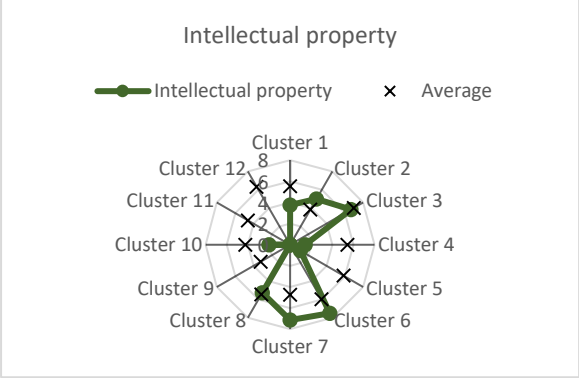


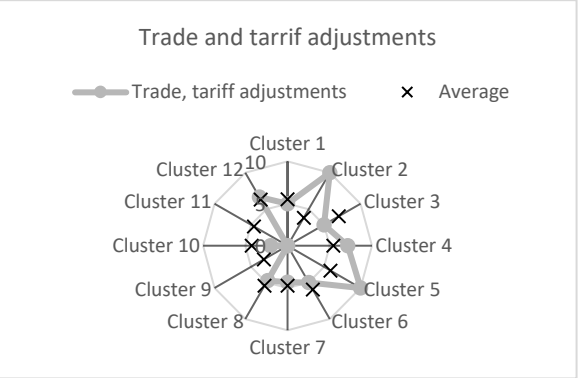


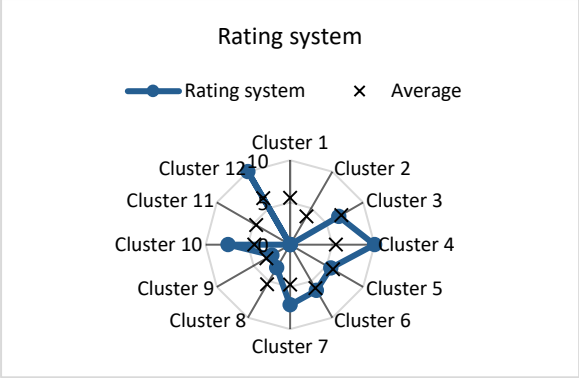
Supplementary material 3 (2 of 4): PPP results

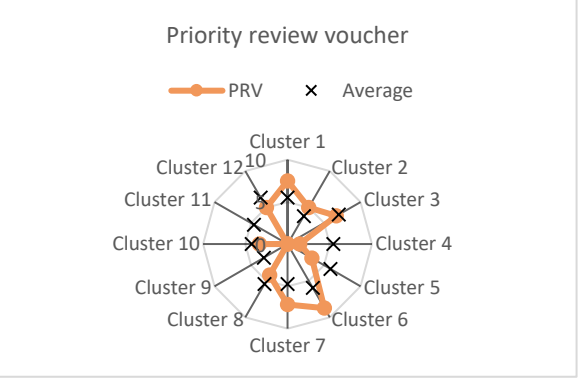


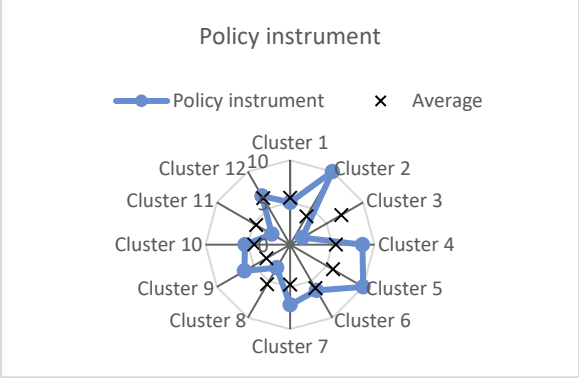


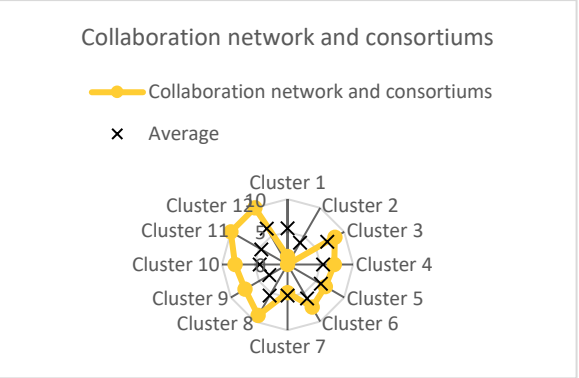




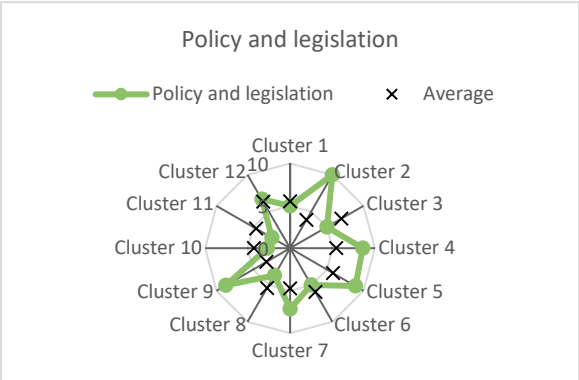


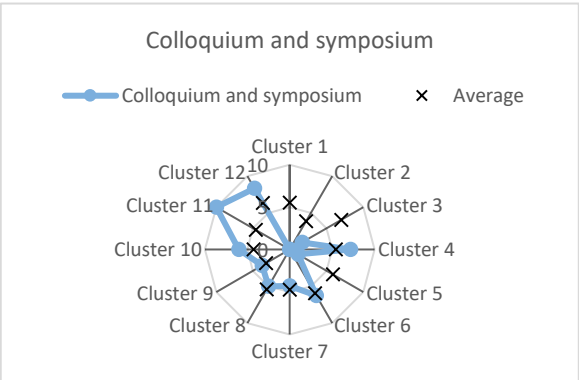


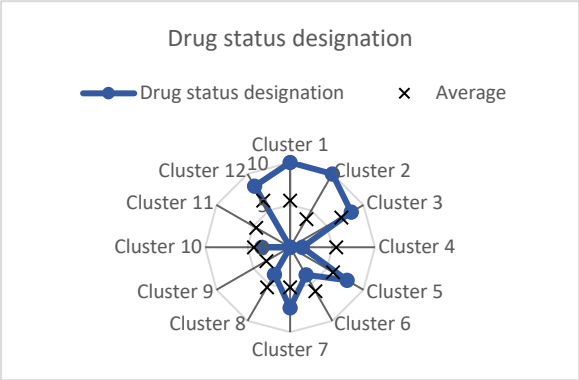


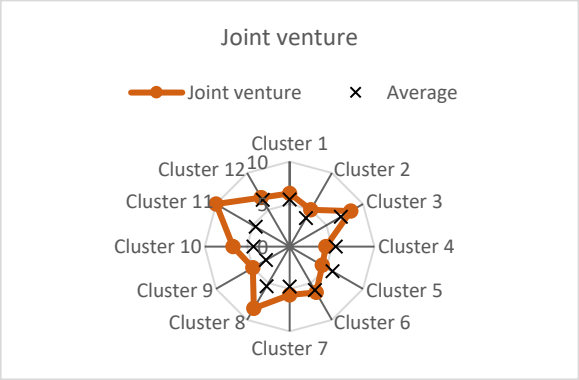


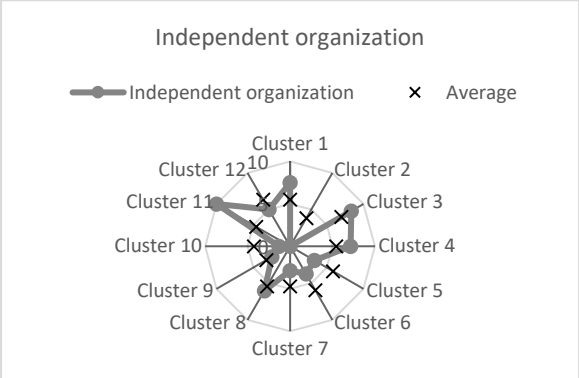
Supplementary material 3 (3 of 4): PPP results

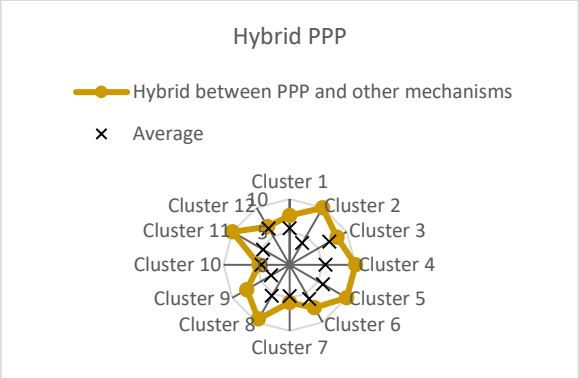


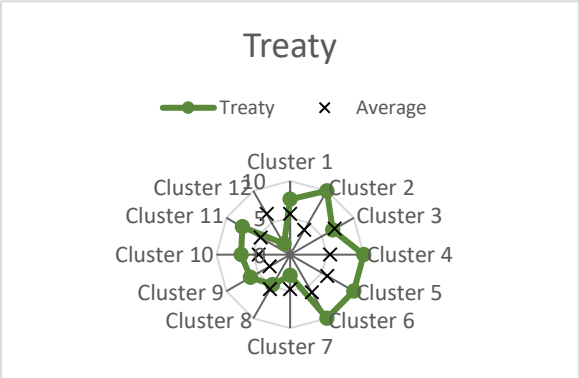


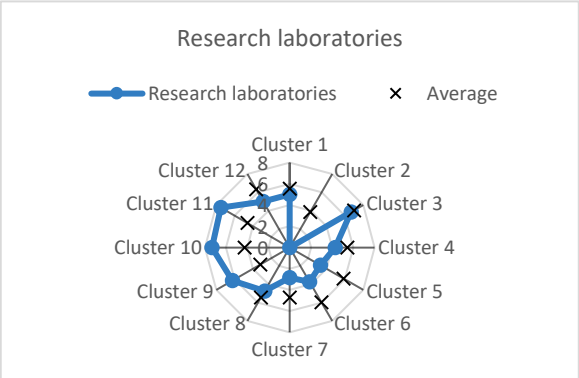




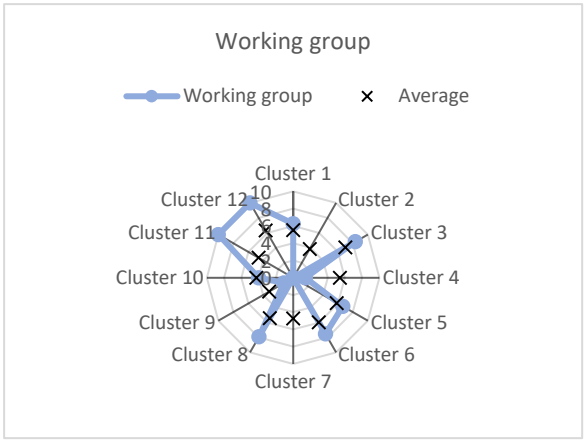


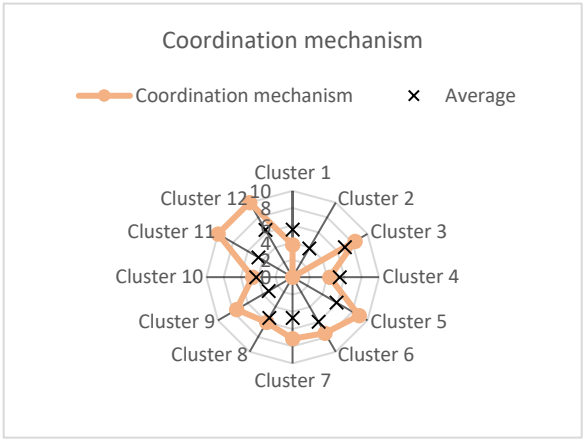






Supplementary material 3 (4 of 4): PPP results





Supplementary material 4 (1 of 2): PPP results

Incentive intervention reference number	Overall Heatmap: Fulfilment of clusters per incentive	Profitability and market forces	Facilitate registration of drug / approval for use	Ability to influence nature of drug that is developed	Improved governance	Population impact and access	Limited enabler resource investment	Encourage competition in the innovation process	Overcome barriers to innovator participation in R&D process	Facilitate clinical trials	Facilitate / improve R&D process and R&D body of knowledge	Facilitate collaboration during R&D	Altruistic / political motivations	Number upper-quartile scores	Feasibility of incentive based on enabler exclusion criteria
4	PPP													10	Feasible
22	Hybrid PPP													9	Infeasible
20	Joint venture													6	Infeasible
21	Independent organization													5	Feasible
16	Collaboration network and consortiums													10	Feasible
25	Working group													9	Feasible
17	Colloquium and symposium													6	Feasible
26	Collaboration platform													9	Feasible
1	Grant													3	Infeasible
23	Research laboratories													6	Feasible
9	Pooled fund													3	Infeasible
10	Prize fund													4	Infeasible
24	Treaty													7	Feasible
7	Differential pricing													7	Infeasible
8	Patent buy-outs													4	Infeasible
12	Intellectual property													5	Infeasible
19	Drug status designation													8	Infeasible
13	Policy instrument													7	Infeasible
11	Rating system													7	Infeasible
2	Open-source initiative													5	Feasible
15	Trade, tariff adjustments													8	Infeasible
18	Policy and legislation													7	Infeasible
3	Patent pool													5	Infeasible
14	PRV													6	Infeasible
5	Tax credits													3	Infeasible
6	Advanced market commitments													4	Infeasible

Supplementary material 4 (2 of 2): PPP results