Development of a Direct ADR Reporting Tool for Patients to Address Under-Reporting of ADRs to the National Pharmacovigilance Unit in South Africa

by

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DECLARATION

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ABSTRACT

High standards of public health can be achieved through efficient and safe utilisation of healthcare products and the continuous monitoring thereof. Pharmacovigilance (PV), defined as the science and activities relating to the monitoring of adverse reactions associated with all medicines, is however hampered by the global under-reporting of adverse drug reactions (ADRs) by healthcare professionals. Several countries have successfully incorporated direct patient reporting into their PV system as a means of addressing the under-reporting challenge. Innovative ADR reporting tools have the potential to enable PV systems through increasing signal detection, assessment, understanding and prevention of adverse effects. Whilst the proof-of-concept of such tools have been promising, the use thereof by patients and consumers with access to the South African healthcare system has not been tested.
The aim of the current study is to develop an ADR reporting tool for use by consumers in reporting ADRs to address under-reporting in South Africa.

The design of the current study and the development of a patient/consumer ADR reporting tool precedes the adoption and implementation of the Med Safety Mobile Application as an online Adverse Event Following Immunisation (AEFI) reporting tool by the South African Health Products Regulatory Authority (SAHPRA) in 2021. If it had not been for the outbreak of the COVID-19 pandemic in 2020 and the immediate need for AEFI reporting tools following the global roll-out of immunisation programmes shortly thereafter by the World Health Organisation (WHO), National Health Departments and Regulators around the globe, this study would have been one of the first to have investigated direct consumer reporting on a larger scale in South Africa.

The standard South African Health Products Regulatory Authority (SAHPRA) Yellow Form was used as a frame reference for designing an online-based consumer ADR reporting tool, which is compatible with a mobile application and a paper-based version. Validation and reliability testing of the tool was carried out in two stages: A content validation by healthcare professionals determined whether the content of the tool is appropriate and relevant for the designed purpose of ADR reporting by consumers/patients and face validation by consumers evaluated the usability of the

tool in terms of readability, how clear/easy to follow the instructions and/or provide the required information.

The developed and tested ADR reporting tool consists of five main elements: consumer's details, consumer's medical history, ADR details, suspected medicine(s), and reporter details. All items included received a majority inter-agreement rating of over 80% each as relevant to include in the tool, except for the reporter initials, the batch number and expiry date of the suspected medicine. Using the McNemar Chi-square test, the test and re-test responses of face validation showed no significant difference in responses across all items in the ADR reporting tool.

Feasibility testing to assess the ease with which the ADR reporting tool could be used, how practical it is to access the tool and submit the report through it was carried out over a period of 1 year and 3 months. Participants were recruited from twelve healthcare centres and through social media, and they have completed and submitted ADR reports via online tool. A total of 348 reports were received with female consumers contributing 58.3% most of which were from those aged 31- 40 years (22.5%). These were associated with birth control medicines, the fourth highest suspected medicines reported (13.5%) with all reported ADRs listed as expected in the respective package inserts.
Hydrochlorothiazide (52.17%) and enalapril (27.54%) were the most frequently suspected medicines within the antihypertensive class. All suspected medicines had well-established safety profiles, except for a lamivudine, tenofovir disoproxil fumarate and dolutegravir fixed-dose combination, nine reports related to investigational medicinal products and twenty-three suspected medicines which could not be identified.
Expectedness of reported ADRs was confirmed in 73.9% of the suspected medicines, with dose reduction in 3.4%, treatment changed in 1.8% and treatment stopped in 6.9% of the consumers.

A total of 5.3% of suspected medicines could not be verified as the names could not be recognised. Only two reports were received from healthcare professionals with the completeness and terminology used being similar to those of non-healthcare professionals.

Reported terms produced 63.4% ‘exact matches’ from the MedDRA search, 8.7% were from ‘contains search’ results and terms used from ‘lexicant variant’ results amounted to 2.5%. Over 25% of the reported terms could not be found in the MedDRA database and therefore an alternative term was used.

The high response rate in this study as well as the manner in which the consumers completed the ADR reports demonstrates their understanding and feasibility of using the tool to consistently submit ADR reports whose information would enable causality assessment over time, which will also boost the local PV system. However, the use of English only in the study limited participation of consumers who cannot use and/or understand the language. There was also no measure on the readability index conducted and causality assessment was not carried out.

With consumer reporting being relatively new in South Africa, this study can be used as a basis to assess and improve on the newly introduced SAHPRA ADR reporting tools. Further studies are needed to assess the interest, understanding and factors influencing consumers to report ADRs.

OPSOMMING

‘n Publieke gesondheidstelsel van hoë standaard is haalbaar deur die effektiewe en veilige gebruik van gesondheidsprodukte, asook die voortdurende monitering daarvan. Farmakowaaksaamheid (FW), wat gedefinieer word as die wetenskap van aktiwiteite wat veband hou met die monitering van nadelige medisyne reaksies (NMRs), geassosieer met alle medisyne, word egter belemmer deur die wêreldwye tekort aan verslagdoening van dié reaksies, deur gesondheidsdeskundiges. Baie lande het reeds, as ‘n poging tot die aanspreking van die uitdagings ten opsigte van ‘n tekort aan verslagdoening, die direkte rapportering van NMRs deur pasiënte tot hul FW sisteme, in plek gestel. Innoverende hulpmiddelle en toepassings vir NMR verslagdoening het die potensiaal om FW sisteme te versterk deur verhoogde sein waarneming, assessering, en kennis en voorkoming van nadelige medisyne reaksies. Terwyl die bewys-van-konsep van hierdie hulpmiddelle en toepassings belowend blyk te wees, is die gebruik daarvan deur pasiënte en verbruikers met toegang tot die Suid-Afrikaanse gesondheidstelsel, nog nie getoets nie.

Die doel van hierdie studie is om ‘n NMR rapporterings-toepassing te ontwikkel wat deur verbruikers ingespan kan word om die tekort aan verslagdoening in Suid-Afrika aan te spreek.

Die ontwerp van die huidige studie en die ontwikkeling van ‘n pasiënt/verbruiker NMR-aanmeldingshulpmiddel gaan die aanvaarding en implementering van die Med Safety Mobile Application vooras as ‘n aanlyn Adverse Event Following Immunisation (AEFI)-verslagdoeningsinstrument deur die Suid-Afrikaanse Gesondheidsprodukte Regulatoriese Agentskap (SAGPRA) in 2021. As dit nie was vir die uitbreek van die COVID-19 pandemie in 2020 en die onmiddellike behoefte aan AEFI-verslagdoeningsinstrumente na die wêreldwye uitrol van immuniseringsprogramme kort daarna dear die Wêreldgesondheidorganisasie (WGO), Nasionale Gesondheid Departemente en Reguleerders regoor die wereld, sou hierdie studie een van die eerstes gewees het wat direkte verbruikerverslaggewing op ‘n groter skaal in Suid-Afrika ondersoek het.

Die standaard *Geel Vorm* van die Suid-Afrikaanse Gesondheidsprodukte Regulatoriese Agentskap (SAGPRA) is gebruik as ’n raamverwysing vir die ontwerp van ’n aanlyn-gebasseerde rapporterings-toepassing vir verbruikers, wat verenigbaar is met ’n selfoontoep en ’n papiergebasseerde weergawe van die toepassing.

Validasie- en betroubaarheidstoetsing van die toepassing is in twee fases uitgevoer: ‘n inhoudvalidasie deur gesondheidsdeskundiges het bepaal of die inhoud van die toepassing toepaslik en relevant is vir die ontwerpte doel van NMR verslagdoening deur verbruikers/pasiënte; aangesigsvalidasie deur verbruikers het die bruikbaarheid van die toepassing, ten opsigte van leesbaarheid en die duidelikheid en verstaanbaarheid van die instruksies en/of die weergee van die verwagte inligting, geëvalueer.
Die ontwikkelde en getoetsde toepassing vir NMR aanmelding bestaan uit vyf hoofelemente: verbruiker se inligting, verbruiker se mediese geskiedenis, NMR inligting, vermoedelike verwante medisyne(s) en die aanmelder se inligting. Alle items wat ingesluit is, het elk ‘n meerderheids-inter-ooreenkoms-gradeing van meer as 80% ontvang, as relevant tot die insluiting daarvan in die toepassing, behalwe vir die aanmelder se voorletters, en die lotnommer en vervaldatum van die verdagte medisyne. Deur die McNemar Chi-square toets te gebruik, het die toets en hertoets response van die aangesigsvalidasie geen betekenisvolle verskil in die response oor alle items heen in die NMR toepassing gewys nie.

Die lewensvatbaarheidstoetsing om die gemak waarmee die rapporterings-toepassing gebruik kan word, hoe prakties dit is om toegang daartoe te verkry en om ‘n verslag daarop in te dien, is oor ‘n tydperk van ‘n jaar en 3 maande uitgevoer. Deelnemers wat van twaalf gesondheidsentra en deur sosiale media gewerf is, het NMR verslae voltooi en via die aanlyn toepassing ingedien. ‘n Totaal van 348 verslae is ontvang met vroulike verbruikers wat 58.3% van die verslae ingedien het, die meeste van hulle was tussen 31- 40 jaar oud (22.5%). Hierdie verslae is geassosieer met geboortebeperkingsmiddels, die vierde hoogste verdagte medisyne wat gerapporteer is (13.5%), met al die gerapporteerde NMRs in die produkte se onderskeie voubiljette, gelys as verwagte newe-effekte. Hidrochloriedtiasied (52.17%) en enalapriel (27.54%) was die mees gereelde verdagte medisynes binne die hipertensiewe-middelklas, wat aangemeld is. Alle verdagte medisynes het goed gevestigde

veiligheidsprofiele gehad, behalwe lamivudine, tenofovir disoproxil en dolutegravir vaste-dosis kombinasie, nege verslae wat geassosieer was met medisinale produkte wat nog ondersoek word en drie-en-twintig verdagte medisynes wat nie geidentifiseer kon word nie.

Verwagtheid van aangemelde NMRs is bevestig in 73.9% van die verdagte medisynes, met ‘n dosisvermindering in 3.4%, verandering in behandeling (1.8%) of staking van behandeling (6.9%).

‘n Totaal van 5.3% van verdagte medisynes kon nie geverifieer word nie, aangesien die name daarvan nie herken kon word nie. Slegs twee verslae is van gesondheidsdeskundiges ontvang met inligting, soortgelyk aan dit wat deur nie-gesondheidsdeskundiges verskaf is.

Van die aangemelde NMR-terme het 63.4% presiese ooreenkomste met die soekterme in MedDRA getoon, 8.7% het soekterme bevat en 2.5% was van “leksikante variante”. Meer as 25% van die aangemelde terme kon nie in die MedDRA databasis opgespoor word nie. ’n Alternatiewe term is in sulke gevalle gebruik.

Die hoë responstempo in hierdie studie asook die manier waarop die verbruikers die NMR verslae voltooi het, demonstreer hulle begrip ten opsigte van die gebruik van die toepassing, asook die lewensvatbaarheid van die toepassing ten einde dit gereeld te gebruik om NMR verslae in te dien. Dit sal oor tyd oorsaaklikheidsbepaling toelaat en ook die plaaslik PV sisteem verbeter.

Met Engels egter as die enigste voertaal in die studie, was die deelname van verbruikers wat nie Engels magtig is nie, beperk. Daar is ook geen maatstaf op die leesbaarheidsindeks uitgevoer nie en oorsaaklikheidsbepaling is nie uitgevoer nie. Met verslagdoening deur verbruikers as ‘n betreklike nuwe metode in Suid-Afrika, kan hierdie studie aangewend word as ‘n platform om die Suid-Afrikaanse Gesondheidsprodukte Regulatoriese Agentskap (SAGPRA) se nuwe bekendstelling NMR aanmeldings-toepassing te assesseer en te verbeter.

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TERMINOLOGY AND DEFINITIONS

Adverse Drug Reaction (ADR) / Adverse Reaction – A response to a medicine which is noxious and unintended, including lack of efficacy, and which occurs at doses normally used in man and which can also result from overdose, misuse, or abuse of a medicine[1]. An adverse drug reaction, contrary to an adverse event, is characterised by the occurrence of a suspected causal relationship between the drug and the reaction, as determined by the reporter or a reviewing healthcare professional / provider.

An adverse reaction includes clinical consequences associated with the use of a medicine outside the terms of the approved professional information / applicable product information or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse)[1].

Adverse Effect – An adverse effect is a negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all[2].

Adverse Event – Any untoward medical occurrence in a patient or clinical trial subject administered a medicine that may present during treatment with that medicine, but which does not necessarily have a causal relationship with this treatment[2,3].

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicine, whether considered related to the medicine, or not[1].

Causality Assessment – The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction[2].

Complementary Medicine – Any substance or mixture of substances that originates from plants, fungi, algae, seaweeds, lichens, minerals, animals, or other substance as determined by SAHPRA. Currently there are six major disciples identified: Homeopathy, Western Herbal Medicine, Traditional Chinese Medicine, Ayurveda, Unani Medicine (Unani-Tibb) and Aromatherapy[4].

Consumer – A consumer in relation to healthcare, means a person who uses or is a potential user of health services, as well as their families and caregivers; for example, a patient, lawyer, friend, relative or carer of patient[1].

For the purposes of this study, a consumer refers to any patient or individual who is prescribed, dispensed and/or utilises a medicine. This includes over-the-counter medicines, herbal products, medicinal supplements, vaccines, and traditional medicine.

Healthcare Professional / Provider – For the purposes of reporting suspected adverse reactions, "healthcare professionals / providers" are medical practitioners, pathologists, dentists, pharmacists, nurses, and other healthcare professionals including allied healthcare professionals[1].

Herbal substance / preparations – all or part of a plant, fungus, algae, seaweed or lichen or other substance

- that is obtained only by drying, crushing, distilling, freezing, fermentation, lyophilisation, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol, oil, or aqueous ethanol; or other permitted solvents; with or without the addition of heat;
- that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical dosage form;
- where part of a plant, fungus, seaweed or lichen refers to a structure such as a root, root bark, rhizome, mycelium, fruiting body, bulb, corm, tuber, stem, inner or outer bark, wood, meristematic tissue, shoot, bud, thallus, resin, oleoresin, gum, natural exudate or secretion, gall, leaf, frond, flower (or its parts), inflorescence, pollen fruit, seed, cone, spores or other whole plant part; and
- that does not include a pure chemical or isolated constituent unless the isolated herbal constituent is formulated with the herbal substance from which it arises and is demonstrated to have "essentially the same" action as the whole herbal substance; or a substance of mineral, animal or bacterial origin[4].

Med Safety App – is a free smartphone application for reporting of suspected ADRs/AEFIs to Regulatory Authorities. It was developed by the United Kingdom (UK) Medicines and Health Products Regulatory Agency (MHRA) as part of the Innovative Medicines Initiative WEB-Recognising Adverse Drug Reactions (WEB-RADR) project[2].

Over the Counter (OTC) – Medicines which are available for purchase without prescription[3].

Pharmacovigilance – The science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions (and adverse events following immunisations) to medicines / vaccines[1].

Programme for International Drug Monitoring (PIDM) – PIDM is a World Health Organisation (WHO) programme established in 1968, to ensure that evidence about harm to patients was collected from as many sources as possible. This would enable individual countries to be alerted to patterns of harm that were emerging across the world and which might not be evident from their local data alone. The PIDM consists of a group of more than 150 member countries (South Africa became a member in 1992) that share the vision of safer and more effective use of medicines. They work nationally and collaborate internationally to monitor and identify the harm caused by medicines, to reduce the risks to patients and to establish worldwide pharmacovigilance standards and systems. UMC has been responsible for the technical and operational aspects of the programme since 1978[2].

Reportable Adverse Reaction – A reportable adverse reaction requires the following information:

- An identifiable source (reporter) of the information. This should include the name or initials and address of the reporter and the reporter's qualification (e.g., doctor, dentist, pharmacist, nurse, or layperson);
- An identifiable patient. A patient may be identified by surname and forename(s) or initials of surname and forenames, or by reference number, or by age or gender;
- Suspected medicine(s) including vaccines; and

- Suspected reaction(s)[1].

Risk-Balance Evaluation – An evaluation of the positive therapeutic effects of the medicine in relation to the risks (any risk relating to the quality, safety, or efficacy of the medicine as regards patients' health or public health)[1].

(Safety) Signal – Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Depending on the seriousness of the event and the quality of the information, more than a single report is usually required to generate a signal[2].

Serious Adverse Drug Event / Adverse Drug Reaction – Any untoward medical occurrence that at any dose results in death, is life-threatening, requires patient hospitalisation or prolongation of existing hospitalisation, results in a congenital anomaly / birth defect, results in persistent or significant disability/incapacity, or is a medically significant / important event or reaction[1].
The term "severe" is often used to describe the intensity (severity) of a specific event[1].

Spontaneous Reporting – A communication to a company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicines, and which does not derive from a clinical study[1].

African Traditional Medicine – the sum total of skills and practices based on beliefs and experiences indigenous to African cultures, which are used to prevent, diagnose, improve, or treat physical and mental illness[5].

Unexpected (Unlisted) Adverse Drug Reaction / Adverse Events Following Immunisation – An unexpected reaction, is one in which the nature, specificity, severity, and outcome is not consistent with the approved professional information for a registered medicine[1].

Uppsala Monitoring Centre (UMC) – is the WHO Collaborating Centre for International Drug Monitoring. UMC works by collecting, assessing, and communicating information

from member countries' national pharmacovigilance centres concerning the benefits, harm, effectiveness, and risks of medicines. UMC is responsible for:

- Co-ordination of WHO Programme for International Drug Monitoring and its member countries;
- Collection, assessment, and communication of information from member countries about the benefits, harms and risks of medicines and other substances used in medicines to improve patient therapy and public health worldwide;
- Collaborating with member countries in the development and practice of the science of pharmacovigilance[2].

VigiAccess® - a web application that allows the public to access the VigiBase® database and retrieve statistical data on suspected ADRs/AEFI related medicines/vaccines reported to the World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM)[2].

VigiBase® - the WHO global database of individual case safety reports (ICSRs). It is developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of the WHO and its member countries. It consists of reports of ADRs/AEFIs related to medicines/vaccines received from member countries since 1968. It is updated with incoming case reports on a continuous basis. The purpose of Vigibase® is to ensure that early signs of previously unknown medicines-related safety problems are identified as rapidly as possible[2].

VigiFlow® - a web-based ICSR management system that is available for use by national pharmacovigilance centres e.g., SAHPRA, and used by the WHO Programme for International Drug Monitoring. VigiFlow® supports the collection, processing and sharing of data of ICSRs to facilitate effective data analysis[2].

Vigilance – in relation to medicine, medical device or IVD, means the continuous monitoring and evaluation of its safety, efficacy and performance profile and the management of any risk throughout its life-cycle[2].

Web-Recognising Adverse Drug Reactions (WEB-RADR) Project – launched in September 2014, sought to utilise the powers of social media and innovative technologies for pharmacovigilance purposes. The project developed mobile applications enabling patients, caregivers, and healthcare professionals/providers to report ADRs/AEFIs and receive up-to-date information and news alerts[2].

ABBREVIATIONS

Abbreviations used in this protocol are listed below; unless the abbreviation is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

ADE	Adverse Drug Event / Effect
ADR	Adverse Drug Reaction
AE	Adverse Event / Effect
AEFIs	Adverse Events Following Immunisations
AIDS	Acquired Immunodeficiency Syndrome
BMI	Body Mass Index
CDC	Centre for Disease Control and Prevention
CIOMS	Council for International Organisations of Medical Science
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
DVT	Deep Vein Thrombosis
US FDA	United States Food and Drug Administration
FPPR	Food Control, Pharmaceutical Trade and Product Regulatory Authority
GCP	Good Clinical Practice
HART	Hoechst Adverse Reaction Terminology
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HR-QOL	Health-Related Quality of Life
ICD-10	International Classification of Diseases 10th Revision
ICH	International Council for Harmonisation

ICSR	Individual Case Safety Report
J-ART	Japanese Adverse Reaction Terminology
MCC	Medicines Control Council
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	UK Medicines and Health Regulatory Agency
MIC	Medicine Information Centre
MIMS	Monthly Index of Medical Specialities
NADEMC	National Adverse Drug Event Monitoring Centre
NNT	Number Needed to Treat
OTC	Over-The-Counter
PEPFAR	The President's Emergency Plan for AIDS Relief
PIDM	WHO Program for International Drug Monitoring
PIL	Patient Information Leaflet
PV	Pharmacovigilance
QoL	Quality of Life
RMP	Risk Management Plan
SAHPRA	South African Health Products Regulatory Authority
SAMF	South African Medicines Formulary
SMS	Short Messaging Services
SOC	System Organ Class
SNOMED-CT	Systematised Nomenclature of Medicine – Clinical Terms
SRS	Spontaneous Reporting System
SSRI	Selective Serotonin Re-uptake Inhibitors

TB	Tuberculosis
UMC	Uppsala Monitoring Centre
USAID	United States Agency for International Development
WEB-RADR	WEB-Recognising Adverse Drug Reactions
WHO	World Health Organisation
WHO-ART	World Health Organisation Adverse Reaction Terminology

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Introduction

High standards of public health can be achieved through efficient and safe utilisation of healthcare products, including medicines, and their continuous monitoring. New medicines are granted marketing authorisation based on limited safety data collected during clinical trials, which are rigorously designed and conducted, but in a controlled environment; such trials are often too small or short term to detect rate or long-term effect[6-10]. The safety profile of the medicine during post-marketing may also be different from that established during clinical trials due to the heterogeneity of the targeted patient population including the existence of co-morbidities requiring co-treatments[11]. To address such limitations, an effective pharmacovigilance (PV) system is required to continue monitoring the safety of medicines post-marketing in order to mitigate any potential risks to patients and preserve the health of the public. During the marketing authorisation application, the applicant is therefore required to provide a risk management plan (RMP) which addresses the safety specification of the medicine, the pharmacovigilance plan (of which spontaneous reporting methods may be part of), and a risk minimisation plan[12].

1.2 Background

New medicines are granted marketing authorisation based on limited safety data collected during clinical trials. As such, safety information on the long-term and rare effects of the medicine and in diverse conditions is unknown at the time of approval for marketing. To address such limitations, an effective PV system is required to continue monitoring the safety of medicines post-marketing in order to detect previously unknown potential harms for further evaluation and mitigate any potential risks to patients where appropriate. Mitigation may include strategies such as contra-indications, black-box/boxed warnings, special recommendations for monitoring, or mandatory registries, amongst others[12].

The success of a PV system largely depends on the voluntary reporting of suspected adverse drug reactions (ADRs), commonly known as spontaneous reporting. Historically, spontaneous ADR reporting has been the domain of healthcare professionals[13]. PV is, however, hampered by their global under-reporting of ADRs, which decreases the sensitivity of, and causes major delays in the detection of, safety signals. A safety signal is defined as "reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously"[2]. The delays in safety signal detection have a potential to negatively impact patients, including their quality of life, increasing the burden on the public health system, as well as the economic burden on society.

Factors associated with under-reporting by healthcare professionals include complacency, fear of being involved in lawsuits or criticism for prescribing a medicine that caused harm to a patient, ignorance, diffidence and indifference[14,15,16]. Several countries have therefore incorporated patient reports directly into their PV system as means of addressing these under-reporting challenges[8,15,17-20].

The quality of reports from patients has been found to be similar to those of healthcare professionals, in terms of completeness and usefulness of the information provided[16,21,22]. An advantage is also the availability of additional information on the impact of the ADRs on their daily lives. Examples of positive contributions from direct patient reporting include detection of an association between the pandemic influenza H1N1 vaccine and narcolepsy, the effects of persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression, and an early detection of 'electric shock sensations' after the abrupt discontinuation of duloxetine[17,24]. Previously documented as reversible in patients discontinuing SSRIs, persistent sexual dysfunction was discovered mainly through consumer ADR reports, to be irreversible in patients who have been on treatment with SSRIs for longer periods (3 months to 3 years)[24]. Additional assessments were also carried out whereby four cases of patients with persistent sexual dysfunction due to SSRI discontinuation was reviewed; the persistence of the sexual dysfunction was also noted[25]. However, more long-term studies to confirm this are required.

The South African PV system meets World Health Organisation (WHO) minimum requirements for a functional PV system[27,28]. However, it is also affected by the under-reporting of ADRs[11,26,28,29]. Inclusion of patients in the ADR reporting system to address the under-reporting should therefore be considered.

1.3 Problem statement

South Africa has a well-designed and established PV system which meets the WHO criteria[27,28], including a national PV centre with at least one full time designated staff member, an ADR reporting form, a database, or system for managing the ADR reports, a PV advisory committee and a communication strategy[1,2]. However, as this is the bare minimum requirement, South Africa is also faced with challenges in the reporting of ADRs[11,26,28,29].

Some of the major challenges to be addressed within South Africa include a growing population of over 55 million people with a high burden of infectious and non-communicable diseases[25], fragmented vigilance activities from different global disease program funders in the country[11,27,28] and the under-reporting of ADRs[11,28]. About eleven key stakeholders in vigilance activities using four different reporting tools with three databases have been identified in some of the recent studies by Mehta *et al* (2017), Dowelani (2017) and Maigetter *et al* (2015)[11,27,28]. This is as a result of different disease program funders requiring the use of their preferred reporting tools. Such programs will often be conducted in the form of surveillance projects, where safety reporting is closely followed up. Though it is not clearly stated in the citations above[11,27,28], the very low ADR reporting rate as noted in a study by Terblanche *et al* (2017) between January 2014 and May 2015 in the Sedibeng region (Gauteng)[29] could be an indication that there is often no link between the different reporting systems/databases and the South African Health Products Regulatory Authority Vigilance unit (national PV unit).

It has also been a challenge to identify South Africa's contribution in signal detection whereby a safety re-evaluation of a medicine had to be undertaken resulting in a regulatory action; South Africa often must rely on reviewing regulatory actions taken

by other international regulators to determine the regulatory action to be taken locally, due to low levels of reporting[11,26,28,29].

The reasons/factors identified to be deterring healthcare professionals from reporting ADRs in South Africa highlight the need to strengthen the PV system in the country. Some of those relate to the complexity of the reporting forms used, inefficiency of the PV unit in collecting and evaluating ADRs, lack of training for the healthcare professionals (HCPs) who are expected to report the ADRs, and communication challenges with the regulatory authority (PV unit)[30,31].

On the other hand, patients/consumers have indicated interest through proactively sending their ADR reports to the PV unit, though their reports were regarded as of inferior quality and considered of less value[28].

Although ADRs are the primary focus of the PV activities, the broader scope of PV also includes medication errors, counterfeit and sub-standard medicines, lack of efficacy of medicines, misuse and/or abuse of medicines, drug-drug interactions, and off-label use of medicines[32-34]. For a functional PV system to address these challenges, the active participation of the patients/consumers of medicines would be of great benefit to the local and global vigilance activities.

In view of these challenges, this study investigates the development of a Direct ADR Reporting Tool for consumers to Address Under-Reporting of ADRs to the National Pharmacovigilance Unit in South Africa.

The design of the current study and the development of a patient/consumer ADR reporting tool precedes the adoption and implementation of the Med Safety Mobile Application as an online Adverse Event Following Immunisation (AEFI) reporting tool by the South African Health Products Regulatory Authority (SAHPRA) in 2021. If it had not been for the outbreak of the COVID-19 pandemic in 2020 and the immediate need for AEFI reporting tools following the global roll-out of immunisation programmes shortly thereafter by the World Health Organisation (WHO), National Health Departments and Regulators around the globe, this study would have been one of the first to have investigated direct consumer reporting on a larger scale in South Africa.

1.4 Aim Objectives and the Research questions

1.4.1 Study Aim

The aim of the study is to institute a direct platform for patients/consumers to report ADRs as part of supporting the improvement of the PV system and address under-reporting challenges in South Africa.

1.4.2 Study Objectives

- Develop a direct ADR reporting tool to allow consumers to report ADRs directly to the national PV unit or designated agencies, and thus enabling consumers to share their experience and impact of the ADRs
- Conduct a pilot study to assess the feasibility of the developed ADR reporting tool and determine the viability of the ADR reporting tool when used in real-life settings.
- Explore different channels for possible use by consumers to send the ADR reports to a PV unit, the methods which consumers can use to submit their ADR reports to the PV unit or designated agencies.

1.4.3 Research questions

- How best should a direct ADR reporting tool that allows consumers to report ADRs directly to the national PV unit or designated agencies be designed and developed?
- How feasible is it to use the tool for reporting ADR by consumers?
- What are the possible different channels which consumers can use to submit the ADR reports?

1.5 Significance of the study

Adopting a novel direct ADR reporting tool for consumers for official use nationally will give them an opportunity to have their voices and/or concerns about their health management heard. The healthcare system will also benefit from the reports directly from medicine consumers as it has been documented that their contributions are very

useful[17]. Consequently, this should also improve the level of ADR reporting in South Africa.

1.6 Chapter layout

This dissertation is divided into seven chapters.

Table 1. Summary of the Dissertation Layout

Section	Content
Chapter 1	Introduction and Background of the study with a problem statement. This chapter also addresses the aim and objectives of the study, research question and significance of the study.
Chapter 2	Literature Review highlighting documented research on this and related topics as well as critical appraisal of the literature
Chapter 3	Research Design and Ethics
Chapter 4	Tool Development: Method and Results
Chapter 5	Tool Pilot: Method and Results
Chapter 6	Discussion
Chapter 7	Recommendations and Conclusions

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This Chapter presents a literature review concerning the study area, covering: the impact of ADR under-reporting and factors associated with under-reporting, inclusion of ADR-reporting by consumers, possible background noise associated with consumer reporting, challenges with coding of adverse events from direct consumer report, and the current status of ADR-reporting in South Africa.

A general search across different databases (PubMed®, ScienceDirect, Scopus®, Google Scholar) and ResearchGate® was conducted using combinations of search terms to source relevant references, including adverse drug reactions reporting, challenges with adverse drug reactions reporting, pharmacovigilance, spontaneous ADR reports, patients adverse drug reactions reports, healthcare professionals ADR reports. There were minimal restrictions and/or search criteria applied on the search strategy for each database to include a broad range of articles with high sensitivity and low specificity, however only outputs in English were feasible to review.

Potentially relevant articles were selected by screening titles of the articles, with articles closely matching the search term at the top. Only the first 3 – 5 first pages of the search results were screened as the further away the articles from the first page the less relevant they were to the search terms. Articles that contained relevant keywords were further screened by reviewing the abstracts. Studies that fulfilled the inclusion criteria were retrieved for a full review.

To broaden the scope of the literature review, references of all relevant articles were then probed to check for any potential further possible articles. Through this search, new search terms and phrases, including under-reporting of ADRs, consumer ADR reports, ADR reporting by the general public, were established and applied to source more publications. General search engines such as Google™, Bing™ and Yahoo™ were also used to access regulatory authority websites.

Table 2. Summary of the Hits on the Outcomes of the Literature Search

Search Word	**Pubmed®**	**ScienceDirect**	**Scopus®**	**Google Scholar**	**Research Gate**
Search criteria	Text Availability: ● Full text ● Free full text Language: ● English Wild cards ()	Article Types: ● Review articles ● Research Articles ● Data articles Wild cards not supported	● Journals	Article type: ● Review articles ● No citations Wild cards ()	● Publications ● Articles Does not yield the sum of the total number of hits/results
Adverse drug reactions reporting	1,517	182,462	1,081	69,000	-
Challenges with adverse drug reactions reporting	756	57,753	2,109	380,000	-
Pharmacovigilance	4,138	6,308	7	145,000	-
Spontaneous ADR reports	259	2,890	934	26,700	-
Patients adverse drug reactions reports	8,206	135,717	1,248	2 700,000	-
Healthcare professionals ADR reports	177	581	1,201	25,200	-
Under-reporting of ADRs	45	14, 093	2,887	10,200	-
Consumer ADR reports	49	1,255	969	24,600	-
ADR reporting by general public	90	2,881	2,507	48,000	-

In total, three hundred and sixty four articles were reviewed in detail. Articles with less relevance to the current research were excluded from the literature review. These included a number of meta-data analyses and systematic reviews articles for which (i) the referenced primary research articles were already included as part of the current literature review, (ii) the design of primary research articles and methods of meta-data analyses was similar, thereby (iii) they yielded comparable results to publication

already considered in the current study. These would not add new knowledge or contribute new/different arguments to the already included articles.

2.2 The Impact of ADRs

A patient's health-related quality of life (HR-QOL) can be significantly impacted by ADRs[35]. ADRs that are classified as 'serious' according to the Counsel for International Organisations and Medical Sciences (CIOMS) criteria are expected to have a major debilitating impact on a patient's HR-QOL. These are reactions that would result in death, severe disability, congenital abnormalities, life-threatening events, lead to hospitalisation or prolongation of hospitalisation. These restrictive definitions do not, however, take into consideration the actual physical and socio-economic impact the ADRs have on patients, and a patient's view on what constitutes a serious ADR may differ from the medical seriousness as defined by CIOMS criteria[35-37]. ADRs considered non-serious as per CIOMS classification (e.g., nausea and itchiness), may be judged to be of serious nature (based on severity) by a patient who experiences them.

ADRs are documented as one of the leading causes of patient-related morbidity, mortality and hospitalisation[33,38,39]. In a study conducted in two hospitals in Europe over a six-month period, 18 820 patients were hospitalised due to experiencing an ADR[21], about 6.5% of all hospital submissions being related to ADRs[30]. In another study conducted in South Africa in 2016, Mouton *et al* established that about 40% of 126 admissions across four hospitals were related to ADRs resulting from inappropriate medicine administered (19%), inappropriate dose regimen (11%) and drug interactions (10%)[40]. This highlights the commonality of medication errors in the Sub-Saharan African hospitals as noted by the same authors in 2020[41]. One fatality due to an ADR which was because of medication error was recorded from one of the South African children's hospitals[41]. A mortality rate of eighteen per one hundred hospital admissions was recorded over the study period, with 16% of these deaths attributed to ADR-related causality[42]. The plight of ADRs impact is noted in the findings from two children's hospitals which were the focus of Mouton *et al* observation file review study[41]. ADR-related admissions were estimated at 1.8%, with one in five serious ADRs being fatal or near fatal, thus supporting Mehta *et al*'s findings on the

substantial ADR contribution to morbidity and hospital admissions in South Africa, over-stretching the cost and burden of the healthcare system[11].

The estimated annual cost for ADR-related admissions from the two hospitals in Europe was in the order of 466m British Pound (€ 706m, USD 847m, R9,305m), with an estimated fatality rate of about 0.15%[21].

2.3 Under-reporting of ADRs

Under-reporting of ADRs by healthcare professionals is a global major setback for spontaneous reporting[14,39,43-45]. It has a significant impact on the known safety profile of medicines. Early detection of safety signals could trigger further investigations or, sometimes regulatory warnings or, changes in product labelling or withdrawals[46-48]. Further to the previous definition, Rolfes *et* al, defined a safety signal as a clinically important event that might have an impact on patient management on the balance of benefits and risks, should it be found to be related to a medicine[35]. However, under-reporting decreases the sensitivity of safety signals and causes major delays in their detection[15], with potentially negative impact on patients and their quality of life, as well as increasing the burden on the public health system[14]. In order to implement systems and methods to improve reporting of ADRs, underlying causes should first be identified and addressed.

2.4 Factors associated with under-reporting by Healthcare Professionals

Several studies have been conducted since the establishment of PV systems in different countries to determine the factors associated with under-reporting by healthcare professionals[6,14-16,22,33,45,48-54]. In a study conducted in Germany, to determine physicians' knowledge and attitude regarding ADR reporting, 68.2% of doctors have suspected an ADR but did not report it[50]. Their reasons for not reporting were similar to those identified in other studies in different regions of Europe, Canada, India, Ethiopia, Portugal, and Northern Nigeria:

- Complacency – a belief that only safe medicines are marketed as all serious ADRs should be well documented at the time the medicine receives marketing approval[14,51].

- Fear of being involved in lawsuits or criticism for prescribing a medicine that caused harm to a patient[50,51]
- Guilt for being responsible for the harm to a patient[51]
- Ambition to collect information to publish data as case series[15,51]
- Ignorance – lack of awareness on how (reporting systems and procedures: forms to use, where to get them, how to and where to send the completed forms) or what needs to be reported (what constitute an ADR, the types of ADRs to be reported)[6,15,33,45,49-53]
- Diffidence – belief that one should only report if there is certainty that it is related to the medicine[33,50]
- Indifference – that one case will not contribute to medical knowledge[49]. This was also associated with lack of interest and lack of time due to many activities in the clinical routine in other studies[14-16].

Research evidence suggests that little has changed (from when ADR reporting challenges were first noted) with regard to barriers for healthcare professionals to report ADRs[6,22,33,39,45,48,49,51,53]. Additional factors reported as barriers include:

- Lack of financial incentives[54]
- Lethargy which incorporates procrastination and lack of time to either report or follow-up with the patient[16,45,51,54]; increased workload[39,49,51] and lack of commitment[55]
- Insecurity – believing that it is not possible to determine if a certain medicine caused an ADR. This also includes the concern of submitting inappropriate reports and/or fear of embarrassment for submitting such[15,33,45,48,50,51,54]
- The reporting process being too cumbersome or bureaucratic[45,54]
- ADR already well known i.e., belief that only ADRs to new medicine and/or new ADRs to established medicines[22,33,45,48,50,51]
- ADR too trivial to report i.e., belief that only serious ADRs should be reported[33,50,51]
- Confusion as to who (patient or healthcare professional) reports ADRs and to whom[6,53]
- Poor workplace environment[39]

- No specific training on PV[15,39] and/or lack of understanding of the purpose of spontaneous reporting system (SRS)[51]
- Lack of feedback from the authority[45]
- Insufficient clinical knowledge[45]. Although this is closely related to lack of knowledge regarding causal assessment, study participants in the *Duarte et al* study[45], which consisted of pharmacists from different fields in healthcare, stated lack of training in specific areas such as clinical pharmacology and therapeutics as one of the reasons deterring ADR reporting
- Belief that it is bad for the company to report ADRs for their products[49]
- Confidentiality – not at ease to report confidential information[51]

Failure to recognise an ADR, (which was estimated at about 57% in Lopez-Gonzalenz *et* al study[16]), may not only lead to inappropriate patient management, but also to increased risk of additional ADRs. About 25% of doctors indicated that they had never diagnosed an ADR[50]. It is not clear whether this was because of lack of knowledge on how causality assessment is done or had never been able to link any signs and symptoms presented to them by patients to any prescribed medicine or they just simply had dismissed patients' concerns. In a study published by Hasford *et al*[50], doctors were found to be less likely to report any ADR due to a medicine taken self-medication or due to a medicine prescribed by another doctor. This could be due to the fear of being held responsible should litigation arise or be embarrassed for causing the patient harm.

Lack of time for reporting an ADR or follow-up with patients, and the reporting processes being cumbersome was cited by healthcare professionals with different care priorities, such as high burden of care or the pressure to assess more patients per day (work load) as reasons for not reporting ADRs[16,39,49]. This could imply that healthcare professionals are left with less time to conduct proper patient assessment for ADRs and reporting, which may require patient follow-up should the regulatory authority request more information.

The attitude (lethargy and lack of time) raises questions in terms of the level of patient management which is offered by the affected healthcare professionals. Proper

diagnosis requires taking a full history from the patient and careful assessment of clinical signs and symptoms[16].

Healthcare professionals should understand that the benefit/risk profile of a new medicine is not fully known at the time of receiving approval for marketing. Reporting of ADRs during post-marketing is therefore one of the mechanisms to expand on the safety profile of such medicines[54]. Reporting of ADRs which are already known or documented may raise awareness on the changes in safety profile of the ADR, with a possibility of improving patients' care[7] and contribute to well-informed policy making. For example, if an ADR was reported as rare, non-serious or reversible during clinical trials, and then more reports of this ADR are received after the medicine has been granted marketing approval, further investigations could be conducted to assess if the frequency of the ADR occurrence or severity of the ADR has changed from that reported prior to marketing. Any changes noted in the frequency of occurrence or severity could affect the benefit/risk profile of the medicine. Clear reporting criteria should be established in the Risk Management Plan (RMP), especially for medicines that have been in the market for some time and/or with an already established benefit/risk profile to avoid overloading the ADR reporting system.

The seriousness of an ADR, unlabelled ADRs and those ADRs that are serious and unexpected were the most quoted factors that prompted most healthcare professionals to report[48-51]. Edward and Aronson defined an unexpected ADR as a reaction whose nature or severity is not consistent with data contained in domestic labelling or market authorisation or expected from the characteristics of the medicine[56]. Other factors that encouraged healthcare professionals to report included the medicine being new in the market, increased frequency of non-serious ADRs, if the ADR was due to drug interaction or if they assessed the ADR as 100% related to the medicine, and confidence in the diagnosis of the ADR[49,51].

To address some of the identified underlying causes of under-reporting, healthcare professionals suggested interventions ranging from simplifying the reporting systems (including availability of broader and/or different reporting options and guidelines), to incentives in the form of feedback on reported ADRs[43,48,49,52,54].

2.5 Inclusion of patients in ADR-reporting

To address the under-reporting challenge, several countries (including Denmark and Netherlands since 2003, Italy since 2004, Belgium 2006, the UK since 2008, Sweden since 2008, and Norway since 2013)[8,15,17-20] started to incorporate direct patient reporting of ADRs into their PV systems. Initially, the objective was to increase the number of reports. However, the contribution of patient/consumer reporting has been proven to go beyond a quantitative contribution[44,57] and there is now growing interest to include this group as official reporters[58]. At the dawn of involving patients / caregivers to report ADRs directly to the regulatory agencies, many concerns were voiced regarding the value such reports would add and the quality of the reports. Misattributing of symptoms to an ADR[37,55], negative effect on the relationship between the patient and their healthcare professional, reports with lower quality and demanding more time to evaluate, higher proportion of non-serious ADRs as well as possible duplication of reports were some of the concerns raised with regard to patients' reports for ADRs[37]. Nonetheless, the involvement of direct patient reporting has presented a new dimension of patients' experiences and views on medicine therapy and PV.

Studies conducted directly with patients themselves revealed that most of the reasons which encourage patients to report ADRs are of altruistic nature:

- Belief that reporting ADRs can improve safety of treatment and limit further recurrence of ADRs (improving medicine safety) – contribute to the greater good[37,46,53,55,59].
- Their (patients') experiences may be filtered by healthcare professionals and deprive the regulators of learning about their experiences, as it is believed that their reports would be more detailed than those of healthcare professionals[10,37,59].
- Raising awareness about the ADRs – including improvement of healthcare professionals' practices[37,53].
- To share their experience[37,60].
- Reporting contributes to research and knowledge[46,60].
- Felt responsible for reporting an ADR[46,60].
- A sense of achieving something positive from that experience[46].

Other motives for reporting ADRs by patients included:

- Perceived dismissive attitude of healthcare professionals – not acknowledging patients' concerns with a notion that healthcare professionals may not report the ADR accurately due to limited time and lack of personal experience of the ADR[7,37,46,53,59,60].
- Seriousness or severity of the ADR, including the ADR's impact on patients' daily life[53,60,61].
- Desiring personal feedback, including wanting to learn and finding others who experienced a similar ADR as well as seeking confirmation that the report was received[37,53].
- Asked to report the ADR by healthcare professionals[53].
- Worried about their own situation[60].
- Unlabelled ADR – not mentioned in the patient information leaflet[60], and if the ADR was from a new medicine or in a child[61].
- As a form of redress[46].

The need to report the ADRs directly to the regulatory authorities to avoid filtering of information by healthcare professionals shows some level of distrust between the patient and the healthcare provider[46,60]. This could deter patients from receiving proper healthcare, encouraging self-diagnosis and/or self-medication in response to any adverse reaction experienced[34,62]. The filtering that healthcare professionals apply is mainly based on their interpretation and expectations such as what is important to report and what is serious/severe based on the medical definitions and observations[57,62]. Patients' views and reports are based on direct experiences of the effects of medicines[22]. Patients' unfiltered information can thus contribute to a new understanding of ADRs, especially unlabelled or unexpected ADRs[23].

Some of the barriers/challenges that patients cited as reasons for not reporting ADRs are linked to the relationship with their healthcare professionals and include:

- Lack of time and opportunity for patients to speak[62]. Hastening patients' consultation deprives patients an opportunity to voice their concerns regarding the treatment they are taking or care they are receiving.

- Patients' reluctance to discuss intimate details such as mental stability and sexual dysfunction[24]; for some patients discussing intimate issues with their healthcare professionals may be embarrassing, some patients may perceive their healthcare professional as not open enough to discuss such details, and/or that they may fear being judged or stigmatised, resulting in patients not being able to report all suspected ADRs[24].
- Perceptions of the help / support they had (received) or did not have (receive) from their healthcare professionals, including not being taken seriously or their concerns acknowledged[23,24,62]. If a patient once reported an ADR which the healthcare professional did not acknowledge or attributed it to other causes, patients may be reluctant to report any further ADRs or raise concerns with regard to the treatment they are receiving[53,59,60].
- Patients understanding of instructions for use or warnings given[62]. Patients may attribute the ADRs they experienced to their perceived lack of understanding or lack of following instructions as detailed in the patient information leaflet. The perception of what 'medicine safety' means could also be a challenge[61]. A considerable number of participants (about 44.4 – 58.1%) in a study to determine the perceptions and experiences of the general public in Liverpool, considered a safe medicine to be one that does not cause any side effects or harm[50,61]. With such perceptions, there is a low probability that the concerned patient will be able to identify an ADR if experienced since there would be no expectation of such. Instead, the patient would probably attribute the symptoms to a new illness or condition. 32.2% of patients thought that prescribed medicines cause more side effects than OTC medicines[61]. This highlights the frequent misunderstanding of medicine safety amongst patients. As the use of OTC medicines is increasing, the resulting increase in ADRs will be met with an alarming rate of under-reporting due to misperceptions[63], such as:
    - Confusion and uncertainty about roles and responsibilities of ADR reporting[46].
    - Concerns that their reports would be inaccurate, and information provided may be of little value due to lack of medical knowledge[46].
- Poor awareness of ADR reporting system[53]. This included the complexity of the reporting procedures and lengthy reporting forms.

- Resolution of the ADR or anticipating the ADR to resolve after completing treatment[53]. This is a sign of poor awareness of ADR reporting rationale and the anticipated value their reports could add onto the PV system. Whereas some patients decided to report the ADRs due to the ADR not resolving long after stopping treatment; those who experienced resolution of the ADR after stopping treatment did not think there would be any benefit for reporting such ADRs[53].
- Lack of feedback on previous ADRs reported[53]. Patients have a vested interest in their own health and are often more knowledgeable about their health condition and treatment[64,65]. As such, the desire to receive feedback on the ADRs they reported might give them assurance that their reports were received and assessed. Furthermore, the kind of feedback they might receive could give an indication/confirmation of their level of understanding of ADR identification and the associated causal medicine. This might encourage patients to become more active participants in spontaneous reporting, and in the process learn how to manage their condition and improve communication with their healthcare providers[39,58].
- A concern regarding the costs involved in reporting ADRs (i.e., mailing costs) was mentioned in two of the developing countries included in one of the most recent studies[53]. This highlights the need to take into consideration the types of reporting tools used in each country, which should be aligned to the economic challenges.
- Prior negative experience[53]. Patients who tried to report an ADR before to their healthcare professional and experienced disapproval may be unlikely to report any ADRs experienced in the future.

Differences were noted in the reported ADRs between patients (based on experience) and healthcare professionals (based on observations)[37,39,66]. Patients' reports contained detailed information such as the description of the ADR, the impact of the suspected ADR on the patient's life, the duration of the suspected ADR including the time/date of onset and/or resolution; information which is comparatively rare or unavailable in healthcare professionals' reports[37,39].

Quality of the reports received directly from patients was similar to those from healthcare professionals[39,66]. Information provided by patients was also useful and adequate to conduct causality assessments in most reports submitted[22,39,67].

For ADRs that are easily identifiable, healthcare professionals were the ones initiating the discussion of those ADRs with patients; whereas in most of the cases where the ADR was unlabelled/unexpected, patients initiated the discussion[7]. This could be one of the causes for selective reporting amongst healthcare professionals[14,67] as they would tend to report ADRs that they were able to recognise. In an ideal healthcare environment, the healthcare professional should discuss with the patient the condition, treatment regimen and provide adequate information about the safety profile of the prescribed medicine (which should include and/or refer the patient to the patient information leaflet for a list of expected adverse reactions) and encourage patients to report any unexpected symptoms[37].

Lack of medical knowledge does not seem to deter patients from identifying an ADR and reporting thereof. The unexpected nature of the ADR and the timing of the occurrence in relation to treatment initiation were mainly used by patients to identify the ADRs[63]. About 86.5% of the 697 patients who reported to have experienced an ADR in the *Krska et al* study, were certain of the causal association[68]. In another study, the majority of the participating patients were able to distinguish between symptoms of disease and the ADRs, with some providing their rationale for their conclusion[37].

In several studies, patients more often than healthcare professionals reported detailed description of the impact of the ADR on their daily lives[46,37,48,69,70], the course and outcome of the ADR, the perceived severity and causality of the ADRs. The reports from healthcare professionals mostly contained clinically related information (objective reporting) such as the medical history, prescribed or suspected medicine and its treatment regimen[18,37,44,69]. The reporting style (i.e., type and quantity/quality of information to be provided) of healthcare professionals is determined by the ADR reporting form, which only requires standardised information necessary to conduct causality assessment. The main focus for healthcare professionals is thus on causality. The combined reports from patients and healthcare professionals would provide a broader picture of ADRs[44].

2.6 Possible background noise associated with patients' reporting

At the dawn of incorporating patients' reports in PV systems, possible background noise, inferior quality reports and PV system overloading, which could significantly delay safety signal detection, were some of the concerns PV stakeholders had[10,37]. Patients' terms of reference of what constitutes an adverse event is expected to differ from that of medically trained personnel. This raised concerns that patients may not be able to differentiate between an adverse event, disease progression and/or lack of efficacy of a medicine[30]. Research shows that, although patients can recognise when something is not right in their healthcare, they have a good understanding of medicine safety. However, their decision to report any adverse events may be influenced by a number of factors such as the level of trust and confidence with the healthcare provider, their beliefs, and expectations, as well as the level of communication or lack of, and level of satisfaction with the healthcare services received[30,71-74].

The profile and quality of ADRs were, however, found to be similar between patients' and healthcare professionals' reports[16,21,22]. The concerns that patients' reports may create a 'noise' in the spontaneous reporting system due to high number of minor ADRs reported and poor documented reports were therefore unfounded[10,37].

The limited medical knowledge of patients can also serve to minimise reporting bias of expected versus unexpected adverse reactions i.e., being discouraged to report known adverse reactions as they are already expected and/or be doubtful of reporting unexpected adverse reactions as they seem unlikely from a medical point of view[75].

Patients' direct reports of ADRs have in fact proven to be invaluable and brought a new dimension to PV[34]. It has the potential to improve knowledge of and (speed up) signal detection, identification of counterfeit medicines, medication errors, investigations of certain medicines leading to medicine recall and/or relabelling as well as a new perspective on the direct and not perceived impact ADRs have in patients[23,57,58,65,76].

Considering the positive contributions that patients' reports may add, insights from those regulatory authorities who have already incorporated them in the PV system could encourage other regulators to consider the same, as well as highlight the challenges they need to address when planning and/or revise their PV systems to incorporate patients' reports.

Some of the attributes of patients' reports to the PV system and signal detection are substantial. The *Panorama* Paroxetine program is one example that confirmed that patients' unfiltered reports can bring a new dimension in the understanding of ADRs[23,24].

The withdrawal effects of paroxetine including 'electric shock' sensation and 'whooshing sensation' reported by patients highlighted the inconsistencies in the coding and classification of symptoms between the regulator, the product label and company core data[7]. It also brought to light the differences and inconsistencies in what the company and the regulatory authority deemed to be withdrawal effects versus discontinuation symptoms.

Further examples of positive attributes of patients' reports include aiding the detection of an association between the Pandemrix Influenza H1N1 vaccine and narcolepsy[17]; the long term effects of persistent sexual dysfunction after the discontinuation of serotonin reuptake inhibitors for the treatment of depression[24], the presence of nimesulide (a non-steroid anti-inflammatory drug) in fotodol (a herbal product used for medicinal purposes and as a food additive), which is known to cause liver damage; an association between pathological gambling and the use of pergolide, a dopamine agonist for the treatment of Parkinson's disease and early detection of 'electric shock sensations' caused by duloxetine withdrawal[17].

2.7 Challenges with coding of adverse events from patient/consumer reports

Coding of adverse events is the process that converts a reported event known as 'verbatim term' or 'literal term' into a standard term[77]. Such classification enables better

searches for signal detection. The differences in terminology used in product labels and company data sheets versus terms used by patients when describing the symptoms could play a leading role in early signal detection. For example, *Medawar et al* revealed that "electric shock" was coded under 'Injury and Poisoning' in the December 2002 Yellow Card printouts for paroxetine, which was interpreted as referring to electricity exposure, whereas in the actual Yellow Card reports "electric shock" sensations was classified under the general heading 'paraesthesia'[62]. The paroxetine data sheet also listed 'dizziness and sensory disturbance' as symptoms of abrupt withdrawal, whereas the Patient Information Leaflet only mentioned 'tingling sensations.

A more general term 'emotional lability' was used in one study when referring to suicidal tendencies in patients taking paroxetine[78]. In a separate instance, language barriers led to a misinterpretation of a word 'intoxicado' during an emergency situation[79], a Spanish word for nauseated left a patient with quadriplegia[79].

Correct coding of adverse events, as well as labelling and interpretation of medical terms play a vital role in the overall management of patients' health care and PV. Standardisation of terms for use in labelling adverse reactions is thus also crucial.

The different coding systems that are used across different regions all serve the same purpose to streamline the processing of adverse events. There are seven coding systems that have so far been identified: the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), developed by US FDA; and later superseded by the Medical dictionary for Regulatory activities (MedDRA); the World Health Organisation Adverse Reaction Terminology (WHO-ART); the Japanese Adverse Reaction Terminology (J-ART); the International Classification of Diseases 11th Revision (ICD-11); the Hoechst Adverse Reaction Terminology (HART), and the Systematised Nomenclature of Medicine – Clinical Terms (SNOMED-CT)[80]. The different terminologies across these coding systems would still pose a challenge in pooling safety data for analysis and discourage comparisons across regions[77,80]. MedDRA, which is one of the commonly used coding dictionaries across the globe[80], has been picked and recommended for use as a global standard coding dictionary by the Council for the International Organisation of Medical Sciences (CIOMS); a decision

endorsed by the International Council for Harmonisation (ICH)[77]. The recent introduction of SNOMED-CT mapping to MedDRA also cements this choice. MedDRA-SNOMED mapping aims to establish a consolidated/single global clinical vocabulary to enable clear exchange and analysis of health data for better health and improved patient outcomes[81.]

2.8 Current Status of Pharmacovigilance in South Africa

South Africa, being a developing country with a growing population (estimated around fifty-four million people in 2016)[82], is experiencing a rise in the use of new medicines and establishment of generic medicine companies[27]. With the increasing use of the internet comes the increased access to medicines, especially over-the-counter medicines[26]. South Africa has also implemented a spontaneous reporting system for continued monitoring of medicine' safety once in the market.

The pharmacovigilance activities in South Africa are legislated by the Medicines and Related Substances Control Act 101 of 1965 and the Regulations to Act 101[83], under the administration of the South African Health Products Regulatory Authority (SAHPRA), previously known as the Medicines Control Council (MCC). SAHPRA fulfills its mandate towards ensuring the safety, efficacy and quality of medicines, through different operational units, with the Vigilance unit being one such unit. The SAHPRA Vigilance unit is responsible for the implementation of pharmacovigilance systems in the South African Healthcare System, thereby providing for the detection, monitoring and management of ADRs and AEFIs in South Africa. The PV unit was established in 1987, with a satellite office, the National Adverse Drug Event Monitoring Centre (NADEMC), located at the University of Cape Town's Clinical Pharmacology division[2,11,28,84]. In 1992 South Africa became one of the first African members of the WHO Program for International Drug Monitoring (PIDM), together with Morocco[11,26].

The South African PV system meets the minimum WHO criteria for a functional national PV system (Figure 1)[27,28]. The NADEMC unit has at least one full time member, who is responsible for servicing the growing pharmaceutical industry in the country, the healthcare professionals as well as the public. South Africa became a full member of the WHO Programme for International Drug Monitoring (PIDM) in 1992[2,85].

WHO PIDM is a group of more than 150 countries that share the vision of safer and more effective use of medicines[85]. The main mandate for the PIDM, established in 1968, is to ensure patient safety information is collected from as many sources as possible, and establish pharmacovigilance standards and systems across the globe. This will then enable individual countries to be alerted of emerging safety patterns. These safety reports are managed through a single database globally, known as VigiBase®, which collects and stores individual case safety reports (ICRS) from the member countries[2]. The WHO PIDM is facilitated by the Uppsala Monitoring Centre (UMC, a WHO Collaborating Centre for International Drug Monitoring), and ensures coordination and collaboration with the member countries regarding the WHO programs and continued development of pharmacovigilance practices[2]. The UMC is therefore also responsible for the development and maintenance of VigiBase®. Only member countries and not consumers or healthcare professionals/providers have access to this database.

Minimum Requirements for a Functional National Pharmacovigilance System

The following are the ***minimum*** requirements that the WHO and partners agree should be present in any national pharmacovigilance system.

1. A ***national pharmacovigilance centre*** with designated staff (at least one full time), stable basic funding, clear mandates, well defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring.

2. The existence of a ***national spontaneous reporting system*** with a national individual case safety report (ICSR) form i.e. an ADR reporting form.

3. A ***national database*** or system for collating and managing ADR reports.

4. A national ADR or pharmacovigilance ***advisory committee*** able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication.

5. A clear ***communication strategy*** for routine communication and crises communication.

Figure 1. WHO Minimum Requirements for a Functional National Pharmacovigilance System (Source: WHO[3])

Under their website, the UMC/WHO PIDM also files a collection of PV guidelines from their member countries. It is however not clear who is responsible for ensuring that these guidelines are updated on an ongoing basis. For some countries, the most

recent updated guidelines are available. However, for South Africa, the guidelines are dated back as far as 2014, with the regulatory authority still referred to as the Medicines Control Council[85].

The UMC resources and support web section contains useful documentation and services to support their member countries with technical, educational and any other support required to assist with development of local pharmacovigilance systems. This includes a guidance document called 'form of the form' containing best practices in designing suspected adverse events reporting form to a national PV centre and focuses on both the paper and online reporting forms. Knowing and understanding who the primary user of the form is, UMC believes is the basic foundation of developing the form and will then influence its overall design and format[85].

South Africa is one of the African countries with a high burden of infectious diseases and non-communicable diseases[26], whereby the infectious diseases are mostly managed through global funding. The Global Fund often requires proper monitoring of ADRs in patients receiving treatment through their funded programs. In response to this requirement, a safety monitoring unit within each funded program would be established. A recent study identified eleven key stakeholders in PV in South Africa, utilising four different reporting tools and three different databases[27]. No collaborations were found to exist between these PV stakeholders and their reporting tools and systems differ in the types and format of information collected[27,28]. The resulting duplication and fragmentation of PV activities further widens the gap of under-reporting in South Africa[11,28].

Although South Africa has been identified as one of the main contributors of cumulative individual case safety reports data in VigiBase® (ADR database maintained by UMC)[26], the reporting of ADRs to the national PV system is very low. Only six ADRs were reported between January 2014 and May 2015 in one of the recent studies in an 800-bed secondary level care hospital in Sedibeng, Gauteng Province[29].

In another recent study conducted amongst community and hospital pharmacists in Northwest Province, South Africa, 50% of the participants indicated that they found

ADR reporting to be time consuming as a major barrier to ADR reporting[86]. Other barriers cited include lack of knowledge of how to report or where to report; poor feedback on the previously reported ADRs; the SAHPRA Yellow Form for ADR reporting not user friendly and/or complicated; the regulatory authority responsible for collecting and evaluating ADRs not efficient; lack of financial incentive for reporting of ADRs, and ADRs not serious. One of the studies conducted in certain parts of Mpumalanga Province, South Africa, reported that a vast number of the participants (about 80% of healthcare professionals including medical doctors, pharmacists, and nurses) did not receive PV training during their formal education and upon commencing employment[31]. Furthermore, there were no functional PV activities in organisations where about 67% of the healthcare professionals were working. These barriers and challenges, which are similar across countries, are the major contributors to the global under-reporting state[6,14,15,16,33,45,48-53].

With such low levels of reporting[26,29], detection of safety signals and risks evaluations would be grossly delayed. To ensure continued patient and public safety, South Africa often reviews actions taken by other international regulators[11], and has as a result, taken regulatory actions based on their safety data[30]. The types of regulatory actions that the regulatory authority can take include requesting additional investigations by the market license holder of the concerned product, amendment of the product label, up-scheduling of the product (move from low to higher schedule) to restrict access or product recall.

NADEMC had been receiving reports directly from patients/consumers through patient support groups or via pharmacies, even though the quality of the reports were regarded as poor and therefore considered to be of less value[28]. The fact that some patients/consumers have taken the initiative to send their ADR reports to NADEMC is an indication of the potential interest that patients/consumers have on being active participants in their own health care. With proper education (about PV) and motivation (why they should be involved), ADR reports directly from patients/consumers can add value in the South African PV system, contribute immensely to early detection of safety signals and provide a new insight in patient management and policy making.

In the wake of the COVID-19 pandemic, South Africa has seen a tremendous revamp on the PV systems and processes. Guidelines were updated to incorporate adverse events following immunisation and/or vaccination. Two reporting tools/processes that allow the patients/consumers and healthcare professionals/providers to report suspected ADRs to the national PV unit were also introduced. Though SAHPRA was already in the process of digitising the healthcare professionals reporting tool (electronic format of the SAHPRA Yellow Form, as a mobile app) (*unpublished source*), the online reporting options seem to have gained momentum during the pandemic. SAHPRA/department of Health also held several sessions virtually mobilising the general public and healthcare professionals to make use of the online ADR reporting systems. The recorded training sessions are available on the SAHPRA website[87].

The first online reporting system, **Adverse drug reaction and product quality reporting,** is a WHO UMC reporting tool. The link to filing an ADR report on the SAHPRA website leads to the WHO UMC reporting site. This tool allows healthcare professionals (doctors, pharmacists, and other HCPs), patients' legal representatives and patients/medicine user/non-healthcare professionals. To access the actual reporting form, the reporter has to undergo a mandatory registration- or verification-kind of like process (Figure 2). After filing the report, the reporter can review the information provided on the ***Summary*** tab before submitting the report, and can therefore make updates prior to sending. The reporter gets an automated confirmation of their submitted report via an email address provided

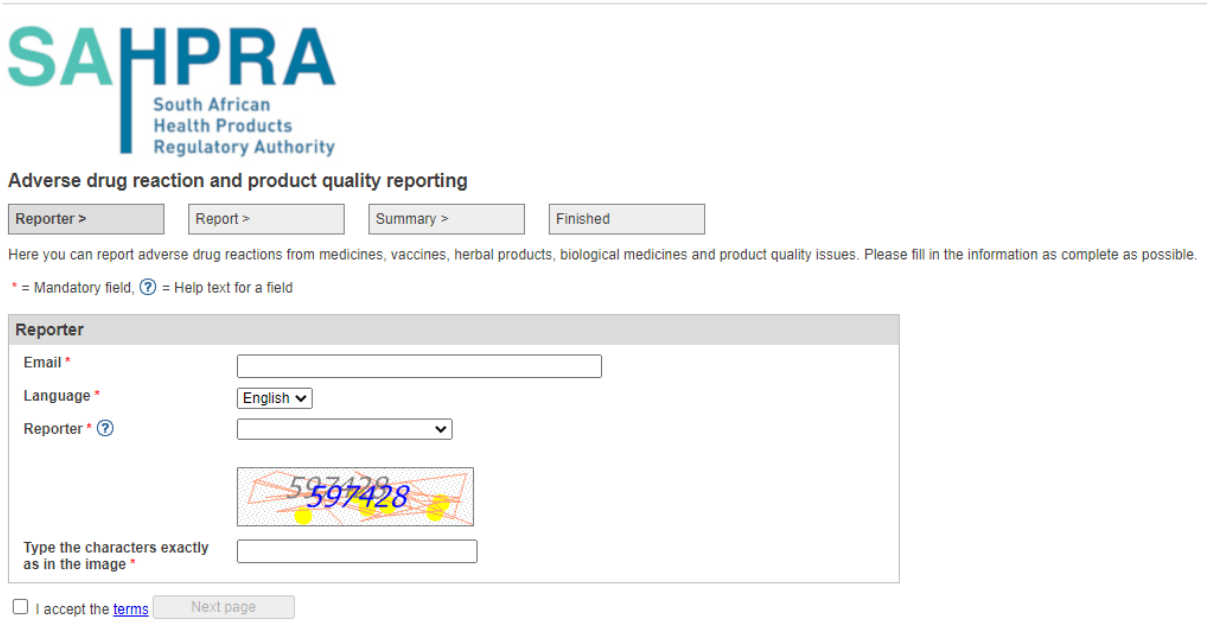

Figure 2. The SAHPRA Adverse Drug Reaction and Product Quality Reporting Screenshot (Source: SAHPRA[88])

The second online reporting system is **The Med Safety App®** (developed by the MHRA), a mobile application developed to engage both patients/consumers and healthcare providers on medicine safety issues[88]. The App is said to be compatible with both latest IOS (minimum version 8.0) and Androids (minimum version 3.0) operating systems, designed to simplify and promote the reporting of suspected ADRs, including adverse events following immunisation (AEFIs) by both the public and healthcare providers. It also allows users to learn about safety news from SAHPRA, thereby creating an awareness of medicines, their potential adverse events and pharmacovigilance[88].

The Med Safety App adopted by SAHPRA was developed by the UK Medicines and Health Regulatory Agency (MHRA) as part of the innovative medicine's initiative Web-RADR project, available to selected regions (i.e., Burkina Faso, Zambia, Armenia, Ghana, Ethiopia, Botswana, Cote d'Ivoire, and Uganda) in collaboration with WHO UMC[88]. As this is a global tool, after downloading the app, one must select the region and language as applicable. To be able to report, one has to login through an account or as a guest. Reports can be created through this app without internet connection. However, to submit the created report, internet connection is required. After submitting

a report, the reporter receives an automated confirmation with a reference number, date of report and reported suspect medicine.

The design of this current study and thus development of a patient/consumer ADR reporting tool precedes the newly introduced SAHPRA online ADR reporting tools, and the latter's functionality and/or feasibility in South Africa is yet to be established. Moreover, during the planning phase of this study, a proposal with a request for collaboration was submitted to SAHPRA in 2018 with subsequent requests for feedback and input in consecutive years (2019, 2020 and early 2021). However, no feedback and/or responses have been received to date.

The study aimed to explore the inclusion of patients/consumers as reporters of ADRs directly to the National PV system to address the current under-reporting challenge. The study looked at developing an ADR reporting tool specifically for patients/consumers. The feasibility of the proposed tool was tested through a pilot study, which was part II of the current study.

Considering the recent developments (use of WHO UMC Web and mobile based reporting systems), the current study (through objectives 2 and 3) also served to create awareness to the general consumers about ADR reporting; assess the feasibility of including consumers in ADR reporting - to determine if consumers can provide the necessary information required for causality assessment and determine the feasibility of consumers to use web/mobile based ADR reporting tool.

2.9 Conclusion

This Chapter presents a comprehensive literature review of post-marketing PV. It outlines the extent of the ADR under-reporting, the challenges and factors involved and the (possible) impact of under-reporting. The inclusion of patients/consumers in suspected ADR reporting directly to the concerned pharmacovigilance agencies was explored, with benefits of and/or improvements noted in those countries where this is currently allowed. The current South African PV situation was examined, whereby the functionality of the PV system is affected by under-reporting. Two recently introduced online ADR reporting systems allow for direct consumer reporting. These have mainly

been established in response to the COVID-19 pandemic but will be useful for all other medicines in future.

The design of this current study and thus development of a patient/consumer ADR reporting tool precedes the newly introduced SAHPRA online ADR reporting tools. The latter's functionality and/or feasibility in South Africa is yet to be established. The current study therefore provides valid and relevant data about the development and implementation of a consumer ADR reporting tool.

CHAPTER 3

RESEARCH DESIGN AND ETHICS

3.1 Research design

This study applied an *Exploratory Sequential Design,* incorporating prospective quantitative and qualitative approaches to answer the research question.

For this study, a direct ADR reporting tool for consumers was developed and its reliability and validity tested (exploratory part of the design, with quantitative data collected) followed by a pilot study to assess the feasibility of the newly developed reporting tool. A quantitative descriptive method was applied to assess the developed tool's reliability and validity while its feasibility was tested by applying the qualitative observation to determine the usability of the tool developed.

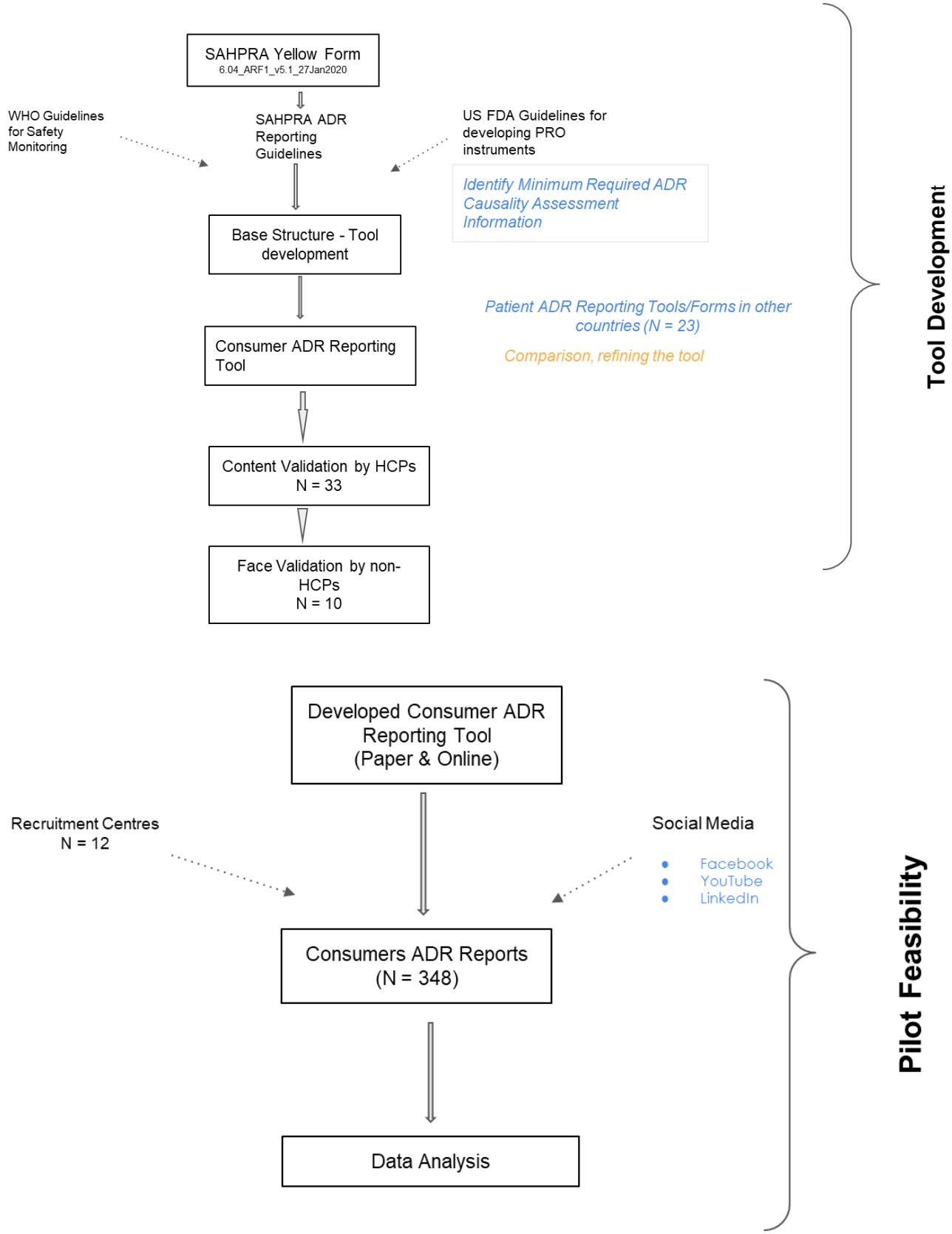

Figure 3: Schematic Presentation of the Study Design

3.2 Ethics

The research protocol, including any supplementary materials such as advertisements, were reviewed and approved by the University of Stellenbosch Health Research Ethics Committee (US HREC, reference number: S18/10/230, Appendix V) and the Ekurhuleni Health District Research Committee (NHRD number: Gp_202007_025, Research project number: 30/06/2020-08, Appendix VI) prior to commencement of the study.

All changes and amendments to the study design were also reviewed and approved by the concerned Research Ethics Committee(s).

CHAPTER 4

TOOL DEVELOPMENT: METHOD AND RESULTS

4.1 Method

4.1.1 Tool design, target population, sample size and sampling method

The SAHPRA Yellow Form, labelled as the adverse drug reaction and quality problem reporting form (healthcare professionals ADR reporting form, 6.04_ARF1_v5.1_27Jan2020) which was the ADR reporting form used at the time of conducting this research study (developing the tool, 2018 – early 2020) was reviewed to identify the minimum information required to conduct a causal assessment of a medicine to a suspected adverse drug reaction. This was done in conjunction with the SAHPRA ADR reporting guidelines[1,2], the WHO guidelines relating to safety monitoring of medicinal products[8] and the US FDA Guidelines for the development of Patient-Reported Outcome instruments regarding the processes of developing patient tools and the recommended terminology to be used in patient facing materials[89]. The information gathered from each of the sources was organised in a simplified format where a comparison on the requirements was conducted. Those requirements found to be common and minimum requirements were used as the base information to design the reporting tool. Information was transcribed into lay language in the new tool, as necessary.

Minimum required information identified from the referenced sources (seven essential components):

- Patient Details
  - Initials
  - Date of Birth or age
  - Sex
  - Race
  - Weight (kg)
  - Height (cm)

  - Pregnancy status and estimation of gestational age at the time of exposure and reaction
  - Allergies
- Suspected Medicine(s)
  - Trade Name (Generic Name if Trade Name is unknown)
  - Route
  - Dose (mg) and Interval
  - Date Started / given
  - Date Stopped
  - Reason for Use
- Adverse Drug Reaction / Product Quality Problem
  - Date and Time of Onset of Reaction
  - Date Reaction Resolved/Duration
  - Description of Adverse Reaction / Product Quality Problem
- Intervention
  - Type of Intervention (Tick all that Apply):
    - No Intervention
    - Intervention Unknown
    - Patient Counselled / Non-Medical Treatment
    - Discontinued Suspect Drug; Replaced with…
    - Decreased Suspected Drug Dosage; New Dose …
    - Treated ADR with …
    - Referred to Hospital: Hospital Name…
    - Other Intervention (e.g., dialysis) …
- Patient Outcomes (Tick all that Apply):
  - ADR Recovered / Resolved – Recovering / Resolving
  - Not Covered / Not Resolved
  - Patient Died: Date of Death …
  - Impairment / Disability – Congenital Anomaly
  - Patient Hospitalised or Hospitalisation Prolonged
  - Life Threatening – Other…
  - ADR Reappeared after restarting suspect drug / similar drug (rechallenge):

    - Yes
    - No
    - Not Done
    - Unknown
- Co-Morbidities / Other Medical Condition(s)
- Details of the Reporter

A search was conducted from the 20th of March 2019 to 31 January 2020 on consumer ADR reporting tools from other countries already having experience with direct consumer reports, for comparison. This was to identify potential pitfalls and ensure that the reporting tool is of international standards. Search resources included the PubMed, Cochrane Library and Medline databases. The terms including the following were applied with different combinations (of note, the word 'form' in the search criteria was not referring to paper forms but both online/electric and print format, as reflected by results from the searches):

- "patient reporting form" – the search returned 3220 items, with only three best matches.
- "consumer reporting form" – the search produced a total of fifty-three hits with only three best matches
- "spontaneous reporting form" – the search produced 142 hits, with only one relevant match which was part of the three best matched under 'patient reporting form'.
- "spontaneous reporting form for patients" – the search produced fifty hits with three best matches, one being part of the first match results under 'patient reporting form'.
- "spontaneous reporting form for consumers" – the search produced zero (0) hits.
- "patient ADR reporting form" – the search produced forty-six hits with three matches. However, only two of these three matches were relevant to the current study and were previously part of the first search results under 'patient reporting form'.
- "adverse drug reaction reporting form for patients" – the search resulted in 135 hits with only one best match which was only synopsis.

- "adverse drug reaction reporting form for consumers" – the search resulted in six hits, two of which were previously included with the initial search. The other articles were not relevant to the current study.
- "pharmacovigilance reporting form for patients" – the search returned forty-eight items, with three best matches which were part of the initial search results under 'patient reporting form'
- "pharmacovigilance reporting form for consumers" – the search resulted in four hits, with two best matches previously included in the results of the first search.

Different combinations of the above searches produced the same best matches of the articles already included in previous search results.

During screening of search results, the reference list of the articles with titles closely related to the current research (best matches) were checked for more information, as well as their appendices to screen the availability of any patient reporting forms. Documents and/or forms not in English were excluded.

Access to websites of regulatory authorities with online patient/consumer reporting was a challenge. The sites with online reporting options were picked up from the different term combinations and visited (see Table 3).

Table 3. Sites with Online Reporting Options which were Accessed during the Study

Website	Comments	Users
German https://nebenwirkungen.pei.de/nw/DE/home/home_node.html	• Language barrier, information not in English • An English option was recently added (mid-2022). However, was unable to access the online reporting option	• Unable to determine
Icelandic Medicines Agency • https://www.serlyfjaskra.is/Aukaverkun/Registration/Registrationsteps.aspx • https://www.ima.is/pharmacovigilance/report-an-adverse-drug-reaction/nr/4337	• Language barrier, information not in English • Two online ADR reporting options available ○ Reporting in humans – not able	• Unable to determine • For patients

	○ to access the reporting site ○ Reporting in Animals	
● The Norwegian Medicines Agency (NOMA) https://iegemiddelverket.no/English ○ Under 'Pharmacovigilance' section, there were no options to report an	● Under 'Pharmacovigilance' section, there were no options to report an adverse event ● English language selected. However, the selection only provided reporting information and no option to fill in the actual report	● Unable to determine
● Finnish Medicines Agency, FiMEA http://www.fimea.fi/laaketurvallisuub_ja_tieto/laakkeidon_turvallisuus/haittavaikutuksista_ilmoittaminen	● Language barrier, information not in English ● Requires login	● Only for HCPs prescribing or dispensing the medicines
● State Agency of Medicines of Latvia	● In Latvia language ● English language available as an option	● Reporting expected from HCPs
● State Medicines Control Agency of Lithuania http://www.vvkt.lt/eng/Lieturiskai/2/337	● Website not found – error message received	● Unable to determine
● The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Italy http://www.urpl.gov.pl/	● Language barrier, information not in English	● Unable to determine
● Danish Medicines Agency http://laegemiddelstyrelsen.dk/da	● Language barrier, not in English	● For both patients and healthcare professionals
● Paul-Ehrlich-Institute, Germany http://www.pei.de/DE/home/de-node.html	● Very limited information available in English ● Primary language is German	● For healthcare professionals
● Federal Institute for Drugs and Medicinal Devices, Germany http://www.bfarm.de/DE/Home/home_node.html	● Language Barrier ● English reporting option available through google translate	● For healthcare professionals
● Health Products Regulatory Authority - Ireland http://www.hpra.il/homepage/about-us/report-an-issue	● No direct online reporting ● Reporting forms are downloaded, completed, and sent back to RA.	● Expected from HCPs prescribing or

	Online reporting option recently made available ● The content of the reporting form was reviewed, minimum required information, format/structure of the reporting form, similarities, and differences with the SAHPRA Yellow Form (content) noted.	dispensing the medicines ● But portal has option to select patient as a reporter
● MHRA Mobile Reporting – Yellow Card – UK https://www.gov.uk/report-problem-medicine-medical-device	● Downloadable app ● only the information under general information, guidelines and first page of the reporting form were accessed and reviewed.	● For both patients and healthcare professionals
● Lareb Mobile Reporting – Yellow Card App http://web-radr.eu/2016/01/29/lareb-launch-the-dutch-version-of-the-web-radr-app/	● Yellow Card App ● The LAREB App ● The HALMED App ○ All require login details ○ Under general section of the webpage, the structure and type of information required for Yellow Card reporting was reviewed	● For both patients and healthcare professionals
● Agence Nationale de Sécurité du Médicament et des Produits de Santé http://ansm.sante.fr/Declarer-un-effet-indesirable/Votre-declaration-concerne-un-medicament-Vous-etes-un-patient-ou-une-association-de-patients	● Form must be downloaded or sent by email – for patients ● Content of form not in English	● For patients
● State Institute for Drug Control Slovakia https://portal.Sukl.sk/eskadra/	● Language barrier, not in English	● Unable to determine
● National Institute of Pharmacy – Hungary http://www.ogyei.gov.hu/	● English option available ● Referral to Eudravigilance reporting system as of 22 November 2017	● Unable to determine
● Agentia Nationala a Medicamentului si a Dispozitiveior Medicale – Romania	● Option to download the form from http://www.anm.ro/anmdm	● Both patients and healthcare professionals are

	• Actual online reporting form in Romanian	encouraged to report
• Bulgarian Drug Agency http://en.bda.bg/index.php?option-com-chronocontact&itemid=52	• English online reporting site – received error messages, page could not be found	Unable to determine
• Republic of Cyprus, Pharmaceutical Services http://www.moh.gov.cy/moh/phs/phs.nsf/dm/yellowcard_en/dm/yellowcard_en?OpenForm	• The content of the online reporting form was reviewed, minimum required information, format/structure of the reporting form, similarities, and differences with the SAHPRA Yellow Form (content) noted.	• For (patients and) Healthcare professionals
• Agenzia Italiana del Farmaco – Italy http://www.agenziafarmaco.gov.it/	• English option contains a selection of contents from the Italian version 'in order to give a general overview of the tasks of the Italian competent authority for drugs'. • Actual patient reporting form was in Italian	• For patients
• Agencia Española del Medicamento y Producto Sanitario http://www.aemps.gob.es/	• Language barrier, not in English	• Unable to determine
• INFARMED. Servicio Nacional de Saúde http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM	• Page could not be accessed, error messages received	• Unable to determine

The type and delivery method of the newly developed tool was then informed by the available ADR reporting options in, and context of, South Africa. With a population of over fifty-five million people in the country, a disparity between the developed (urban to sub-urban) and under-developed (rural poverty stricken) communities, a system/format and/or delivery method to be used should take into consideration the (lack of) availability of resources to enable ADR reporting across the varying socio-economic demographic populations in the country. An understanding of this aspect of

the current population is what informed the decision on the type and method of delivery. The delivery methods planned to be explored therefore included both the paper-based and web-based methods: an electronic – online via a dedicated consumer ADR reporting website; paper - drop-off box at participating healthcare facilities and scanning of the completed paper ADR reporting sending it via WhatsApp®.

4.1.2 Validation of the tool

Reliability and validity concepts were used to evaluate the quality of the developed ADR tool. These parameters indicate how well a method, technique, test, or application measures a variable(s) against an expected predetermined outcome / requirement / functionality, with reliability being about the consistency of a measure, and validity about its accuracy[90].

4.1.2.1 Content Validity

Content validity, defined as the ability of the selected items to reflect the variable of the construct in the measure[91], was performed to determine whether the content of the ADR Reporting tool is appropriate and relevant for the designed purpose. This was achieved through healthcare professionals, independent of the study, with knowledge and experience in ADR causality assessment ascertaining if the proposed information to be collected/solicited from the consumers when reporting an ADR would be appropriate, relevant, and sufficient to enable causality assessment.

i. Sample size and sampling method

To assess whether the content of the ADR Reporting tool is appropriate and relevant for the designed purpose, a non-probabilistic purposive sampling was used to select the expert healthcare professionals with knowledge/experience in ADR reporting and causality assessment. This sampling method enabled effective use of the limited resources and maximised efficiency.

The frequently recommended approach when performing this type of research was used to calculate the sample size: **the subject to item ratio, with a minimum subject to item ratio of 2:1.** This method requires that each item or variable in the ADR

reporting tool be validated by at least 2 subjects (**n=2**). Items referred to the grouped dataset such as consumer details (which would include initials, age, gender etc), medical history, ADR details, suspected medicine details, and reporter details. Non-responders were not replaced. The minimum number healthcare professionals required was ten.

Eligible employees (medical doctors and other healthcare professionals such as safety specialists and pharmacists) of Sanofi-Aventis South Africa (PTY) Ltd and clinical trials Investigators in the Sanofi-Aventis database were the sample as they have current knowledge and experience in reporting and assessing of adverse drug reactions. A generic email was sent to the potential Sanofi-Aventis South Africa (Pty) Ltd participants with a brief introduction to the project, an invitation to participate in the validation process and a survey link. Email addresses of clinical trials investigators were entered onto the CHECKBOX® 6 survey to enable sending of invitations to participate in the study anonymously. The primary researcher's affiliation with Sanofi-Aventis South Africa (PTY) Ltd (the then employer) was anonymised to minimise bias. Responses from the healthcare professionals who completed the validation were anonymised. Though there was no intended bias, the method was prone to selective bias as only healthcare professionals with expertise in this area of study were preselected and invited to participate.

ii. Validation Procedure

The content validation was conducted through a CHECKBOX® 6 survey in English. Each HCP was asked to rate the relevance of including each item on the proposed draft ADR Reporting tool, using a 4-scale Likert scale, with 1 = not relevant, 2 = somewhat relevant, 3 = relevant and 4 = very relevant. An email with a survey link was sent to the selected HCPs' pool with an introduction about the study and a request for their participation in the validation process (Appendix I).

The content validation started on the 12th of April 2019 and concluded on 09 May 2019.

The turnaround time for sending feedback was 2 weeks from the date of receipt of the invite to participate. A reminder was also sent to HCPs at least 3 days prior to the due date of returning the feedback.

4.1.2.2 Face Validity

Face validity, which is the measure of the tools acceptability by consumers based on appearance and apparent attractiveness[91], was performed by consumers, to evaluate the usability of the ADR reporting tool in terms of readability, clearness of the information required as well as clarity of the language used. This will be measured by the ability of consumers to correctly complete an ADR report, using the pre-provided case scenario.

i. Sample size and sampling method

The *subject to item* ratio was used to estimate the sample size for face validation, **with a minimum subject to item ratio of 2:1.** This method requires that each item or variable in the ADR reporting tool be validated by at least 2 subjects (**n=2**), with an overall minimum number of participants required as, 10.

Non-healthcare professional employees of Sanofi-Aventis South Africa® were targeted as the sample frame for inclusion in the face validity process. Due to a very low response rate from the above proposed sample frame, the sample population was extended to recruit participants from a faith-based organisation located in Tembisa, Gauteng Province. The selected sample population was easily accessible to the researcher and conducting a re-test was then feasible.

ii. Validation Procedure

The face validation consisted of a mock case scenario depicting a patient who was given a particular medicine and then experienced an adverse event (Appendix II). Participants were asked to file an ADR report for this event using the newly developed reporting tool and send this via any one of the reporting channels to a mock PV unit recipient. Two of the three reporting channels were explored: online and paper-based (refer to further details below). Online reporting refers to completion of the ADR form

directly on the website which is hosting the developed ADR tool or through the mobile App and submitting it. Paper-based reporting referred to completion of the printed hard copy ADR report form and submitting it through the designated drop-off boxes. The third channel referred to email or fax-2-email submissions.

An email containing an introduction and a link to a CHECKBOX® 6 survey was prepared and sent anonymously (information about the primary researcher anonymised) to the proposed sample of Sanofi-Aventis (Pty) Ltd participants inviting them to participate in the validation process. The email was sent through the organisation's people development support coordinator's mailbox. For members of the faith-based organisation, the introductory information about the study and how to access the survey were printed on a single page and given to the organisation's administrator to distribute anonymously (information about the primary researcher anonymised) to all members after the weekly services. With the require permission, the email addresses where applicable, were sourced from the organisation's database and used to send potential participants an introduction along with the invitation to participate in the current study. As the concept of reporting ADRs and the terminology used may have been new to most non-healthcare professionals, participants were encouraged to have a quick look through the 'general information' section on the tool. The general information section contained brief information on what side effects are, why they should be reported, what information to provide and how to report.

Participants were eligible for inclusion in the study once they have provided consent through the survey, completed the ADR report and submitted it.
Participants were encouraged to complete the ADR report using the information from the case scenario within one session and were requested not to discuss the case scenario with any other person before, during and after doing the validation. Each participant was allowed to complete the validation only once. Once the participant has attempted to complete or completed the validation, they were not allowed to access the survey containing the case scenario again.

Paper reporting referred to participants completing the paper ADR reporting form and submitting it. The ADR reporting tool was also prepared in the paper format, by

transcribing the items required for an ADR report and formatting the structure for legibility and clarity. The other side of the reporting form contained a brief overview on the basics of ADRs and requirements for reporting them. An additional page with the case scenario and the consenting section were included and given to the potential participants. A drop box for submitting the completed reports was prepared and placed in an accessible and convenient area for participants at both organisations where participants were sourced from. Participants were requested to return the consent and case scenario documents when submitting the report. This was to ensure all paper ADR reporting forms are received back from the participants for possible inclusion in the retest phase to measure reliability (see section 4.3.3). Any participant who did not return the original copies of the mock scenario were not eligible for participation in the retest process. The box was checked regularly to collect any reports submitted during the validation period.

The third reporting channel which was not used during the face validity is electronic reporting, which referred to completion of the paper ADR reporting form and sending it via email or fax-2-email. This was due to very limited options to control access to the previous completed ADR reporting forms i.e., if a participant receives the mock scenario via an email and returns the completed ADR reporting form via an email, there was high likelihood that they may revisit the case scenario and/or previously provided responses during the retest period.

The face validation process was conducted from the 20th of September 2019 until the 1st of December 2019.

The online reporting tool was deactivated immediately after completion of the validation process. This validation was then used as a baseline during reliability testing. The survey with the case scenario was also closed and therefore no longer accessible to participants.

4.1.3 Reliability testing

Reliability of the newly developed ADR reporting tool was conducted to assess if the tool could consistently measure an attribute without any major differences over a

certain period. A test-retest method was used, and this process was completed in two separate occasions with the same participants.

Participants who took part in the face validity assessment were again invited to participate in the reliability test process with their participation during face validity used as baseline. After a period of about 6 weeks, participants were re-invited to take part in the re-test procedure. Only participants who completed the first validation (baseline) were re-invited. The same mock case scenario was given to participants to complete the ADR reporting tool.

The retest validation was conducted from the 17th of January 2020 until the 4th of February 2020.

4.2 Data analysis

Continuous variables were summarised as mean (standard deviation) and categorical variables were summarised as count (percent).

4.2.1 Content Validity

Analysis was carried out to evaluate whether the HCPs who participated in the validation of the ADR reporting tool agreed with regard to the relevance of each item included in the tool. This was to assess whether the item should be included in the tool (relevant) or not (irrelevant). Any item given a score of 3 (relevant) or 4 (very relevant) by majority of the validators was regarded as an “agreement” and was included in the tool. Any item with a majority score of 1 (not relevant) or 2 (somewhat relevant) was considered an “agreement” and was therefore to be excluded. Any comments or additional information shared by the validators in support of the scoring were also reviewed and input considered accordingly.

Inter-rater agreement between the HCPs was calculated and Cronbach’s alpha (α) was used to measure the reliability of the agreement.

4.2.2 Face Validity

The usability of the tool was measured in terms of the readability; clearness of information required as well as clarity of the language used. This was assessed by

how the participants completed the ADR report: by being able to identify the information to use in the ADR report, placing information in the relevant sections of the report, and the overall completion of the ADR report whereby the participant had to provide their own information as the reporter under the relevant section.

4.2.3 Reliability

The results of baseline face validation (baseline test, t_0) and re-test (t_1) after six weeks were compared to check consistency and reliability. Results were expected to be very similar.

McNemar Chi-Squared test was then used to determine if the responses at baseline were the same as the responses after six-weeks (re-test).

4.3 Results

The basic ADR report framework was prepared (from the seven elements identified in section 4.1.1) and contained five main elements:

- Consumer's details: initials, date of birth, gender, weigh and, height
- Consumer's medical history: medical history, pregnancy status at the time of experiencing the AE
- ADR details: date and time of onset of AE; date of AE stopped and/or duration of AE, describe the AE experienced in detail
- Suspected medicine(s): name of the medicine(s) suspected of causing AE, route of taking the medicine(s), reason for taking the suspected medicine(s), if you stopped taking the suspected medicine(s), did the AE go away, batch number and expiry date of the suspected medicine(s)
- Reporter details: initials of the reporter, contact details of the reporter, other additional information

A total of twenty-three online reporting tools from different countries were also visited to assess the content and/or type of information they have included in their reporting tools as indicated in Table 3 below.

Table 4. Summary of Consumer and Healthcare Professionals ADR Reporting Sites Visited

Characteristics of ADR Reporting Sites Visited	
Total Number of sites (n)	**23**
Reporting Sites with Language Barrier	13
Reporting Portal not accessible	3
Reporting Options not Available	1
Reporting Sites Accessed, content reviewed	6

Reviewing of the content in these reporting portals included assessment of basic information to be solicited from ADR reporters, the terminology used, how instructions and/or guidance were structured, presented, and worded; mandatory information required, if there was any use of pictograms and the overall size of the report (i.e., number of pages to be completed versus the amount of information to be provided). This information was assessed solely for ensuring that the overall structure and design of the ADR reporting tool being developed is of similar standards, quality and comparable to the global standards. There was no comparison done between reporting tools in different countries, including the SAHPRA Yellow Form. The knowledge gained from these assessments was applied to further enhance the overall structure, design, format, content, and presentation of the ADR tool under development.

Consultations with the IT developers who assisted with the electronic design of the tool were held over a period, briefing the team on the expected design, structure, presentation, and functionality of the drafted reporting tool framework in an electronic format. Testing of the electronic tool was carried out at every stage of development by the IT team until completion, to identify and address any glitches with its functionality. Further tests with non-IT staff members of the IT company were carried out: to assess that all drop-down icons, tabs, forward and backward buttons, checkboxes, in-built calendars, submission buttons etc are functional.

4.3.1 Content Validity by Healthcare Professionals

A total of sixty-six healthcare professionals received the invite and accessed the validation survey link. One healthcare professional attempted to start the validation

and thirty-two did not attempt to start. Only thirty-three healthcare professionals completed the content validation phase of the study.

Table 5. Frequency Results of Content Validation Presented as Number (n) and Percentage (%) of Agreements per Item

Likert Scale	**Not relevant (1)**	**Somewhat relevant (2)**	**Relevant (3)**	**Extremely relevant (4)**	**Missing**	**Total Responses Received**
Consumer initials (n)*	14	6	10	3	0	33
(%)**	42.4%	18.2%	30.3%	9.1%	0	100%
Consumer date of birth	3	6	12	12	0	33
	9.0%	18.2%	36.4%	36.4%	0	100%
Gender	0	4	13	16	0	33
	0.0%	12.1%	39.4%	48.5%	0	100%
Weight	1	6	12	14	0	33
	3.0%	18.2%	36.4%	42.4%	0	100%
Height	6	8	13	6	0	33
	18.2%	24.2%	39.4%	18.2%	0	100%
If female, pregnancy at the time of onset of event	0	1	3	29	0	33
	0.0%	3.0%	9.1%	87.9%	0	100%
Medical history	1	3	6	23	0	33
	3.0%	9.1%	18.2%	69.7%	0	100%
Date and time of onset of AE	3	0	4	26	0	33
	9.1%	0.0%	12.1%	78.8%	0	100%
Date of AE stopped and/or duration of the AE	0	1	6	26	0	33
	0.0%	3.0%	18.2%	78.8%	0	100%
Describe the adverse event/reaction experience in detail including actions taken in response to the AE	0	2	11	20	0	33
	0.0%	6.1%	33.3%	60.6%	0	100%

Name of medicine suspected of causing the AE (how often the medicine is taken)	0 0.0%	0 0.0%	3 9.1%	28 84.8%	2 6.1%	31 100%
Route of taking the medicine	0 0.0%	1 3.0%	10 30.3%	20 60.6%	2 6.1%	31 100%
Duration of taking the suspected medicine(s) (i.e., Date started to date stopped if no longer taking the medicine)	1 3.0%	0 0.0%	6 18.2%	24 72.7%	2 6.1%	31 100%
Dose and Frequency of taking the medicine(s)	1 3.0%	2 6.1%	10 30.3%	18 54.5%	2 6.1%	31 100%
Reason for taking the medicine	1 3.0%	0 0.0%	5 15.2%	25 75.7%	2 6.1%	31 100%
If you stopped taking the suspected medicine(s), did the AE go away	0 0.0%	3 9.1%	6 18.2%	22 66.7%	2 6.0%	31 100%
Batch number and expiry date of the suspected medicine(s)	1 3.0%	4 12.1%	16 48.5%	10 30.3%	2 6.1%	31 100%
Other additional information	5 15.2%	7 21.1%	14 42.4%	5 15.2%	2 6.1%	31 100%

Information about the reporter of the Adverse Event	1 3.0%	6 18.2%	14 42.4%	10 30.3%	2 6.1%	31 100%
Contact details of the Reporter	5 15.2%	3 9.1%	16 48.4%	7 21.2%	2 6.1%	31 100%

*(n) = number of observations
**(%) = number of observations in percentage

Although the validation results show conflicting information regarding the relevance of including the consumer initials (irrelevant by >60% agreements) and reporter details (relevant by > 69% agreements), this information is part of the mandatory or minimum required information to meet the criteria of a reportable ADR.

The consumer pregnancy status, medical history, date and time of AE onset, date and time AE stopped/duration of AE and description of AE including action taken were each rated by majority of healthcare professionals as relevant information to collect with inter-agreement rates of above 87% on each item. No missing values were found on these items (Table 5).

Additional comments on requiring date and time of onset of AE from one of the respondents stated:
"*I don't think it makes sense for the exact date and time to be stipulated, because it forces you to provide info that may be inaccurate. "Approximately 5 years ago/ last week / a couple of months" is different to an exact date and time, which the tool currently forces one to give. It would be better left open ended surely, but with a guide that says if you can give exact info to the date and time, this would be most helpful*".

"*In addition, some conditions require a polypharmacy of meds. I have seen scripts with thirteen or more products on for people who suffer heart conditions. Is it not possible to ask that you list a condition, and then under that add the meds, instead of having to retype the same info repeatedly, especially if they were all prescribed for same condition and at the same time?" Respondent 1.*

Details of the suspected medicine(s) items (name of suspected medicine, route, duration, dose and frequency, reason for taking the suspected medicine, and if you stopped taking the suspected medicine did the AE go away) also received a majority inter-agreement rating of over 80% on each item as relevant, with a 6.1% non-response rate. Assuming a threshold of 10% in missing values, a 6.1% missing value did not cause concern. The results to these items could still be maintained since missing values did not exceed the threshold of 10%. Should the latter have happened, a follow-up would have been conducted to ensure validity of results.

There was also a 3% rating on duration of taking the suspected medicine(s) as an irrelevant item to include.

The batch number and expiry date of the suspected medicine(s) had a majority of healthcare professionals rating of 79.3% as irrelevant information to include. However, 2 of 33 missing values of non-response rate were depicted from this item.

Other additional information was also found to be relevant by 57.6% of the healthcare professionals in the majority compared to 36.3% who do not find this information as relevant to the tool. This item also had a 6.1% missing value or non-response.

According to Cronbach's alpha (α) criteria, if the α – value is above 70%[92], then there is internal consistency. In this tool, the α – values for all variables were above 70%.

Generally, all items included in the tool combined gave the average α – value of 87,6%, indicating that the average inter-item correlation was constant (Table 6). Therefore, items included in this tool can be used to collect data that could provide the expected/required results. The tool is thus found to be reliable.

It is often helpful to assess the influence/impact of the removal of a particular variable on the alpha values, as a considerable impact may be indicative of that variable not necessarily being relevant in the tool. Sensitivity testing was carried out on the gender, weight, consumer, and reporter details to determine their impact on the tool.

Table 6. Results for the Measure of Reliability of Agreement amongst Healthcare Professionals

No.	Variables	N*	Cronbach's alpha (α)
1	Consumer initials	33	81.6%
2	Consumer date of birth	33	80.0%
3	Gender	33	81.3%
4	Weight (kg)	33	80.4%
5	Height (cm)	33	80.3%
6	If female, pregnancy at the time of onset of event	33	79.7%
7	Medical history	33	79.0%
8	Date and time of onset of AE	33	78.7%
9	Date of AE stopped and/or duration of AE	33	77.9%
10	Describe the AE experienced in detail	33	78.5%
11	Name of the medicine(s) suspected of causing AE	31	79.6%
12	Route of taking the medicine(s)	31	79.7%
13	Duration of taking the suspected medicine(s)	31	78.5%
14	Dose and Frequency of taking the medicine(s)	31	77.9%
15	Reason for taking the medicine(s)	31	80.3%
16	If you stopped taking the suspected medicine(s), did the AE go away?	31	79.9%
17	Batch number and expiry date of the suspected medicine(s)	31	79.3%
18	Other additional information	31	79.9%
19	Initials of the reporter	31	78.9%
20	Contact details of the reporter	31	80.9%
	Cronbach's Alpha (α)	0.8046856	87.6%

*Number of healthcare professionals who participated in the content validity part of the study

Removal of gender, weight, consumer details and reporter details from the analysis resulted in an α – value of 88.5%, 87.7%, 88.3% and 88.5% with a 0.9%, 0.1%, 0.7% and 0.9% improvement on Cronbach's alpha, respectively. Therefore, the remaining items could still be used to collect data that can enable causality assessment (i.e., the tool could still yield reliable and valid results).

4.3.2 Face Validity Results from Consumer Participants

A total of fourteen consumers participated in the initial stage of the face validation process. According to the information provided under the reporter's profession section, 25% of the participants are in the science and medical related professions. Apart from 14.3% (2) participants, all other 12 (85.7%) participants used the information from the case scenario to complete the ADR report and were also able to complete the reporter details section using their own details, as expected. The two participants also completed all sections correctly. However, the information provided in the consumer details section was not from the case scenario. Participants seem to have provided their own information and thus, provided real ADR reports. Though they did not follow the instructions with regard to using the case scenario to complete an ADR report, the two participants were included in the repeat test as their input was considered valuable.

Across all participants, information was correctly placed in the relevant sections.

4.3.3 Reliability Test Outcomes from the Consumer Participants

Of the fourteen participants who participated in the initial stage of the face validation process, only ten participants completed the repeat test validation stage. This included the two participants who submitted the ADR report with their own information.

There was no change between the initial test (t_0) and the repeat test (re-test, t_1) on the Reporter's Initials variable amongst the 8 consumer participants, whereas the remaining 2 participants provided incorrect results from what was expected during the initial and repeat test. However, no significant difference was detected, with $p = 0.50$ (Table 7).

Table 7. Results of the Consumer Participants Relating to the Reporter's Initials

		Reporter's Initials Re-test		
		Correct*	Incorrect**	Total
Reporter's Initials Test	Correct*	8	0	8
	Incorrect**	2	0	2
	Total	10	0	10
	Chi-square	0.16		
	p-value	0.50		

*Correct – indicates that correct information required for the section was provided
**Incorrect – indicates that information provided for this section was incorrect

For all the other items, there was no significant difference detected in the responses given at the initial test and at the repeat test, with *p*-value of 1.00 (The exact McNemar *P*-value is reported) (Table 8).

Table 8. Measure of Change in responses for All Other Items in the ADR Tool from the Consumer Participants

Item	*p*-value
Reporter Email Address	-*
Reporter phone number	1.00
Patient initials	1.00
Patient Gender	1.00
Age (years)	1.00
Patient weight	1.00
Allergies	1.00
Medical conditions	1.00
Side effects start date	1.00
Side effects end date	1.00
Side Effects Adverse Reactions Experienced	1.00
Side effect actions taken	1.00
Suspected Medication	1.00
Amount taken and how often	1.00
How did you take the medicine	1.00
For which disease	1.00
Medicine start date	1.00
Medicine end date	1.00

* None of the participants provided an email address during the initial and repeat testing.

4.3.4 Summary of the validation and reliability results

The tool had internal constancy as majority of the items had $\alpha > 0,70$ indicating that there was internal consistency in the items included in the tool.

There was a high inter-agreement rate between healthcare professionals' responses where majority indicated that *Consumer date of birth, Gender, Weight (kg), Height (cm), If female, pregnancy at the time of onset of event, Medical history, Date and time of onset of AE, Date of AE stopped and/or duration of AE, Describe the AE experienced in details, Name of the medicine(s) suspected of causing AE, Route of*

taking the medicine(s), Duration of taking the suspected medicine(s), Reason for taking the medicine(s), Reason for taking the medicine(s), If you stopped taking the suspected medicine(s), did the AE go away?, Other additional information, Initials of the reporter, Contact details of the reporter were relevant information to be collected as data entries. The Batch number and expiry date of the suspected medicine(s) were rated as irrelevant to include.

There was no significant difference on the results between the initial test (t_0)) and repeat test (re-test, t_1) responses for all consumer participants, and therefore providing the evidence required to confirm the tool as acceptable and reliable to accurately collect safety information which will enable ADR causality assessment, over time.

CHAPTER 5

PILOT FEASIBILITY STUDY: METHOD AND RESULTS

5.1 Feasibility Method

The newly developed ADR reporting tool was assessed to explore its usability and practicality through a pilot study in a real-life setting. Feasibility testing in this study was therefore regarded as the ease with which the ADR reporting tool could be used, how practical it is to access the tool and submit the report through it

The feasibility of the ADR reporting tool was then conducted by assessing:

(i) the completeness of data submitted by participants to enable causality assessment. The following criteria were applied to reports with:

- 0 – 20% data completeness = poor
- 21 – 40% = below average
- 41 - 60% = average
- 61 – 80% = good
- 81 – 100% = excellent

Reports with 'good' and 'excellent' data completeness were accepted for further analysis as listed in points below.

The percentages above are estimates based on the amount of data required as minimum information that would enable ADR causality assessment. According to WHO guidelines on development of a reporting system for the general public[93], the following minimum information is critical to constitute a valid ADR report:

i. Reporter, at least the name or initials
ii. The consumer or patient, including initials, age, and gender as well as a brief medical history
iii. At least one adverse reaction
iv. At least one suspected medicine, including the name, doses, route of administration, a start and stop date

This amount of information constitutes less than 50% of the information required in the SAHPRA Yellow Form (ADR reporting form for healthcare professionals), used as a basis, and point of reference for this study. This was estimated by counting the number of items set out as critical minimum information in the WHO guideline for a report to be valid versus the number of items in the SAHPRA Yellow Form. It is therefore assumed that consumers can provide more information than the required minimum.

The method used to estimate the sample size as well as outlining the criteria for ADRs to be included in the study analysis was based and supported by methods used in similar studies below.

A study to pilot-test the Front-Line SMS mobile phone-based tool for reporting of adverse events during vaccination in Cambodia recruited 184 participants and had a response rate of 71.7%. The outcome of the study showed that the tool can be useful for reporting of ADRs by patients and healthcare professionals[29]. Of the 837 participants in a study to develop a systematic generic method of enabling patients to report symptoms they suspected to be due to a particular medicine, 88.6% (742) reported at least one symptom, majority of which were considered as possibly or probably related to the medicines being studied. The study outcome shows willingness of patients to report ADRs as well an understanding of what to report and how to report[65]. During the Influenza A (H1N1) Vaccines mass immunisation campaign in France between 2009 and 2010, 1006 of the 4746 reports of ADRs received were from patients. There were no major quality issues found with these reports, the profile of the ADRs reported was consistent with that of healthcare professionals and the reports contributed to a total of 21.2% increase of ADR reports received[64]. The above are examples of how patients or consumers can provide required information and more to constitute a valid report and contribute to quality PV data. Thus, reports with more than 60% completed data that include the required minimum

information can be useful for ADR causality assessment and therefore classified as “good” or “excellent”.

It was acknowledged that some consumers may provide information that could be more than 80% complete (lots of information) but omit to provide information on one of the critical required items, thus making the report invalid/not usable. For example, a report could be received from a non-medical (lay person) person explaining in detail symptoms in a relative treated for diabetes, but without giving any information about the medicine taken. This report could be 80% complete but lacks one of the minimum criteria (suspected medicine) which then makes the report not usable. Assessment of the completeness of data therefore included assessing the availability of the minimum criteria as outlined above.

For this tool to be defined as feasible, it was assumed that ≥ 80% of the participants would provide ADR reports that would fall under the ‘good’ to ‘excellent’ criteria (i.e., 61% – 100%), this percentage would be estimated with a desired precision of ±5%. In addition, the lower limit of the confidence interval around this estimate would have to be above 70% for the tool to be accepted as being feasible[92].

(ii) the seriousness of the reported ADRs. The CIOMS criteria for determining the seriousness of the ADR was applied, and where additional information was available, the impact of the ADR on the consumers’ ability to carry on their day-to-day activities was also considered, in line with the ICH E2A guideline on the definition and classification of seriousness of the ADR[94]:

- *A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:*
  - *results in death,*
  - *is life-threatening,*

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the

event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
- ***results in persistent or significant disability/incapacity, or***
- *is a congenital anomaly/birth defect.*

(iii) the expectedness of the reported ADRs. The ICH E2A ADR reporting criteria were used for the definition of expectedness as follows:

- An adverse reaction, the nature or severity of which is not consistent with the applicable approved product information.

5.2 Sample size and sampling method

Participants for the pilot feasibility study were recruited from public primary and regional healthcare facilities in Tembisa (N = 7), private doctors' rooms (N = 3) and pharmacy outlets in Midrand and Tembisa (N = 2), both in the Gauteng Province. Other targeted areas included Kempton Park and Tembisa regional hospital. These parts of the Gauteng Province were targeted, as they accommodate diverse groups of citizens representing the demographics of medicine consumers within South Africa. However, approval or consent to recruit participants from these other targeted areas (Kempton Park and Tembisa regional hospital) were not obtained from the facilities, the facilities did not respond to the requests submitted.

Participants were also passively recruited through the online advertisements in social media. In instances whereby a consumer was unable to complete the ADR reporting tool, a parent, legal guardian, or caregiver could complete and submit the report.

Due to the nature of the feasibility study, consumers (and parents / legal guardians) who are not able to read and/or write English (language of instruction used in the study) were excluded from participation in the study.

For the purposes of this study, a person with an ADR is defined as any person who was dispensed or bought a medicine (including over-the-counter medicines like herbal

substances and health supplements) for a certain condition, and when used, that person experiences a suspected adverse reaction.

5.2.1 Sample Size Calculation

The following were considered for sample size calculation:

a. With an anticipated 80% of participants providing reports with completeness of data that are classified as 'good' or 'excellent' reports, with a desired precision of ± 5%, 309 participants were required.

b. The lower limit of the 95% confidence interval (CI) around the estimate of the percent of participants providing reports with completeness of data that are classified as 'good' or 'excellent' to be above 70% for the tool to be considered feasible; setting the null hypothesis as 70% and alternative hypothesis as 80%, significance level of 5% and power of 80%, 137 participants were required.

   Sample size estimation was done using WINPEPI (http://www.brixtonhealth.com/pepi4windows.html)

Convenience or consecutive sampling and time saturation were used as the sampling method for this part of the study. Consumers wishing to participate were consecutively selected in order of appearance according to their convenience to complete the online reporting form or appearance at any of the selected participating facilities or through the online reporting portal.

5.2.2 Pilot Feasibility Study Procedure

The following media were considered and used for posting advertisements to inform consumers and the public about the pilot study and invite them for participation:

- Advertisement pamphlets (paper print, see Appendix III)
- Facebook page (page ID 101887241401039) Side Effects Reporting | Facebook
- YouTube® – deactivated after study completion
- LinkedIn® - deactivated after study completion

The advertisements contained a brief overview of what pharmacovigilance is, its role, how it works and who the stakeholders are. The paper ADR reporting forms (Appendix IV) for consumers were also distributed to participating doctors' rooms, pharmacy outlets and healthcare facilities along with the advertisement materials. Healthcare professionals at these facilities were requested to make consumers aware of the pilot study.

An informed consent form was included in the online ADR reporting tool and paper form for participants to complete prior to sending the report. On the online ADR reporting tool, the consent statement was included in the landing page of the ADR report page, to ensure participants provide consent prior to submitting an ADR report. On the paper ADR reporting for, the consenting statement was included on the same page at the top part of the ADR report. The completed consent was to be received along with the ADR report from participants.

Since the pilot feasibility study had a dual function of the actual ADR reporting and to test the feasibility in a real-life setting, permission was also sought from the reporters if they agree that the information they provide be used for research purposes as well as possible re-contact for further information where necessary.

To accommodate the diverse participant population, the following reporting channels were planned to be explored during the pilot study:

- Electronic – fax-to-email or email
- Online via a dedicated consumer ADR reporting website
- Drop-off box at participating healthcare facilities
- Scanning of the completed paper ADR reporting sending it via WhatsApp®, fax-to-email or email

5.2.3 Inclusion and Exclusion of Participants in the Study

Due to the nature of the study, the inclusion/exclusion criteria were retrospectively applied on the reports that were submitted (i.e., the tool is available in the public domain and any consumer with access can complete and submit the report. The inclusion/exclusion criteria were then applied on the actual reports during the review

and analyses stage). Consumers were eligible for inclusion in the study once they have completed the ADR report and sent it via one of the reporting channels. Special codes known as consumer report numbers were automatically issued for each report submitted via the online reporting tool.

Reports were included in the analysis if they met the 'good to excellent' data completeness criteria as outlined in section 4.3.4 (i) above.

Exclusion criteria for the reports included:

- Data completeness less than 60% as outlined in section 4.3.4 (i) above
- ADR reports which did not contain any suspected medicine (i.e., no information on any medicine that could have been taken under the suspected medicine section).
- ADR reports which did not list any ADR. In these instances, the report contained the current condition and the treatment therapy included under suspected medicine(s) section.

5.3 Data Analysis

The pilot phase of the study was conducted over a period of 1 year and 3 months. Thirty-four potential recruitment centres were identified and invited to participate in the study (by allowing recruitment of consumers from their centres to report ADRs using the newly developed tool). This included nineteen private doctors' practices, six healthcare centres/clinics, eight pharmacies and one regional hospital. Only 14.7% (four private doctors and one pharmacy) responded to the invite and agreed to participate in the study.

Recruitment posters, study information pamphlets as well as paper ADR forms were distributed to the participating centres from 12 February 2020. At each centre, the centre administrator(s)/receptions/main contact person were briefly orientated about the study requirements and processes (i.e., informed on what the study is about, ADR reporting requirements and reporting process). Their main role was to show patients/consumers coming to their centres the study poster and pamphlets. A drop-off box was also provided at each centre for consumers to drop their completed ADR

forms in. The drop-boxes were clearly marked for the purposes of the study and placed in a visible, yet safe spot within the centres. Distribution of these study materials and brief orientation at the centres was completed by 06 March 2020. Within 2 weeks, the country went on hard lock-down (level 5 lockdown with movement restrictions).

To aid with recruitment to meet the recruitment target and minimise the impact on the recruitment timeline delays, four primary healthcare facilities and three provincial healthcare facilities in Ekurhuleni were added as recruitment centres (relevant approvals from ethics and departments were obtained). At least three times a week, the primary researcher went to one or two centres per day to create awareness about pharmacovigilance amongst patients, its importance, requirements, and processes as well as making them aware of the tool which was under testing as part of the study. Consumers would then be handed pamphlets with study and reporting information. Interested consumers would request and be provided with the reporting forms and shown the drop-off boxes – only few consumers agreed to take the paper ADR forms, citing the spread of COVID-19 infection as a concern for not preferring the paper-based ADR forms. Most of these healthcare centres are equipped with wi-fi which enabled easy online access. Although network coverage was often a challenge, especially while patients/consumers were still waiting outside the healthcare facilities. However, none of the paper ADR forms were returned. Most of the young and middle-aged consumers preferred assistance with navigating to the online ADR reporting tool using their smartphones. The elderly consumers would mostly request assistance with actual completion of the online ADR reporting tool. The centres allowed the researcher to address patients/consumers in their reception and/or waiting areas. Some (numbers not recorded) of the healthcare services providers took interest in the project, requested more information, and wanted to know how best they could assist and support the research (creating awareness to patients/consumers).

Language of instruction during awareness sessions was a mix between IsiZulu, seTswana (with a mix of seSotho and sePedi dialects) and English. English remained the language of instruction when completing the ADR tool. Responses were given using the consumers' preferred language (the language that the consumer used when asking a question). Recruitment ended when the target number of reports was met in May 2021.

There were no paper-based ADR forms received and all reports received in the study were through the online reporting tool. Data were then extracted from this tool by exporting data onto an Excel spreadsheet to create a database for analysis, allowing for all information to be grouped together for individual and group classification, report assessment and analysis. This was carried out in four steps:

5.3.1 Deconstruction of data

Deconstruction of data involved dataset pairing of reported ADRs to suspected medicines. This process included the review of the suspected medicines' package inserts (PIs) to check if the reported ADR was listed, therefore expected. In addition to the PI, the South African Medicines Formulary (SAMF) and the Monthly Index of Medical Specialities (MIMS) were used as references in instances where the suspected medicines PI could not be located. The international non-proprietary names (INN) of the suspected medicines were also added (as applicable) to aid with data analyses.

Using the INN, medicines were classified according to their therapeutic groups.

5.3.2 Coding Process

Prior to coding of the data, incomplete (i.e., missing of crucial information that would enable the conduct of the causality assessment such as suspected medicine/s), and duplicate reports were identified and excluded. Identification of duplicate reports was carried out using certain characteristics such as gender, age, date of birth and date of exposure to medicine. Reports with complete required minimum information were then de-identified. The de-identification step involved manual search of all data to check and remove any personal identifying information that would have been missed in the earlier processes.

Coding of ADRs was conducted manually using the latest version of the MedDRA® medical coding dictionary (MedDRA® Web-Based Browser, version 3.0 updated August 2018) by the primary researcher. The reported terms (the term as reported by the consumer) was used in the coding process. The medical coding involved searching

for an appropriate match to the reported term within the System Organ Class (SOC), the lowest level term (LLT) in the hierarchy of MedDRA and assigned the MedDRA preferred term (PT).

According to MedDRA.org[95], "the 27 System Organ Classes (SOCs) represent parallel axes that are not mutually exclusive. This characteristic, called "multiaxiality," allows a term to be represented in more than one SOC and to be grouped by different classifications (e.g., by aetiology or manifestation site), allowing retrieval and presentation via different data sets.

Each MedDRA Preferred Term is assigned a primary hierarchy and, in some cases, secondary hierarchies. For example, the PT *Influenza* represents an important respiratory tract problem as well as an infection. For this reason, each PT is assigned to a primary SOC, but may also be assigned to one or more secondary SOCs. The PT *Influenza* is primary to the SOC *Infections and infestations*, but this PT is also secondary to the SOC *Respiratory, thoracic, and mediastinal disorders"*.

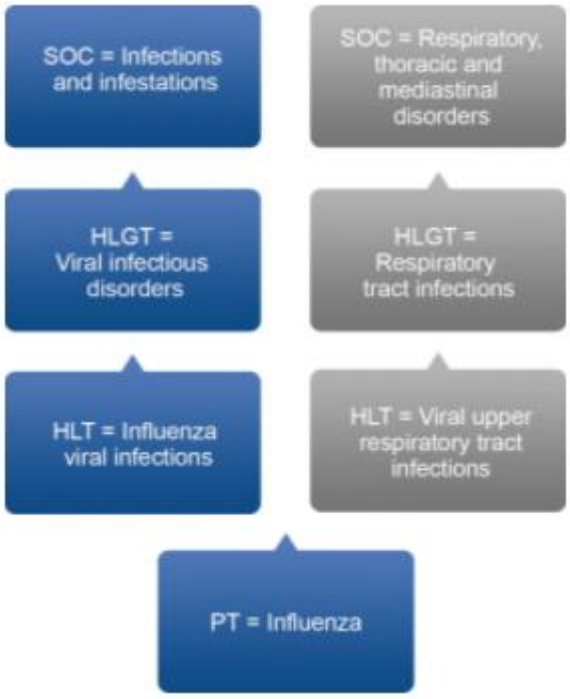

Figure 4. An Example of Multiaxiality Using the Primary Term Influenza (Source: https://www.meddra.org/multiaxiality)

The search for each reported term provided at least 1 to 4 different types of results (multiaxiality):

- **Exact Match** – the reported term used in the search matches at least 1 or more LLTs in MedDRA
- **Lexical Variant** – mostly in cases whereby the reported and/or search term consist of two words or more. The construction of the term in the reported/search term is slightly different to the LLT(s) in MedDRA. For example, the reported/search term '*skin irritation'* would result in one lexical variant, ***'irritation skin'***.

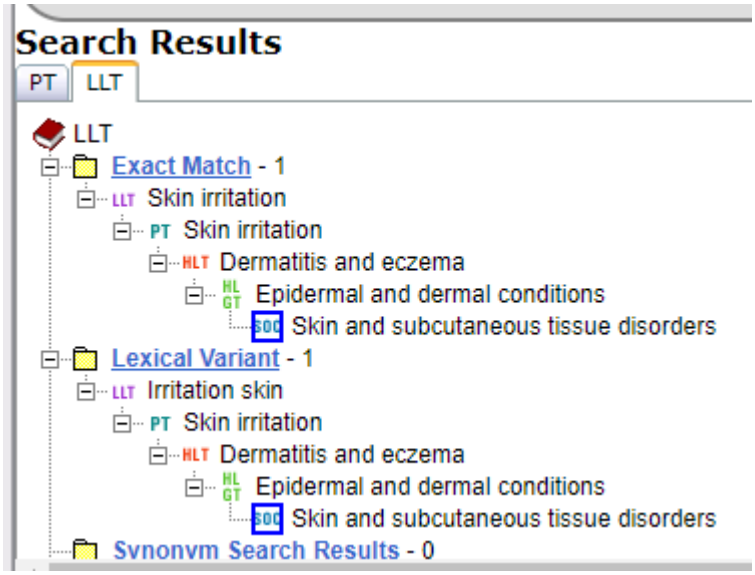

Figure 5. An Example of a Lexical Variant using Skin Irritation as the Search Term

- **Synonym Search Results** – results with synonymous term(s) to the reported/search term
- **Contains Search Results** – results containing at the least one term used in the reported/search term. For example, the term constipation would return 15 'Contains search results'.

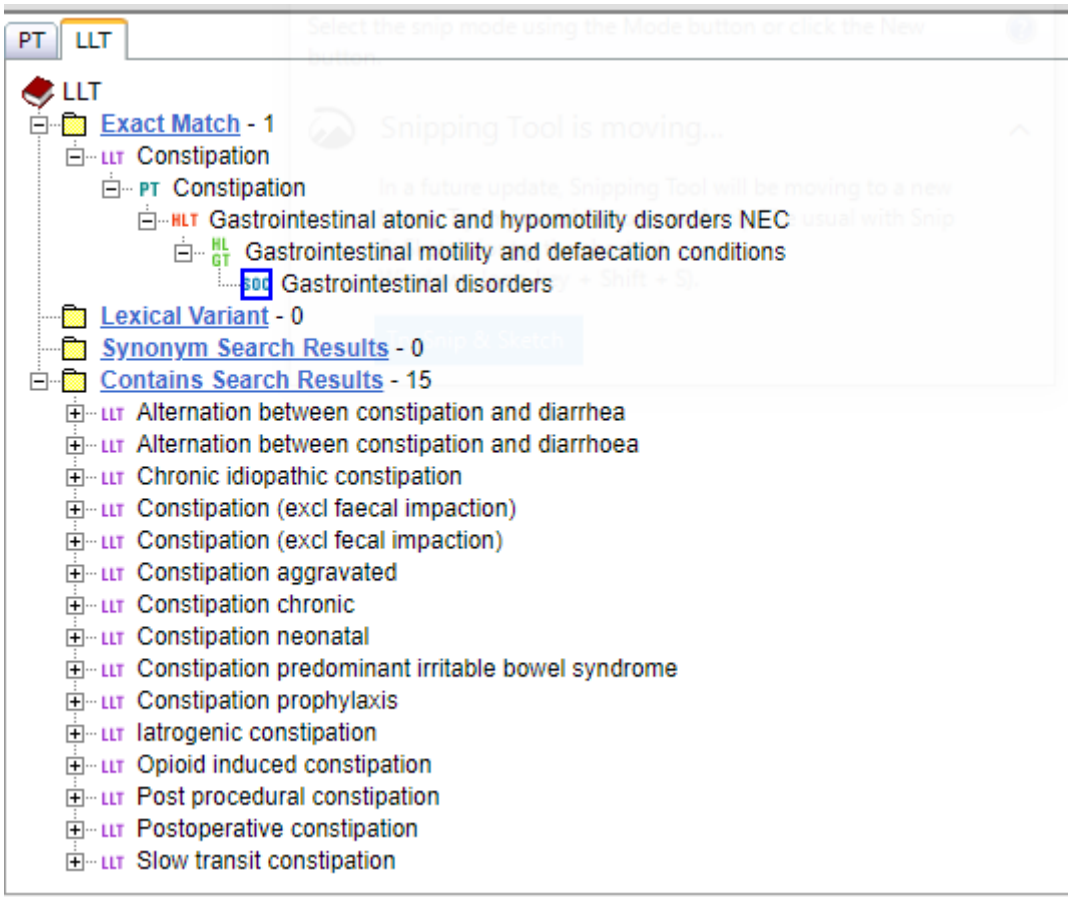

Figure 6. MedDRA Screenshot Showing the 4 Possible Types of Results for Constipation

In instances where the exact match would contain no results, the *lexical variant* would be considered first for classifying the ADR, and/or the *contains search results* term if the lexical variant also returns no results.

In cases where the reported terms returned no results at all, a variation of the reported term was used as a search term. For example, '*skin peeling off*' yielded no results. '*Skin peeling'* was then used as a search term, yielding one exact match (LLT – skin peeling, PT – skin exfoliation). The exact match and/or lexical variant of the search term and/or a closely related 'contains search' results would be selected to continue coding the reported term as applicable. Variations due to spelling were also noted under '*Contains Search Results'* as shown in Figure 7 below.

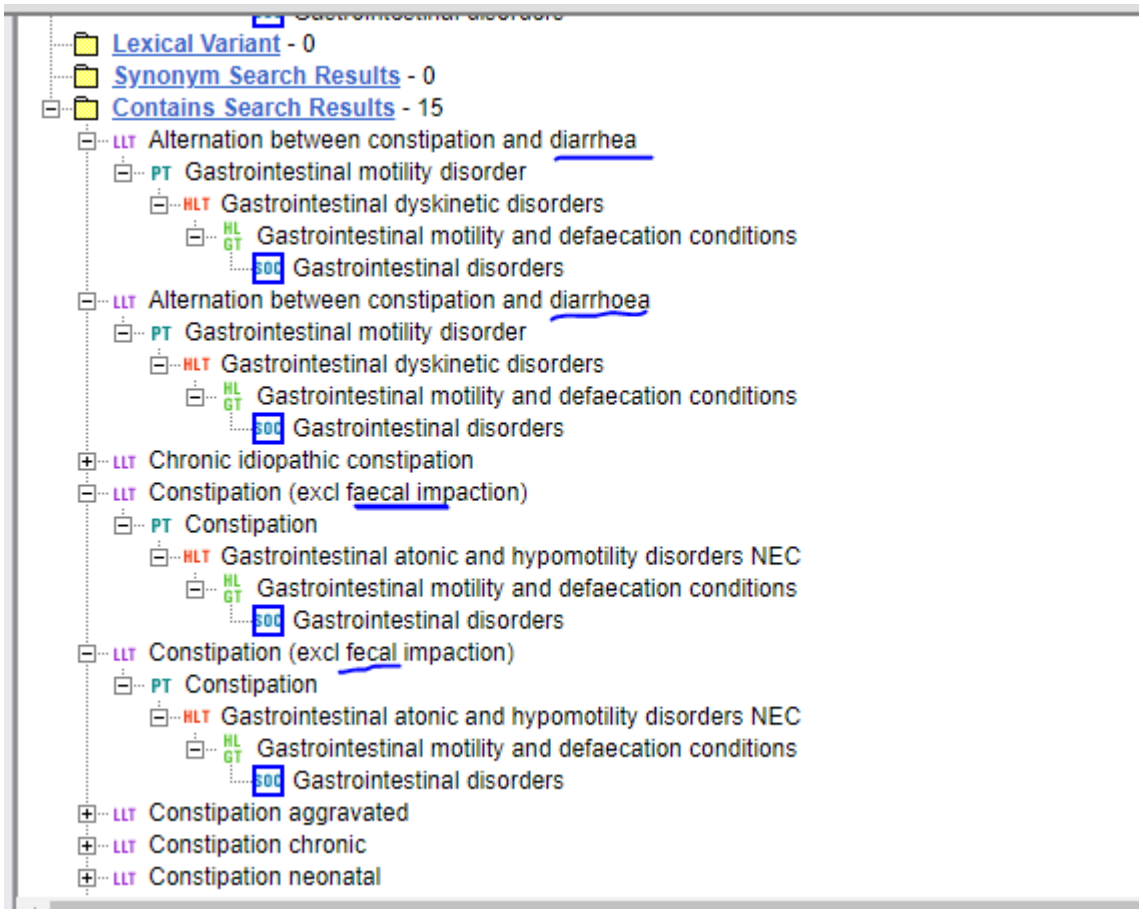

Figure 7. An Example of Results for Search Terms with Variant Spellings

Certain LLTs would be associated with one PT and more than one Higher Level Term and the resulting SOC, such as ‘hot flushes’ and ‘Tight Chest’ as examples from the ADR reports received (Figure 8 and Figure 9).

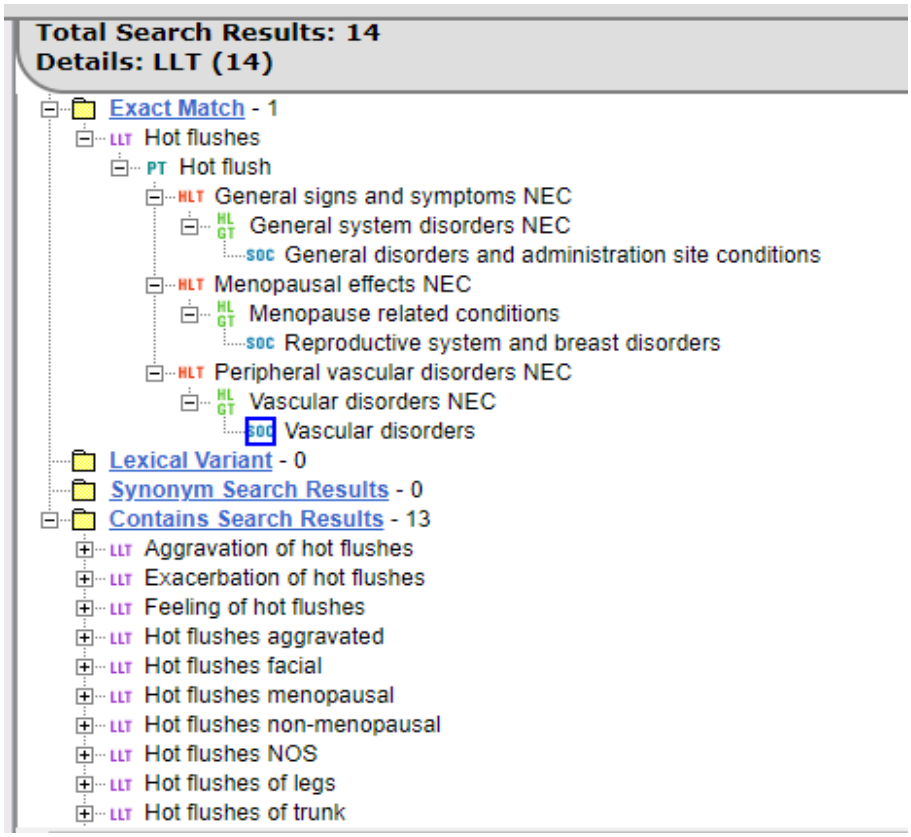

Figure 8. Example 1 of Search Term Yielding Results with more than one HLT and corresponding SOCs, Search Term used ‘Hot Flushes’.

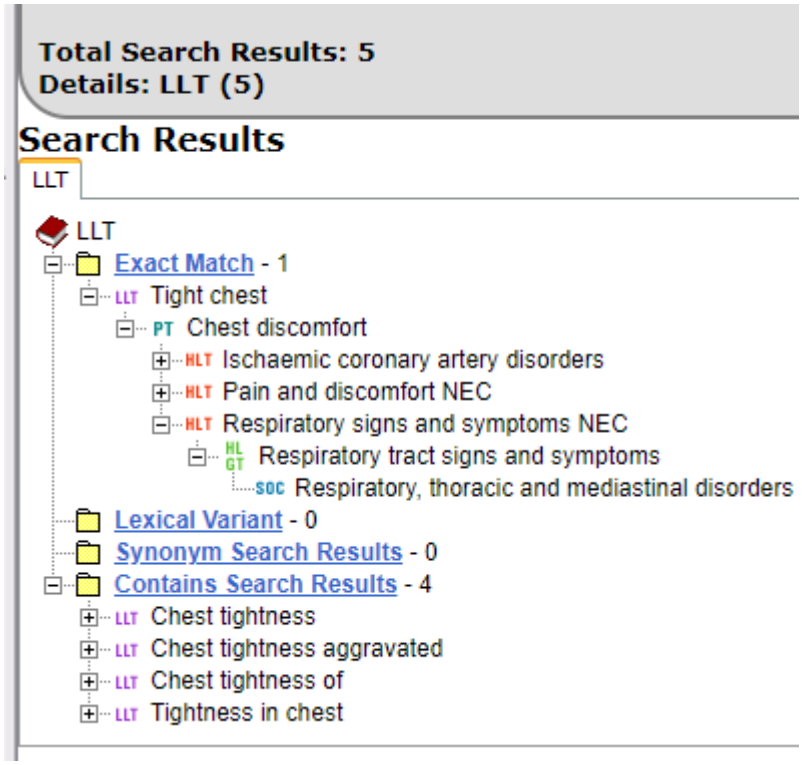

Figure 9. Example 2 of Search Term Yielding Results with more than one HLT and corresponding SOCs, Search Term used ‘Tight Chest’.

5.3.3 Interpretation of data

Reports from HCPs and related fields (i.e., Clinical Trials Study Coordinator and Clinical Trials Assistant) were compared to those of non-HCPs (consumers/caregivers etc) in terms of completeness, quality and detailing of information. Assessment on expectedness of ADRs, identification of frequently reported ADRs, suspected medicine classes commonly reported with ADRs and the system organ class most implicated in ADRs was carried out. The number of ADR reports with suspected medicines considered new in the market was compared with those from well-established medicines. This was to check if there was more intense reporting with newly registered medicines as compared to those that have been in the market for longer periods. According to FDA guidelines, ADR reports are required to be submitted quarterly for the first 3 years of registration or marketing if there are delays from registration to marketing, then annually thereafter. For the purposes of this study, a 5-year period was chosen to mark the status of products which would be assessed as new versus old products.

5.3.4 Causality assessment of Reported ADRs

Causality assessment was planned to be performed for unexpected suspected ADRs using the Bradford-Hill Criteria and the WHO Causality Assessment Tool[96]. This refers to the assessment of the relationship between the use of medicine and the occurrence of an adverse event[98]. However, none of the ADRs reported met the criteria requiring causality assessment. As such, causality assessment was not done on any of the reported ADRs.

Assessment of the seriousness/severity of the reported ADRs was performed using the Hartwig and Siegel scale[99] (Table 9).

Table 9. Hartwig and Siegel Severity Assessment Scale

Severity	Level	Description
Mild	1	Required no change in treatment
	2	Drug dosing or frequency changed
Moderate	3	Required treatment, or drug administration discontinued
Severe	4	Result in patient transfer to higher level of care
	5	Caused permanent harm to patient or significant haemodynamic instability
	6	Directly or indirectly resulted in patient death

5.3.6 Statistical Analysis

Demographics and clinical characteristics of the participants were described and summarised using frequency tables, means or medians. Variables such suspected medicine, medicine class, systems involved (using the MedDRA SOC), type of ADR and its management, severity and expectedness were expressed as frequencies and percentages

5.4 Results

5.4.1 Demography

In total, 348 reports were generated and received during the pilot feasibility phase of the study. Reports from female consumers/patients amounted to 58.3% (203) of the total reports, with male consumers/patients contributing 39.4% (137). In the remaining 2.3% (8) of the reports, the gender of the consumer/patient was not indicated. These reports also did not meet the completeness inclusion criteria, with critical information missing i.e., ADR being reported and/or suspected medicine(s). These reports were therefore excluded from any further analysis. The demographic characteristics of the ADR reports received are summarised in Table 10.

Table 10. Summary of Characteristics of Received ADR Reports

Demographic Characteristics	**Total ADR Reports Received (N = 348)**
Female Gender - no. (%)	203 (58.3%)
Male Gender – no. (%)	137 (39.4%)
Age - years	
Mean (SD)	41.8 (15.2)
ADR Reports which did not meet the inclusion criteria - no. (%)	8 (2.3%)
Number of ADR Reports which met the inclusion criteria - no.	333
ADR Reports with concomitant/multiple medicines listed - no. (%)	8 (2.4%)
Reports with multiple ADRs listed in one report - no. (%)	22 (6.6%)
Multiple ADRs per report - Mean (SD)	2.14 (0.35)
Total number of ADRs reported - no.	358
Total number of suspected medicines reported - no.	436

The highest number of reports were received from females within the age group 31-40 years (22.5%). Reports received from male consumers were highest at 10.5% for the age group 51-60 years old (see Figure 10). Women above the age of 50 years contributed 11.1% of the total reports with 43.8% accounting for those in their reproductive stage (21 to 50 years old).

The paediatric, minor children to adolescent population within the age groups 0-10 years and 11-20 years, contributed 1.5% and 4.2%, respectively. Reports from consumers above the age of 60 years comprised 9.3% of the total reports.

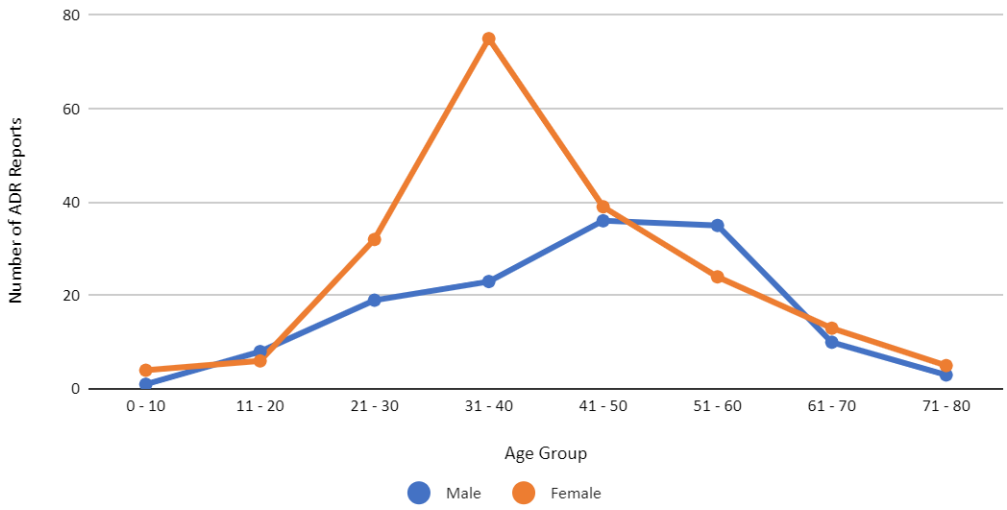

Figure 10. Number of ADR Reports received by Age Group vs Gender

5.4.2 Deconstruction of data

Apart from one suspected medicine which was first registered within the last four years (lamivudine, tenofovir disoproxil and dolutegravir fixed-dose combination, August 2018), nine reports for suspected medicines undergoing clinical trials investigations (the name of the suspected medicines was given as 'Investigational product") and twenty-three suspected medicines which could not be identified, all other reports were for medicines with well-established safety profiles (i.e., has been registered and available in the market for more than 5 years). The ADR suspected to have been caused by lamivudine, tenofovir disoproxil and dolutegravir fixed-dose combination was already listed in the product's PI and classified as serious. The suspected medicines in the nine reports from clinical trials were still under investigations and their safety profiles still being established.

In total, from the 333 ADR reports, 358 ADRs were reported with 6.6% of the reports listing multiple ADRs in a single report (mean = 2.14, SD = 0.35). Concomitant/multiple suspected medicines in a single report were indicated in 2.4% of the reports (see Table 10), resulting in a total of 436 suspected medicines across all reports.

Expectedness

Expectedness of reported ADRs was confirmed in 73.9% of the suspected medicines, whereby the suspected medicine(s)' dose was either reduced (3.4%), treatment changed (1.8%) or treatment with the suspected medicine(s) was stopped (6.9%) (see Table10). There were no actions taken and/or no information provided on actions taken for the majority of the reported ADRs (85.6%), with 2.3% indicated to have taken other actions which did not affect continued treatment with the suspected medicine(s). Such actions included *going to the clinic or doctor*, *got used to living with the side effects*, *drinking less water* etc (see Table 10).

Table 11. Characteristics of Reported Suspected Medicines

Medicines Characteristics	**Total Suspected Medicines N (%)**
Number of Suspected Medicines Reported - no.	436
ADR Expectedness confirmed for the suspected medicine	322 (73.9%)
ADR resulted in dose reduction	15 (3.4%)
ADR resulted in treatment stopped	30 (6.9%)
ADR resulted in treatment being changed	8 (1.8%)
Other actions taken	10 (2.3%)
No action taken/information not provided on action taken	373 (85.6%)

Antiretrovirals were the most commonly reported medicines suspected to have caused an ADR, contributing 18.1% to the total reported suspected medicines, followed by antihypertensive medicines at 15.8% and non-steroidal anti-inflammatory drugs (NSAIDs) at 15.1%. Birth control medicines were the fourth highest class of medicines (13.8%) reported. This would then also explain the majority of ADR reports to have come from the female consumers. Expectedness of ADRs from the suspected medicines was also high in the antiretrovirals, with 91.1% ADRs already listed in the PIs (see Figure 11). All ADRs reported to have been caused by birth control medicines, were listed in the PIs of each reported suspected medicines. The assessment on the expectedness of the suspected medicines still undergoing clinical trials investigations would have resulted in unintended bias, as the expectedness could not be confirmed due to unavailability of the safety profile of the suspected medicines.

A considerable number of suspected medicines (5.3%) could not be verified – the name given on the reports could not be confirmed. Either the spelling of the suspected medicines was incorrectly captured by the reporters, or the suspected medicines are not registered as orthodox medicines with SAHPRA and/or any other recognised regulatory authority. These medicines contributed 5.3% (23) to the total number of suspected medicines reported. Majority of these unknown suspected medicines (69.6%) were indicated to be taken as treatment for HIV (condition suspected medicine taken for), 21.7% were indicated to be for the treatment of high blood pressure and the rest were for flu, pain, and stomach ulcers. Expectedness of the reported ADRs could also not be confirmed on these unknown suspected medicines. Information on actions taken in response to the reported ADRs was also not provided. This further prevented the assessment of the ADR's severity and/or seriousness, and thus the possible causality assessment.

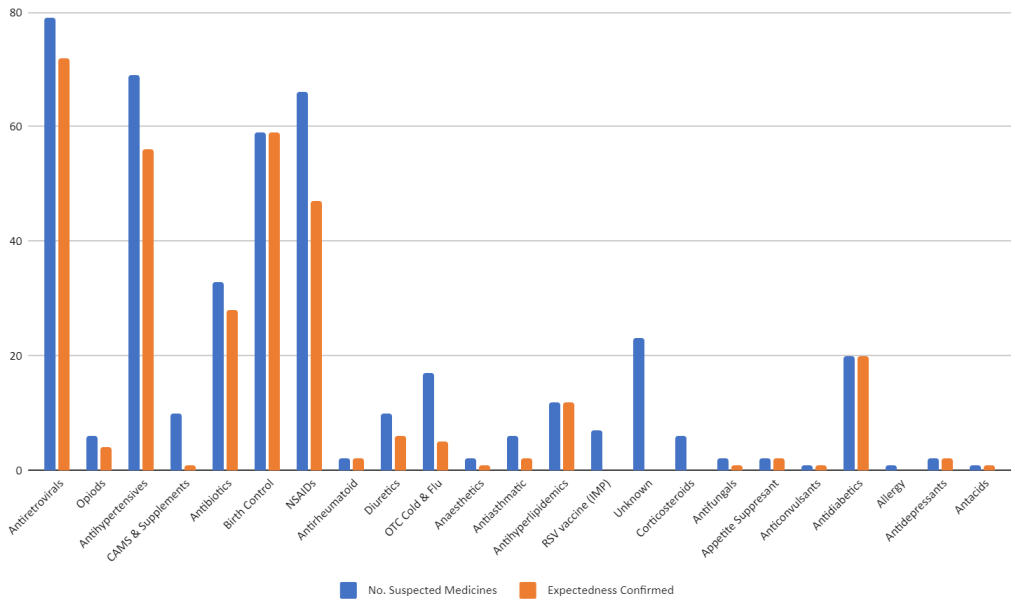

Figure 11. Classification of Suspected Medicines by Therapeutic Area and the Expectedness of the Reported ADR(s)

Seriousness

Over 90% of the ADRs were classified as mild (87.4% level 1 and 3.4% level 2) according to the Hartwig and Siegel scale (see Table 9). Majority of reports classified under this category did not have information on actions taken by the consumer in

response to the ADR. It was assumed that the consumer continued with the medicine suspected to have caused the ADR. Only 0.5% of the reports with an ADR under serious classification, wherein the report indicated that the consumer had returned to the clinic/doctor for further care. ADRs with moderate (level 3) severity classification had constituted 8.7% of the total ADRS reported.

Table 12. ADR Seriousness/Severity Assessment using the Hartwig and Siegel Scale

Severity	Level	Description	No. of ADRs at each severity level	
			n	**%**
Mild	1	Required no change in treatment	381	87.4%
	2	Drug dosing or frequency changed	15	3.4%
Moderate	3	Required treatment, or drug administration discontinued	38	8.7%
Severe	4	Result in patient transfer to higher level of care	2	0.5%
	5	Caused permanent harm to patient or significant haemodynamic instability	0	0
	6	Directly or indirectly resulted in patient death	0	0

Only two reports were received from healthcare professionals in the nursing field. The terminology used by the two nurses (and the types of ADRs reported) is simple and commonly used (nausea and diarrhoea). Three reports from health research-related professions (Researcher, Study Coordinator and CTA [Clinical Trial Assistant]) were also noted. These titles are common in the clinical trials research field and hence assumed to be from health research-related professions. Drowsy, headaches and '*hot feeling on my face*' were the ADR terminologies used by these professionals, respectively. Reports were also received from an assistant nurse and care givers/takers. These reports have been noted with interest as their roles are within the healthcare field.

The completeness and quality of reports and/or information provided is similar to those of non-healthcare professionals, with only one report indicating the action taken in response to the ADR experienced. None of their reports had additional information and/or descriptive information on the ADR and/or action taken.

Coding process

Coding of ADRs was conducted manually and used the reported terms to search for the possible ADR codes.

Reported terms produced 63.4% exact matches from the MedDRA search, 8.7% were from contains search results and terms used from ‘lexicant variant’ results totalled to 2.5% (see Figure 12).

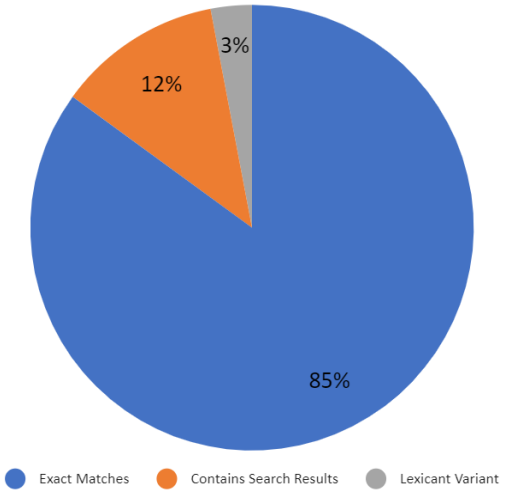

Figure 12. Breakdown of MedDRA Coding Search Result Types

A total of 25% of the reported terms could not be found in the MedDRA database (i.e., they did not yield any search results). In these instances, an alternative term (titled ‘search term’ – often a simplified/shortened form of the reported term) was then used (see Table 13). From the search terms used, 51.3% yielded exact matches from the search, 2.6% did not yield any results as the reported term and the search term used were too general/vague. There was only one lexicant variant from the search term used, with 43.5% of the terms used for coding selected from ‘contains search’ results.

Table 13. Reported Terms not Found in MedDRA

Reported Term	Search Term (Term used in cases where reported term yields no search results)	Associated Term Selected (which means there were no exact matches and no lexicant variants - term selected from 'Contains search term')	Lexicant Variant	Exact Match
Loss of appetite	Appetite	Appetite loss		
Headaches	Headache	Frequent Headaches		
Body Rash	Rash			x
Skin peeling off	Skin peeling			x
Swollen body	Swelling			x
The medication made it hard to breath	Difficulty breathing			x
Hard Breathing	Difficulty breathing			x
Swollen legs	Feet swelling	Swelling of feet		
Fast heartbeat	Heartbeat	Heartbeat increased		
Urinating a lot	Urination	Frequency of Urination and Polyuria		
Made my chest tight which led to difficulties in breathing	Tight chest			x
My skin turned black	Skin black	Black dermatographia		
Hot feeling on my face	Hot feeling		1 - Feeling hot	
Sleeping a lot	excessive sleepiness	Excessive daytime sleepiness		
Skin irritated	Skin irritation			x
Bleeding nonstop	Bleeding			x
Heavy breathing	Breathing	Laboured breathing		

Heart problem	Heart	Terms specific to a certain heart condition, not easy to select based on the reported term, vague		
Minor headache constantly	Headache			x
I had small rush when I started using the cream the rush became worse	Rash			x
Temporary extreme pains	Extreme pain	Paroxysmal extreme pain disorder		
Feeling dizzy most of the time	Dizzy			x
Running tummy / running stomach	Diarrhoea			x
Problem breathing even used the spray	Difficulty breathing			x
Constant headaches	Frequent headache	Frequent Headaches		
Lump on my neck	Lump on neck	Swelling, mass or lump in head and neck		
Constant hungry	Hunger	Feeling hungry		
Sore stomach cramps	Stomach cramps			x
Running nose	Runny nose			x
Excessive urination	Urination	Frequency of Urination and Polyuria		
Constant urination	Urination	Urination frequency of		
Bad skin rash	Skin rash			x

Excessive weight gain	Weight gain			x
Irritation of the biceps	Irritation	Skin Irritation Administration Site Irritation		
Tired joints	Stiffness joints	Stiffness joints		x
Weak, painful joints	Painful joints			
Sore joints	Painful joints			x
Weak joints	Joints	Discomfort of joints		
Facial pimples	Pimples			x

The most frequently reported ADRs included vomiting, nausea, rash, diarrhoea, fatigue/tiredness, and headaches (19.06%, 12.97%, 8.06%, 7.47%, 6.88% and 5.89%, respectively). Using the system organ class (SOC) categories, the most reported ADRs fall under the gastrointestinal disorders, followed by nervous system disorders, skin and subcutaneous disorders, then general disorders and administrative site conditions (43.81%, 11.20%, 10.41% and 8.45% respectively, See Table 14 below).

Table 14. List of Frequently Reported ADRs and Frequently Reported ADRs by SOC

Most Reported ADRs per Reported Terms (%)	Most Reported ADRs per SOC
Vomiting (19.06%)	Gastrointestinal disorders (43.81%)
Nausea (12.97%)	Nervous system disorders (11.20%)
Rash, all types (8.06%)	Skin and subcutaneous disorders (10.41%)
Diarrhoea, *including running tummy/stomach* (7.47%)	General disorders and administration site conditions (8.45%)
Fatigue, *including tiredness* (6.88%)	Musculoskeletal and connective tissue disorders (4.32%)
Headache (5.89%)	Psychiatric disorders (3.93%)
Drowsiness (3.73%)	Renal and urinary disorders (2.75%)
Weakness *including weak, tired & sore joints* (3.14%)	Respiratory thoracic and mediastinal disorders (1.77%)
Constant urination (2.75%)	Metabolism and nutritional disorders (1.77%)
Constipation (2.55%)	Investigations (1.57%)
Swelling (2.16%)	Vascular disorders (1.18%)
Skin irritation (2.16%)	
Heat/hot flushes (1.57%)	
Dizziness (1.38 %)	

Parts of the ADR reporting tool being piloted had free text sections. This enabled reporters to provide as much additional details as they can in these corresponding sections. The type of descriptive ADRs reported and actions taken are highlighted in Table 15.

Table 15. Types of Descriptive ADRs and Responses to ADRs by Reporters

Types of Descriptive ADRs	Types of Descriptive Responses to ADRs
● The medicine made it hard to breath ● Heat too much heat ● Urinating a lot, sometimes I feel thirsty always ● Coughing, swollen lungs** ● Made my chest tight which led to difficulties in breathing ● My skin turned black ● I had hip dislocation ● Hot feeling on my face ● Sleeping a lot ● Heavy breathing, blocked after steaming ● Minor headache consistently ● I had small rash when I started using the cream, the rash became worse ● Dizziness and urinating a lot ● Temporary extreme pains ● Feeling dizzy most of the time ● Running tummy and blood in my stool ● Problem breathing, even used the spray ● Constant headaches ● Lump on my neck ● Always thirsty ● Constant hunger ● Excessive urination ● Excessive bleeding ● Excessive weight gain ● Irritation on the bicep ● Bleeding nonstop ● Bad skin rash** ● Itchy rash	● Got used to living with side effects ● Outgrow the asthma but the doctor said it can come back when she (the child) is old ● I don't take it at all anymore ● Stopped taking the medicine after the first week ● Applied betamethasone, drank allecint ● Stopped medication as instructed ● Drink less water ● Changed zileuton to zariflukast ● Stopped the medicine instructed by nurse ● Lamivudine replaced by Abacavir ● Went back to the doctor ● Not to use ● I went to the clinic ● Given betablockers ● Stopped medicine when deliver ● Stopped the supplement

**There were two reported ADRs which we noted with interest, '*Coughing, swollen lungs'* and '*bad skin rash*'. These ADRs could not be coded in MedDRA as reported, variations had to be considered such as only using coughing and skin rash.

Table 16. Breakdown of ADR Reporters by Employment Classification

Socio/Professional Status	No. of ADR Reports	Examples of ADRs Reported in each Category
Employed/self-employees	151 (45.3%)	General terms e.g., dizzy, nausea, vomiting, skin irritation etc. Steven Johnson Syndrome (General worker)
Unemployed	58 (17.4%)	Lipodystrophy, hallucinations & general terms
Student / Learner	11 (3.30%)	general terms. Two on RSV Clinical trials
Pensioner	6 (1.80%)	general terms
Unknown	107 (32.1%)	general terms, hallucinations

As the educational background of the reporters/consumers was not collected, it would not have been feasible to use the socio-economic status classification in this study. The types of employment would also not give an accurate overview of the socio-economic status of these reported/consumers due to the high employment rate in the country.

Reporters/consumers who submitted the reports ranged from employed (45.3%), which contributed the highest amount of ADRs, to students/learners and pensioners (1.8%). Over 30% of reports did not indicate the profession of the reporter. A general assessment of the type of ADRs that were received from reporters in these different categories indicates no difference in terms of the terminology used, the quality of data provided (providing the required information in the correct section and presenting the information as accurately as possible). The employed category included two reporters within the healthcare field, and three reporters within the healthcare related field. The terminology used in their reports is general/common language (i.e., nausea, vomiting, diarrhoea etc). However, none of these reporters (healthcare and related fields) had given information in a descriptive manner in any of the sections that allowed free text. One of the reporters from the employed category, employed as a general worker has reported Steven's Johnson Syndrome. The highest number of reports (17.4%) with

more scientific/medical terms was from the unemployed category, with 0.9% of the reports listing ADRs such as hallucinations, lipodystrophy.

Reporting Channels

All reports were submitted via the online (directly through the reporting tool) reporting tool. This then limited the assessment of the ADR reporting channels which were planned to be explored in the study. One of the challenges encountered when starting the pilot feasibility study was consumers who wanted to report but felt discouraged by the requirement to complete a form (paper, electronic or online). They felt that this is time consuming and would prefer having to narrate their information to someone who is willing to note everything down on their behalf. In other instances, consumers inquired if they could send text messages with the required suspected ADR information instead of having to complete the paper or online form due to time constraints.

CHAPTER 6

RISKS AND BENEFITS

6.1 Assessment of Potential Risks

A risk could be a potential for harm or discomfort to a prospective participant. The current study did not pose any direct harm to participants. However, potential risk of discomfort due to collection of personal and health-related information existed, as their confidential information could be accessed or exposed to unauthorised personnel.

The above risks were minimised by keeping personal identifying information confidential and separate from the data that was to be analysed throughout the study. Part of the confidential information could only be shared with the relevant authorities as permitted and required by law. More detail is provided under section a) and c) below.

6.2 Management of Potential Risks

a) Confidentiality

Due to the nature of the study, information could not be collected from consumers anonymously. As safety information was the primary data being collected, certain personal information was therefore required. However, such information was collected, analysed, and reported without compromising identification in compliance with the current applicable Personal Data Protection legislation in South Africa, and the POPI Act (Act 4 of 2013). All identifying information was removed, separated from the data analysed and stored in separate, password encrypted files. Participants' confidentiality was therefore maintained throughout the study.

b) Waiver of Informed Consent Document

Due to the nature of the pilot study proposed, it was not practical to obtain a written informed consent from all consumers who participated; identifying and contacting an unknown number for a short duration was not feasible. Therefore, a waiver was obtained from the Research Ethics Committee.

Implied consent was then adopted, whereby participants agreed to participate in the study after being informed about it, and their participation was only through completing the ADR reporting tool. Participants were informed of the nature of the study as well as the possibility of forwarding their information to the relevant authorities, where there could be safety concerns. By providing contact details in the ADR reporting tool, willingness to be contacted by the researcher was thus implied. A disclaimer to keep their information confidential throughout the study and at least 2 years after completion of the study was also included in the ADR reporting tool. After 2 years, all personal identifying information and raw data will be destroyed.

c) Management of Medical Information

The minimum requirements for reporting an SAE to NADEMC are[1]:

- An identifiable patient. A patient may be identified by surname and forename(s) or initials of surname and forenames, or by a reference, or by age or gender.
- An identifiable reporter
- Suspected medicine(s); and
- Suspected reaction

Should the researcher receive a report with an SAE, the following steps were intended to be taken:

i. The affected consumer would be contacted immediately.
    - The consumer would be informed of the nature of the SAE they have reported, and that immediate medical attention is required. They would be requested to visit their HCP without delay for proper medical care.
    - Details of the HCP they planned on visiting would be requested.
    - A reference number (assigned consumer report number) would be shared with the consumer and instructed to share the reference number with the proposed HCP to be visited.

ii. The proposed consulting HCP would be contacted.

- A report containing only pseudonyms would be forwarded to the HCP with the same reference number as shared with the consumer. The HCP would be informed of the possible detected SAE and that the affected consumer has been requested to visit him/her without delay. The HCP could then assess the reported AE and use his/her discretion to manage the consumer's AE.

6.3 Anticipated Benefits

The anticipated benefits for participation in the study include increased possibilities of receiving immediate proper care for any reported SAE, gaining better understanding of their condition and its management as well as an opportunity for the participants to participate in the improvement of the healthcare system in South Africa.

CHAPTER 7

DISCUSSION

7.1 Tool Development

The study aimed to develop and pilot the feasibility of an ADR reporting tool which consumers/patients can use to submit their ADR reports directly to the national pharmacovigilance unit, as well as exploring the channels they can use for submitting the ADR reports. All three objectives set for the study were met.

Pharmacovigilance is used globally as key to improve patient safety and healthcare management[94]. A robust PV system which will enable collection of safety reports from all possible/available avenues is therefore required to meet this objective. At the time of initiating the current study, there was no ADR reporting platform/tool which enabled the public or consumers to report ADRs directly to the PV unit in South Africa. The current study therefore aimed to develop a tool that can be used by the public consumers to report ADRs directly to the PV unit.

7.1.1 General Overview of the Consumer ADR Reporting Tool

The content of the consumer ADR reporting tool developed during this study is comparable to those of the WHO ADR reporting initiatives (primaryreporting.who-umc.org and The Med Safety App), containing the five essential elements of consumer details, details of the ADR(s), suspected medicine(s), medical history, and the reporter. The tool was developed in two formats: online and a paper form. As with the Med Safety App, the online format is compatible with mobile devices and therefore can be easily converted into a default App to be downloaded through mobile devices App stores. The flow of information/items to be completed, the length of the report (short), the clear and direct instructions using lay terms was designed to encourage and enable consumers to complete and submit the reports with ease, not too busy/cluttered and less complicated based on the size/length of report). The paper form was designed to ensure there is an alternative for consumers who may not have access to the online reporting tool.

Similar to direct ADR reporting tools in other countries, the landing page of the online ADR reporting tool contains general information to educate consumers on ADRs, requirements for reporting, reporting process and the importance of doing so. In contrast to WHO ADR reporting tools initiatives, accessing the ADR reporting page does not require any login/sign in details, no option to select a language for use (the WHO ADR reporting tool contains this option as a drop-down, though only the English language is available to select), and the type/profession of the reporter is part of the reporting tool itself and not incorporated in the login/sign in section of the tool. The impact of these on consumer reporting decisions would need to be explored further, through qualitative studies with the intended audience.

Creating login/sign in credentials could be beneficial if previous submitted reports and/or outcomes of the assessment can be visible to the consumers as this could encourage continuous reporting and enable submission of additional/follow up information to previously submitted ADR reports. Notwithstanding the added value of the password protected ADR reporting system, forgetting of passwords and the often-lengthy processes of resetting a password may deter future reporting[100].

7.1.2 Items included/excluded in the Consumer ADR Reporting Tool

The elements not included as separate items in the current consumer ADR reporting tool include outcome of the reaction (this was only included as part of the ADR details where consumers can indicate if the reaction has stopped on not versus the multiple options available in other reporting tools for consumers to select: recovered, recovering, not recovered, reaction ended but with after effects, fatal, unknown), what the reaction lead to and source of the medicine(s) taken. Within each of the ADR elements included, variations also exist. For example, some countries including South Africa (the SAHPRA ADR reporting tool), require information on the manufacturer of the suspected medicine and the batch number under the suspected medicine(s) section; patient hospital number, general practitioner, or trial number under consumer details; first and last name instead of initials under reporter details.

During the validation process, the healthcare professionals did not find it relevant to include the suspected medicine(s) batch number and expiry date ($\alpha \sim 79.3\%$). These items were therefore excluded from the consumer ADR reporting tool.

Though a batch number would be critical to ensure traceability in product recall or quality issues with the batch, it is not a mandatory requirement for ADR reporting. ADR reports without the batch number of the suspected medicine would still enable causality assessment and signal detection. The validity and reliability tests performed on the current ADR reporting tool along with the outcomes of the pilot feasibility study confirms the viability of ADR reports without batch numbers.

The requirement to include the batch number is however mandated for biological medicines, mainly due to inherent variability in the manufacturing processes, immunogenicity and traceability[101]. Such variabilities render the generics of biological medicines (biosimilars) to be non-identical to their reference medicine, resulting in variabilities in different batches of the same medicine[101,102]. Hence, it is essential to include the batch number when reporting ADRs related to biological medicines (biologics). The results from the survey conducted amongst healthcare professionals in Ireland on the knowledge of ADR reporting, healthcare professionals who used biologics in their practice rated the reporting of batch numbers as being more difficult, though considered valuable[101]. Furthermore, the functionality of the recording systems was not enabled to capture the batch numbers; and this is dependent on the availability of the original packaging.

However, such variabilities do not exist among the generics of the chemical medicines[101].

An expiry date is allocated to each medicine as part of the regulatory requirements for product labelling. This date is based on the manufacturer's standard storage conditions[103]. Though there seems to be a lack of availability of published data on the effects of using expired medicines, ADR reports containing this information could help establish any potential hazards. However, collection of this piece of information is currently not mandated when reporting ADRs. Amongst the thirteen countries ADR forms for which Singh & Bhatt[104] did a comparative evaluation, only three (United States, Canada, and India) countries required the expiry date, and 8 countries (Argentina, New Zealand, United States, Canada, India, United Kingdom, Malaysia and Singapore) required the batch number of the suspected medicine to be provided when reporting an ADR.

These two parameters (batch number and expiry date) including parameters which were not proposed for inclusion though could be of great value in causality assessment (e.g., laboratory data) were thought to be unnecessary to include as consumers would be unlikely to provide such data. This more especially since the aim of the tool also included having a simplified reporting tool, and this included requesting consumers to provide information which they may easily provide and/or identify. As the public becomes more aware and familiar with ADR reporting, such additional parameters may be explored with future improvements.

7.1.3 Involvement of Stakeholders in PV System

The introduction of the consumers' reports in the PV system was mainly to complement reports from healthcare professionals for a timelier signal detection. Another value added through consumers' reports is additional information included mostly as narratives which can complement the clinical aspects of the ADRs as well the impact of the ADRs on the quality of their lives. Considering all stakeholders involved in the PV system and current challenges faced, the ADR reports received through this tool could help narrow the ADR under-reporting gap and improve the PV system. The PV stakeholders would include the regulatory authority through the PV unit, the pharmaceutical industry (marketing authorisation holders of the medicines), the government (through enacting laws), the healthcare professionals, and consumers along with patient advocacy groups.

With the traditional PV system set up, when a consumer reports an ADR directly to the marketing authorisation holder of a medicine, the company is required to advise the consumer to report the ADR through their healthcare provider[103]. Only if this approach fails, the company can then accept the ADR report from the consumer. Reflecting on some of the given motives for consumers to report ADRs (i.e., their experiences may be filtered healthcare professionals[10,37,59], dismissive attitude of healthcare professionals[7,37,46,53,59,60]), this kind of push back may have a negative impact on the willingness for consumers to report ADRs in the future. Saohatse[105] has also highlighted some of the difficulties that patients encounter when seeking medical care at South African government hospitals (the language barrier leading to frustrations and inadvertent outcomes, the hostility from the nurses and doctors after reporting an ADR

and still given the same medicine that caused an ADR etc) which may further deter consumers from reporting ADRs as they would need to reach out to the same healthcare professionals to do so. A platform using this study's tool will empower and encourage consumers to submit ADR reports independent of the healthcare system if such barriers are present, and at any given timepoint, outside of appointments; together with reports from healthcare professionals, this is likely to speed up signal detection.

It is not clear from the available literature if healthcare professionals have been receiving feedback from the PV unit on the ADR reports they submitted, not from the marketing authorisation holder of the suspected medicine. It is therefore unlikely and may also not be feasible for the PV unit to provide such feedback to the consumers and similarly, healthcare professionals.

Only few consumers took the paper ADR forms from the recruitment centres, citing the spread of COVID-19 infection as a concern for not preferring the paper-based ADR forms. Most of these healthcare centres are equipped with wi-fi which enabled easy online access. Although network coverage was often a challenge, especially while patients/consumers were still waiting outside the healthcare facilities. However, none of the paper ADR forms were returned. Most of the young and middle-aged consumers preferred assistance with navigating to the online ADR reporting tool using their smartphones in order to orientate them on how to navigate through the tool. The elderly consumers indicated a need for assistance with actual completion of the online ADR reporting tool. Such assistance was mainly offered by young consumers at the facilities out of interest to learn more about the study and/or tool.

With the increasing use of the digital media, an online based PV system that would enable medicine consumers to report adverse drug reactions at any timepoint may have a positive impact on PV, with regard to improving the number of ADRs submitted. Such improvements were experienced in Germany following a second Covid-19 lockdown, whereby ADR reports were submitted through an online portal (web-based tool)[106]. The fact that medicine consumers and/or patients may not need to visit a doctor or a healthcare professional in order to report the ADR, or to wait for 'normal'

working hours when healthcare professionals are in operation to report would be an added advantage.

7.1.4 Refining of the Consumer ADR Reporting Tool

The ADR reporting tool was initially developed such that it required the exact date and time of when the ADR occurred, a mandatory field that was a prerequisite for moving to the next section and submitting the report. This requirement was, however, removed based on feedback from HCPs during validation (see Section 4.3.1). Internal testing by the researcher and IT developers to check the possible impact the requirement might have meant the tool could be reformatted to allow flexibility on providing the information. In fact, during validation and pilot feasibility, none of the participants provided the time of ADR onset and stopping, only the dates. The time therefore indicated the default timeline of 00:00 in all ADR reports received.

With regard to the second comment from the HCPs during validation and taking into consideration those consumers with multiple concomitant chronic conditions, the sections requiring information on the condition of the consumer and the corresponding medication were adjusted. Such patients are likely to be affected by polypharmacy, with possibilities of not being able to match the medications to the condition being treated. This was also thought by the researcher to be another possible deterrence to consumer reporting. The section was therefore modified in such a way that it enables the consumer to list all conditions they have, as well as have a separate section where all medications being taken (whether as treatment, vaccine, supplements etc) could be listed in any order without the need to match them to a specific condition. This was to lessen the expectation on consumer reporters to have to link any ADR to a particular medicine to avoid discouraging reporting altogether. If all conditions are listed including the treatment for each, this would enable the assessors to determine any disease-medicine and medicine-medicine interactions. Consumers would then also indicate if any of the medicines listed is the suspected medicine. However, none of these sections were made mandatory to complete i.e., unable to continue to other sections in the report, save or submit if the information is not provided, and/or if a suspected medicine is not selected. The main reason for the modifications of the two sections above was to lessen the expectation on consumer reporters to have to link

any ADR to a particular medicine to avoid discouraging reporting altogether. If all conditions are listed including the treatment for each, this would enable the assessors to determine any disease-medicine and medicine interactions. However, the reporting tool encourages consumers to provide as much information as they can in these sections. This positive attribute to the reporting tool eases the burden on consumers to have to determine which of the medicines is likely to cause the experienced ADR(s) (the insecurity of not being able to know or suspect the responsible medication as indicated in few other studies[15,33,45,48,50,51,54]). This would also encourage consumers to report the ADRs without any fear of 'talking bad' of any medicine as reported in one other study[49].

7.1.5 The format of the Consumer ADR Reporting Tool

The consistency on the outcomes between the initial and re-test reports during face validation also highlights the ease with which consumers were able to access and use the reporting tool as well as the instructions were clear and simple to follow. When the invitation was sent out to the volunteers to invite them to participate in the study, in addition to the Survey Monkey® link (link to the consent form, the case scenario and a link to the electronic reporting tool) the email invitation also contained the consent and reporting tool in paper format (printable copies). The case scenario was only available electronically to ensure access is disabled after the initial testing was completed. None of the participants completed the printable/paper format of the ADR reporting tool. Since no personal information was collected from this sample of participants other than the contact details (email and contact number to enable follow up invite to the re-test phase), it was not possible to determine the age-group and/or literacy/educational background of this sample to assess what could have influenced their choice of the reporting format.

It should however be stated that recruiting participants who were employees of a Pharmaceutical Company is likely to have introduced an unintended selection bias. A junior degree is often a minimum requirement to join such a company.

In addition, since most Pharmaceutical Companies have annual awareness sessions to orientate their employees on company PV processes, inclusion of such a company's employees in the validation stage might have introduced response bias.

Without any information on the demographics of the participants from the faith-based organisation, it was not possible to make any assessments or assumptions on the type of participants who responded to the invite.

The ADR reporting tool is designed to enable collection of information required to enable an ADR causality assessment as well as enable inclusion of ADR reports from and by the national PV unit in VigiBase®. The minimum required information for ADR reports to be included in VigiBase are: (1) one identifiable patient, (2) one identifiable reporter, (3) one reaction/event, and (4) one suspected medicine[108]. The reporter's contact details are not required and should then be extracted from the reports prior to submission to VigiBase®. Such uniformity will enable for the same analysis (mainly ADR causality assessment) done on the ADR reports received from the healthcare professionals to be also carried out on ADR reports from consumers, with further sub-analysis to compare the different aspects of the reports between the healthcare professionals and consumers possible.

7.1.6 Availability of ADR Reporting Options in South Africa

Of the twenty-two African countries wherein Adedeji-Adenola and Nlooto[107] has reviewed the availability of documentation/publication on ADR reporting between the period of January 1992 to October 2015, only sixteen countries allow consumers to report ADRs directly to PV centres. At the time of conducting the review in these countries, South Africa was one of the remaining six countries without healthcare consumer enabled ADR reporting platform. Instead, consumers were required to report any ADR through healthcare professionals. Interestingly, Maigetter *et al*[28] noted that during this time, the South African PV unit (NADEMC) was receiving ADR reports from consumers.

Even though South Africa has been a member of WHO PIDM since 1992, it only joined the use of the WHO established ADR reporting initiatives (web-based safety reporting [Primary eReporting[108]] and the mobile app safety [called **The Med Safety App**] reporting) and rolled them out in response to the Covid-19 pandemic in 2020. This hasty reaction resulted in certain outdated administrative errors being carried over to these newly adapted systems i.e., SAHPRA being referred to as MCC, contact

numbers and email addresses of the old MCC premises/institution. These tools allow reporting of ADRs by consumers, marking it as the first time for consumers in South Africa to be allowed to report ADRs directly to the PV system.

The use of WHO ADR reporting tools is expected to harmonise the information being reported/collected across all participating countries. This would improve the reporting due to consolidated efforts on public awareness and ADR reporting processes/requirements across the countries.

7.2 Pilot Feasibility Study

The number of responses received, and the type of information provided indicate the level of consumers' awareness and interest/involvement in the management of their health. The pilot study was conducted during the COVID-19 pandemic, when more information was being sought to characterise the virus and develop vaccines and treatment against it. As of 05 March 2022, Clinicaltrials.gov[109] has recorded about seventy-eight clinical trials in which South Africa was participating. There were numerous discussions ongoing in social media, newspapers, radio stations and television broadcast on the issue. The South Africa government through the Department of Health undertook educational strategies to support the global initiatives to combat the spread of COVID-19, through educating the public using the available media platforms. All these activities might have heightened the interest of the public to report ADRs and, contrary to the findings of Hasford *et al*[50] and Krska *et al*[61], created a certain level of awareness about personal health management, which amongst them would include the awareness on medicine safety. The recruitment methods and strategies used to create public awareness about the current study may have also contributed to its success. A Facebook™ page was created and the link shared on different public groups on Facebook™, through WhatsApp™, social groups, YouTube™ videos, Instagram™, LinkedIn™ and through patient network groups such as DiabetesSA. Moreover, the online tool is compatible with mobile phones, enabling easy access by consumers at any timepoint.

The study conducted by Agoro *et al*[100] in Kenya demonstrated the benefits of using technology for reporting ADRs, which then supports the need to develop and explore

ADR reporting tools that are compatible with available technology advances. The study reported a very high response rate of using mobile devices and desktop applications during participation in PV surveys and sending safety reports. The availability of wireless network connection at the recruitment centres used in the current study was often a challenge and was supplemented by connection through mobile hotspot from the primary researcher's mobile phone where feasible. No assessment was done on the impact of internet connection to willingness to submit an ADR report. It is however believed that availability of alternative internet connection other than using the consumers' personal mobile data has contributed to the responsiveness of the consumers. The cost of purchasing data bundles for internet connection and/or visiting an internet café which may also require transportation if situated at a distance (and thus additional time) in order to access the internet and complete the survey or submit a report was reported as a barrier in using electronic reporting system[100] Knowing that availability of a medicine for public use does not imply absence of untoward adverse effects and/or that the safety profile of a medicine is established through weighing of its benefits against the risks, could have sparked curiosity in medicine consumers to pay more attention to what they take (medicines and health-related products) versus the overall outcomes they experience after taking them.

7.2.1 Characteristics of Reports Received

Similar to findings in a study by Hasford *et al*[106], the majority of reports (59.5%) were submitted by women. The most frequently suspected medicines in the reports submitted by women were birth control medicines. Similarly, the European Union (EU) statistics reported a higher usage of prescribed medicines by women and deduced the use of contraceptive pills and hormones for menopause as the underlying cause[110]. In this study, women above the age of 50 years accounted for 11.1% of the total reports analysed (N = 333) with 43.8% accounting for those in their reproductive stage (21 to 50 years old). This high number of ADR reports from women agreed with the birth control medicines accounting for the fourth highest suspected medicines reported (13.5%), after ARVs (18.1%), antihypertensives (15.8%) and NSAIDs (15.1%), respectively. All ADRs reported with birth control medicines as the suspected cause

for the ADRs were confirmed to be expected as listed in the medicines package inserts, with nausea and weight gain being the frequently reported ADR in the study.

Between 1.5% and 4.2% in this study related to the paediatric, minor children to adolescent population within the age groups 0-10 years and 11-20 years, respectively. Reports from consumers above the age of 60 years comprised 9.3% of the total reports. The high likelihood of comorbidities in this elderly population requiring concomitant multiple therapies[111,112] could be contributing to the ADRs reported. The types of medicines that the elderly patients are often prescribed due to their chronic conditions (e.g., cardiovascular medicines and NSAIDs) also increases the risks for experiencing ADRs[112]. Since these consumers are often underrepresented in clinical trials[100,106,113], the ADR reports would present an opportunity to enhance the confirmation of the safety profiles of medicines in these populations. In agreement to this, Elbeddini *et al*[111] highlighted the need for ADR reports from the children and elderly due to their high susceptibility to medicines adverse effects. The mean age of consumers who reported an ADR in the current study is 41.8 years, which has been noted as the age at which patients begin to experience the onset of multiple chronic conditions[111].

7.2.2 Types of ADRs Reported

Relevant key elements required to conduct causality assessment were present in all the reports included for the study analysis, a finding similar to that of Kheloufi *et al*[111] study. Over 90% of reports received from patients contained crucial components required for ADR assessment. The number of single ADR reports with multiple suspected medicines (i.e., a single report listing more than one medicine, 2.4%) is close to what was reported in another study[114]. This highlights that consumers have a good understanding of what an ADR is, and their ability to associate the reactions to medicines they are taking/have taken. In cases of multiple concomitant medicines, though consumers may not know exactly which medicine may have caused the adverse reaction[115], they may however, be able to link some of them using the time point of starting each therapy i.e., if the first treatment they started on did not cause any negative reaction and once they start on the next medicine, then they experience the negative reaction. Some of the reactions could be due to drug-drug interactions in

these kinds of scenarios and consumers would therefore not be able to diagnose such. However, sharing information on the relations of the adverse reaction and the start of each treatment would have narrowed down the suspected medicine for them. In the study conducted by Jacobs *et al*[115], most patients were able to identify an ADR and associate it with a causative medicine. However, some patients could not recall or did not know the name of the medicine they were prescribed, which could be a challenge when reporting the ADR and/or when the ADR is being assessed. The study also noted the dispensing practice whereby the medicine is dispensed from bulk original containers into small packages (repackaging), which are then labelled by hand. This practice is also common in South Africa, especially in private doctors' rooms, government clinics or healthcare centres (often by dispensing nurses) and some pharmacies. The hand-written labels are often not legible, which could hamper ADR reporting. The high number of reports in the current study with strange medicine names which could not be verified may have also been affected by these kinds of practices.

In contrast to findings in other studies where consumers mostly reported serious ADRs[114,116], the majority of ADRs reported in this study can be classified as mild with only 8.7% reports on moderate ADRs. It is assumed that the mild ADRs are likely to have not bothered consumers to an extent of disrupting their daily activities since over 85% did not take any action in response to the ADRs experienced. This could be a matter of consumers tolerating their treatment as noted from one report "***got used to living with side effects***" and similar to the findings from Addo *et al*[117] study. For those consumers who have had their treatment dose reduced (3.4%), stopped (6.9%) or changed (1.8%), it is likely that the ADRs were too bothersome for them to have complained and visited their healthcare practitioner to have the ADRs reported and thus review of their treatment. From the reports received, it cannot be confirmed who recommended modification of treatment for these consumers. Based on some of the narratives from the consumer reports, it seems that some consumers decided to stop taking their medicine without first consulting with their healthcare professionals ***"I don't take it at all anymore, stopped taking the medicine after the first week, stopped the medicine when delivered, stopped the supplement"***. In agreement with this observation, Kalisch *et al*[112] noted that about 15% of patients may not report

the experienced ADRs to their healthcare providers and subsequently discontinue the treatment.

Tiredness/fatigue, drowsiness and constant/frequent urination were the most frequently reported ADRs associated with the antihypertensive class of medicines, followed by constipation and headache.

In terms of SOC classification, reports of the Gastrointestinal disorders, Nervous system disorders, Skin and subcutaneous disorders and General disorders and administration site conditions were the most common in the current study. This is a similar pattern as that reported in Ampadu *et al*'s study[26] on the ICSRs review for Africa and the rest of the world.

7.2.3 Types of Reporters

The socio-economic status of the consumers who submitted their reports could not be assessed since the developed ADR reporting tool is not enabled to collect such data. However, based on the information gathered from the reports received, the majority of the consumers are employed in various sectors. When the reports received from consumers who are employed were compared to those not employed, the students and pensioners, there were no differences noted in terms of the terminology used, completeness and the quality of information provided. Though some scientific/medical terms were noted in the reports from consumers who are unemployed, the overall terminology used was similar across the various categories. Based on the quality of information received, employment status does not determine health/medical literacy of a consumer.

Comparison of the terminology used by reporters in the health-related field and non-healthcare consumers, completeness and quality of reports showed no difference between the two groups, similar to findings in other studies[39,66].

The types of centres from where consumers were recruited, and the recruitment methods used, might have played a role in the demographics of reporters noted in the study. The social media adverts are likely to have attracted the young and technological savvy consumers. Depending on the programs and/or medical

conditions that the department of health might have been prioritising (through the conduct of routine awareness sessions) at the time of conducting the pilot feasibility study, inadvertent bias on the selection of the demographic profile of consumers might have been introduced.

7.2.4 Types of Suspected Medicines Reported

The additional comments from consumers also shed a light on the lack of consumer awareness on treatment compliance, the impact of non-compliance and what best options they ought to consider in situations where they experience an ADR. Though the ADR associated with such responses from consumers would not be classified as serious ADRs, but for consumers to rather choose treatment discontinuation, they may have had a serious negative impact on their health. No further information available to determine if they later sought (medical) assistance for the condition being treated prior to experiencing an ADR. It would be interesting to find out what informed their decision to discontinue with their treatment, what further actions they took to address the condition initially being treated after treatment discontinuation, if they have reported the ADR to their doctor/clinic. Not following the doctor/healthcare provider's instructions on treatment management (when to take the medicine, how often and how i.e., taken with, before or after food; avoiding certain kinds of food; taking medicines a number of hours apart to avoid interactions etc) is also likely to cause ADRs[118]. A typical example would be when a consumer has forgotten to take their medicine at a particular time and only remembers later, then takes a double dose to make up for the forgotten one or take the forgotten dose too close to the next scheduled dose. Using Citenvir and HEXA-BLOK as examples, the consumers are instructed to not take a double dose if they missed one but only take it as soon as they remember unless it is time for the next dose[119,120]. Some consumers take a higher dose with a thinking that this will help them get better much quicker, without realising the overdose is likely to cause them more harm. At times, the doctor's instructions may not be clear enough for the consumer to follow properly and lack of medical judgement on how much the consumer has understood could have adverse outcomes on the consumer's health[121]. For example, when a doctor instructs a consumer to take the medicine three times a day. Most consumers interpret this as taking the medicine in the morning, afternoon, and evening before bedtime, without taking into consideration the time difference

between taking the doses. The consumer is then likely to take the morning dose around the time when they have breakfast, the afternoon dose taken around lunchtime and the evening dose around supper time. There is likely to be a 4 – 6 hours difference between each dose instead of the eight hourly-intended dose interval. The concept of a day being 24 hours and dividing those hours by a number of times one needs to take their medicine to determine the appropriate dose-interval is foreign to many consumers and often not discussed with the healthcare professionals during consultations.

In a study conducted in Ghana to determine the prevalence of noncompliance among patients with chronic diseases[117], a high noncompliance was reported (55.5%, N = 200). Majority of patients (81.5%) from the study were reported to be taking at least two medicines at a time, with 58% being aware of complications which could result from noncompliance.

Other actions taken by some consumers in the current study in response to the ADRs included going back to their doctor or clinic. However, in those cases, further information on the outcome of the visits was not provided. It could be that their treatment was not changed after consulting and/or clarification was also provided on how medicines work, and therefore should the ADRs experienced be tolerable, they need not make any adjustments on their treatment. Additional actions are also likely to have been taken though not included in the report. Other actions reported in the study by Jacobs *et al*[115] include self-medication and discussion of the ADR with other people. Such discussions would even include warning other patients who may be taking the same medicine to be vigilant, not to take it or visit the health centre.

The growing use of herbal, complementary and alternative medicines (CAMs), off-label use, self-medication (which is obtaining of medicine without a prescription) and can include/OTCs medicine without a prescription and can include CAMs and OTC)/OTCs (include schedule 1 and 2 medicines which can be obtained with or without a prescription) and use of combination therapies for chronic conditions have been noted to be contributing to the increasing safety concerns[100,117]. The findings from this study show a noticeable percentage (6.19%, combined) of ADR reports in which the complementary and OTC medicines are suspected to have caused the reactions. Many of the complementary medicines seem to have undocumented side

effects as only 10% of the ADRs could be verified as listed in the medicines package insert. Furthermore, 5.28% of the suspected medicines could not be identified (i.e., no information about the medicine on the references used in the current study, nor through general search on the internet). Since there is no available database for all herbal and natural products that are easily accessible in the local markets (pharmacies and grocery shops), and traditional medicine it is even difficult to determine what the active ingredients in these products could be. With the recent amendment of Act 101 of 1965 in 2014 to include regulation of CAMs, many manufacturers of CAMs are in the process of updating their products' labels and submit them to SAHPRA. This is an ongoing process and many of these complementary medicines are allowed to remain in the market with a condition that a disclaimer is added "this medicine has not been evaluated by the South African Health Products Regulatory Authority. This medicine is not intended to diagnose, treat, cure, or prevent any diseases". Without prejudice to the claims made on the safety of these CAMs, their safety profiles remain unconfirmed. The safety information provided on many of the CAMs labels, especially where no clinical trials were conducted, are mostly based on the established safety profiles of the individual ingredients/herbs used, with no established safety data on the combined ingredients/herbs. African traditional medicines are still excluded from the CAMs regulation, despite a high consumption rate (72%) amongst the Black South African population across a diverse age group, education, religious and occupational status[122]. These consumers are of the view that traditional medicines provide a more holistic treatment option, whereby consumers are offered a personalised treatment with counselling prior to being dispensed the medicine[123].

In a study by Hariraj & Aziz[116], traditional products constituted 48% of the total suspected ADR-causing medicines reported; half of which were suspected for serious adverse reactions and only 5% had marketing authorisation. Available samples for some of the products (47 in total) reported to have caused an ADR were tested and twenty-three products were found to have been adulterated with prescription medicines and four were cosmetics products with exceeded limits for some of the restricted substances. In the Addo *et al* study[117], 22.5% of patients reported to be taking herbal products in conjunction with prescribed medicines whereby 8% of these patients eventually discontinued the prescribed treatment. In a study to assess patients' perception on treatment noncompliance in Fiji[118], many patients reported to

be substituting prescription medicine with herbal treatment as they perceive them to be more effective for their conditions. Lack of regulations and available safety data on the increasing use of traditional medicines present another dimension on safety reporting as there are no references on the content, quantities, and quality of these medicines. There are also no standardised names or reference list for these medicines, the names or identification varies across the traders/healers, region, and culture; with at least 771 indigenous plant species recorded to be involved as traditional medicine sources[122]. Some of the unidentified reported suspected medicines (total 5.3%) in the current study could be falling into this category.

Adverse drug reactions are recorded to be responsible for 3% of hospitalisations in France and are amongst the top ten leading causes of morbidity and mortality in the US[124]. The increasing use of self-medication and traditional medicines adds to the current challenges[125]. This study highlights the need for a robust PV system with a strong collaboration from the local traditional doctors and CAMS manufacturers to ensure safety issues arising from use of these medicines are well documented to safeguard the well-being of consumers. This would require establishment of safety data and proper labelling of each product allowed into the market.

The Covid-19 pandemic could have also contributed to the increasing use of the herbal and traditional medicines with less or undocumented safety profiles. The promotion on the use of herbal and supplementary medicines by the media and some public figures at the onset of the pandemic could have encouraged the off-label use and inappropriate concomitant OTC medicines by the public[111].

The high number of ARVs from reports in the current study is in line with the findings of Ampadu *et al*[26] and corresponds to the prevalence of HIV infection in South Africa[126]. ARVs were found to be the dominating product class in the individual case safety reports (ICSRs) from Africa[26]. Amongst other classes included the antibiotics which is the fifth highest reported suspected medicine class in the current study. In the sub-analysis study for cardiometabolic medicines from Sub-Sahara Africa, Berhe *et al*[127] has highlighted the possibility of frequent infectious diseases such as TB and HIV in patients with cardiometabolic conditions which may pose safety concerns to the patients resulting from medicine interactions, drug-disease, and disease-disease

interactions. This may then explain the high number of antihypertensives, and antidiabetics reported as suspected medicines causing the ADRs reported in the current study. Antihypertensives at 15.8% are the second highest class of medicine frequently reported in the current study, with hydrochlorothiazide, a diuretic (52.17%) and enalapril, ACE inhibitor (27.54%) most often suspected within this medicines class. It is not surprising to have enalapril as the second highest suspected medicine in this class, as it has been documented to be the second most used antihypertensive medicine in South Africa[127]. However, as Berhe *et al*[127] has indicated, it is concerning that this medicine which has been established to be a less effective treatment and poorly tolerated in a Black population. A robust PV system should also enable reports on lack of efficacy of therapies taken. However, this may require more awareness/education to the consumers as they may struggle to differentiate the disease symptoms versus adverse effects from the treatment being taken. Getting a prescription to treat an unrecognised ADR which is mistaken as an emerging condition, may further put the consumers' health at risk, a phenomenon known as prescribing cascade[112]. Consumers are more likely to report on ADRs that they can easily identify and do not require a diagnosis from an HCP[124]. This would then also require close monitoring from the healthcare providers on patients' response to prescribed treatment, review the treatment and report any concerns with the treatment outcomes such as lack of efficacy and/or lack of patient response to treatment.

7.2.5 Coding

When using MedDRA for coding an ADR, the multiaxiality of the systems allows for a single term to be coded into different preferred terms, allowing retrieval and presentation via different data sets.

Communication barriers between the consumer and the healthcare practitioner can jeopardise the safety of the consumer, hinders consumers' ability to seek healthcare services and negatively affect the quality-of-care received[128,129]. Partida[128] also outlines the vital factors that play a role in harmonious communication, two of which would have a major impact on ADR coding and assessment: an inevitable association between culture and language, an interdependent relationship between cultural competency and effective communication. Understanding of a consumer's culture

becomes crucial interacting with high illiterate communities and/or where the use of English language is limited. The complexity of the terminology used in the healthcare environment is an additional challenge; some college graduates and professionals in the teaching and engineering field in the US were found to have difficulties understanding typical health information[129].

Collaboration between healthcare providers with professional medical interpreters and cultural sensitivity training for medical doctors have been shown to improve healthcare services in situations where language is a major challenge[130,131]. However, these services are not always available and the use of informal interpreters such as family members, hospital security guards and other healthcare professionals such as nurses is cluttered with bias and not sustainable[131,132]. This setup may produce sustainable positive results in high-income countries where language barriers are mainly due to refugee populations. In countries like South Africa with diverse multi-cultural and heteroglossic society the use of professional medical interpreters may have low success rates. South Africa has eleven official languages with inherent multiple dialects and cultural differences, four main religions and a large number of African migrants[132,133]. To effectively use a language for communication, cultural sensitivity should also be taken into consideration as they are intertwined. When registering a pharmaceutical product, the labelling is required to be provided in at least two languages, with English as the primary language. Emanating from the historical set up, the second language used is Afrikaans. According to Statistics South Africa[134], the Afrikaans language is only spoken by 9.7% of the total population, whereas isiZulu is the most common spoken language by majority (25.1%), followed by English at 16.6% and then isiXhosa at 12.8%. These languages are also dominantly used in the Western Cape, Gauteng, and KwaZulu-Natal, in a country with only 12% literacy rate[135].

As part of her doctoral studies, Saohatse[106] looked at a variety of languages at Baragwanath Hospital in Gauteng, South Africa. About 40% of patients seeking health services were Zulu speaking, followed by Southern Sotho (20%), Tswana (19%) and Xhosa (12%) with other languages at 3% (Tsonga) and the rest below that. Of the eighty doctors who work at the hospital, forty-five were South Africans and only eleven could speak one of the African languages, though not necessarily speak it to question

and diagnose as they mostly understand the basics. The doctors had a support structure of one hundred nurses who were all South Africans and spoke a mix of all eleven official languages, though none could speak all African languages spoken by patients at the hospital. At the time of conducting the study[106], 75% of patients interviewed did not understand English and the doctor would rely on fellow patients in the same ward to assist with interpretation since nurses were not always readily available to assist with interpretation due to their routine duties. Some of the observations from Saohatse's study highlighting the plight of language barriers in healthcare, offsetting appropriate and quality services given to patients and thus ADR reporting included:

- A Sotho-speaking patient reported an ADR (vomiting and stomach cramps, feeling very ill) to the nurse and asked the nurse to inform the doctor who prescribed the medicine to her. The nurse did not convey the ADR and simply returned with the same medicine and instructed the patient to drink. The patient was shouted at by the nurse and later by the doctor for refusing to drink the medicine and was left by herself, which caused her further distress.

The case above highlights the disparities that patients are faced with when seeing health services. This scenario is in line with literature regarding some of the factors reported by patients as the reasons for not reporting ADRs[22,62]. Such an unfortunate experience is likely to discourage this patient and any other patients who may have witnessed the incident from reporting ADRs in the future[53,59,60]. The language barrier and the dismissal attitude of the doctor and nurse have also cost the patient the much-needed medical assistance due to her. The attitude of the nurse is also a call for concern. How many patients could have suffered the safe fate in her hands and at the hands of other healthcare providers with a similar attitude?

Coding of ADRs into the medical dictionary requires reading and interpretation of the reported adverse reactions. Similar to communication between a patient and a healthcare provider, the language used in describing an ADR can have an impact in the coding process which may then impact the signal generation process[136]. Due to the natural ambiguity (i.e. the consumer reported ADR has a different connotation/meaning in medical/clinical practice) of reported ADRs, over 25% of the reported terms could not yield any results in the MedDRA dictionary, whereas 2.5%

had lexical variations and 8.7% had results which contained the search word used (i.e., the reported ADR term). None of these ADRs had any MedDRA fit/exact code and were therefore given a MedDRA code slightly different from the reported verbatim. The variation of some of the ADR reported terms to get a closely related classification code could have also distorted the original meaning of the reported term due to language and cultural differences which were unknown to the researcher.
Inacio *et al*[136] reported a high linguistic variation from HCPs' ADR reports in 2004 with insignificant improvement in 2012. An improvement in the language used was expected due to the maturity of the PV system and their level of experience in using the medical jargon.

With consumers coming onboard to submit their ADR reports, the linguistic variations and language inaccuracies are likely to increase as consumers may not be familiar with the medical terminology used for most ADRs. Secondly, consumers report the ADRs in more descriptive format than single or two terms, and some would often add the extent of the ADR's impact on carrying out their daily activities. Due to this, lexical variations may also be more common from consumer ADR reports. The diverse culture in South Africa and other African countries may add another layer of coding challenges. A high number of reports not conforming to the biomedical framework and not initially filtered by HCPs will increase as awareness increases and more consumers send their reports. Lack of understanding of the linguistic variations and associated cultures would reduce the value of these ADRs during the coding process, which uses a medical coding dictionary with a predefined list of possible adverse reactions. Understanding of Language and cultural sensitivity of where the ADR originates, would assist in ensuring the most appropriate and relevant code is used.

Two ADRs from the current study would be used as an example of the challenges with linguistic variations in reported ADRs: '*Coughing, swollen lungs'* and '*bad skin rash*'. These ADRs seem to be a direct translation from the reporters' native language(s). Using the primary researcher's native language as a reference (based on indigenous knowledge), when one has chest congestion, it is loosely and directly described as having a swollen chest or swollen lungs. This is mainly due to the experienced symptoms such as laboured breathing, tightness in the chest and producing of phlegm. Without any X-rays done, the consumer cannot determine the physiology of the lungs

when inflamed. As such, this reported ADR could be interpreted and classified incorrectly due to language barrier and/or cultural language practices. With *'Bad skin rash*', this could be referring to severe/serious skin rash and/or worsening of skin rash. The word '*bad'* is loosely translated and commonly used to refer to something that is adversely severe or serious. When it comes to interpreting ADRs from non-English speaking consumers, native language background may be an added advantage to vocabulary knowledge and understanding of the reported ADR terms.

Some of the medical terminologies are very difficult to interpret in native languages. Some non-healthcare professional consumers have indicated to be comfortable with using the English medical terms as they are perceived to be similar with their native language, and thus are able to derive the meaning of those terms[137]. As most consumers may be unaware of the differences in meaning divergences with medical terms to their native languages, healthcare professionals have cautioned this attitude as one of the major challenges in communication with consumers. Such would result in consumers misusing and misinterpreting medical terms which may have a different meaning to the healthcare professional[138]. A medical term and lay term exist for most of the words, though the meaning may differ which may result in misunderstandings between the patient and healthcare professional. An example given by one of the non-native English speaking Chinese patients in Dahm's study[137] is '*inflammation'*. In the Chinese terminology, bacterial and viral infections are responsible for causing all inflammation, and antibiotics are then understood as the treating therapy.

The pronunciation and spelling of the medical terms are also likely to play a role in medical terminology confusion with consumers. This was observed by another researcher in patients diagnosed with hypertension, where the majority of those patients thought they had Hyper-tension (defined as a physical illness characterised by excessive nervousness and untoward social stress)[138]. In this study, conducted to assess the understanding of common health terms, a wide gap in understanding of the common terms used versus the psychological terms between doctors, nurses and patients was recorded. The differences in the understanding of the terms were mainly due the different meanings attached to the words when using the clinical definitions as compared to the common lay term definition.

Some patients, particularly those with chronic and/or life-threatening conditions, have demonstrated to have a better understanding and thus use of medical terms within the field of their health condition[139]. However, for any other conditions, they may have superficial knowledge or less familiarity with medical terms used.
Heartburn is another example which is sometimes interpreted as a cardiac condition by non-English HCPs (B Rosenkranz, personal information). A more general term 'emotional lability' was used in one study when referring to suicidal tendencies in patients taking paroxetine[78], whereas others were coded as aggression. Singh[140] reflected on a case where medical translation errors resulted in devastating outcomes, whereby an 18-year-old Spanish young man was rushed to the emergency room and got treated for alcohol intoxication. Due to lack of interpreters, the emergency room medical staff incorrectly interpreted the Spanish word '*intoxicado'*, which means *nauseated*. The patient suffered brain haemorrhage, resulting in permanent paralysis due to language interpretation error.

The linguistic variations could also include the shortened words which are often noticed in social media, which may be due to character limitations and in other cases, the dialect used when consumers express themselves. The latter was noted by Freifeld *et al*[141] during an assessment of medicine safety information shared via Twitter™. One patient reported two ADRs in one post, with one product reported as ineffective and expressed as "Humira never really worked for me". The second ADR, which was classified as gastrointestinal perforations, was reported as "*Xeljanz was the best but ate a hole in my stomach*". To contextualise the latter ADR and correctly code the ADR required an understanding of the local language use in addition to the product label during interpretation.

A variety of codes were used to code for the same ADR type during a review of clinical coding of paediatric ADRs[142]. Such disparities would limit the ADRs contribution in identifying the safety parameters of the suspected medicine, causality assessment and thus delay in signal detection. At times, a single report may contain one adverse reaction with multiple suspected medicines and or multiple adverse reactions linked to a single suspected medicine. These scenarios should also be taken into consideration when coding.

Poor understanding of health-related terminologies used by non-English speaking consumers may lead to misinterpretation of ADRs. This may have a cascade of devastating outcomes, including miscoding of the ADRs, delaying signal detection, changing the safety profile of the suspected medicines, incorrect diagnosis and/or treatment given to the affected consumers which may further worsen their adverse reaction and negatively impact their health.

Improvements in the MedDRA dictionary would require harmonising ADR terminology across the globe, similar to the SNOMED-CT (Systematised Nomenclature of Medicine Clinical Terms) project – which aims to standardise multilingual vocabulary for single clinical terminology[143]. This would require consideration of establishing the reference terminology in each country and region to standardise the vocabulary to be used during coding, thus minimising the local/regional language variations and improving accuracy. Understanding of the different languages and cultural sensitivity would be crucial for the successful establishment of such a reference database.

Partnering with patient networking groups to create awareness and ongoing reminders to consumers to report ADRs through the groups' available communication channels (e.g., websites, regular newsletters, featuring on special events, etc) should also be considered. Schroder *et al*[144] has found that regular review of comments from patients' group discussion forums also add other patients' perspectives on the treatment challenges they encounter, which are often not reflected elsewhere. They noted the challenges discussed to be of qualitative nature and what caused the patients more concerns, provided timely to the event and will be useful supplemental data to clinical trials data. Freifeld *et al*[141] conducted an ADR surveillance through Twitter™ to assess feasibility and reliability of review social media platforms for any possible AEs. One of the safety information picked up during the assessment, was a Twitter™ posted by a medical doctor on the possibilities of rivaroxaban causing recurrent tonsillitis when taken for Deep Vein Thrombosis (DVT). This prompted a recommendation for post hoc analysis from label studies, peer-reviewed research, and regulatory databases on rivaroxaban.

Use of social media networking sites such as Facebook™ and Twitter™ have also been shown to be reliable sources of patients' experience with their treatment including possible ADRs[125]. This could include SAHPRA creating their own Facebook

page and Twitter account that would enable facilitation of awareness creation, interact with consumers, and allow consumers to share their experiences, concerns and ask any questions they may have regarding their treatments. To meet the regulatory requirements for an ADR report, the Facebook and/or Twitter account would represent an identifiable reporter and/or an identifiable patient[141].

7.2.6 Other Challenges with Consumer ADR Reports

Though it was noted in another study that patients were able to identify an ADR based on the unexpected nature of the ADR and the timing of the occurrence in relation to initiating treatment with the suspected medicine[63], it could not be established in the current study how consumers were able to identify an ADR. This is especially since there were no time points indicated on the emergence of an ADR in relation to the suspected medicine(s) in all the ADR reports received. Furthermore, in those instances whereby the consumer and/or reporter has discontinued treatment with the suspected medicine, reduced the dose or changed the treatment, it was not confirmed if the ADR stopped. For ADRs which are time-sensitive in relation to their occurrence following administration of the suspected causality medicine, this will be a limiting factor as the ADR reporting tool does not make this information as mandatory information to included, and may cause delays in signal detection.

With the rising levels of self-diagnosis and thus self-medication, this may have a negative impact not only on the consumer but on the processing of the ADR reports submitted from such consumers. Some of the consequences as highlighted by Chouhan and Prassad[146], include

- misdiagnosis,
- inappropriate therapy choice,
- inability to recognise that the active ingredient in self-medication is the same with that of another treatment they may already be taking, resulting in overdose,
- inappropriate storage conditions,
- inappropriate and/or prolonged usage,
- inability to recognise and/or comprehend the pharmacological risks, including contraindications, warnings and interactions with other medicines or food.

7.3 Limitations

The limitations of the current study included the particular use of English language in a country with high illiteracy and eleven official languages. Though lay terms were used in the ADR reporting form, the readability index was not measured. Due to limited resources, not all initially planned reporting channels could be explored. However, they remain viable and worth assessing: zero rated mobile reporting, paper/print form completed and sent via social media screenshots, SMS reporting options, and/or voice-recorded notes.

Reports were received only from consumers who used the online reporting system. This accommodates mostly consumers with easy access to internet connection and familiar with the use of social media (where recruitment and awareness materials were shared through). Inadvertent bias is likely to have been introduced through the demographic profiles of participants used in the ADR tool validation process as well as the types of recruitment centres used to create awareness and recruit consumers to report the ADRs through the developed tool.

The method used to sample the participants to complete the validation processes was prone to selection bias and error, though not intended. This sampling method was employed to maximise efficiency with the use of limited resources (i.e. selection of healthcare professionals who were known to have knowledge and experience in the field). To minimise bias, invitations for participation in the study were distributed anonymously.

There were no causality assessments done of the ADRs submitted through the tool, which is one of the critical elements in determining the feasibility and value of the tool. A collaboration with SAHPRA was desired for this project. However, there was no feedback and/or response received from the regulatory authority.

7.4 Conclusion of the Chapter

The current developed ADR tool for consumers has been validated and its feasibility successfully tested and confirmed. The tool received a good response rate from consumers during the feasibility testing period, enabling a proper assessment on the

usability, accessibility, and practicality of the tool. The study demonstrated the feasibility of the tool to collect the intended information and the understanding of consumers in identifying and reporting an ADR. The quality of ADR reports from the consumers, the completeness and the terminology used indicates ability of consumers to understand the ADR reporting requirements.

The consumer ADR reports would boost the healthcare professionals' spontaneous ADR reports, add value to the PV system in terms of quantities and quality reports and thus contribute to signal detection, medicine safety knowledge and management in the country. Combining these reports with the reports from healthcare professionals already in the PV system would increase the number of ADR reports in the country, which will help with an overview of the safety use and management of medicines in the country. It will also enable direct comparison of ADR reports between consumers and healthcare professionals in South Africa. It will further enable assessment of the gaps in ADR reporting and medicine management to determine the best approaches in promoting ADR reporting. Since consumer reporting is still very new in the country, this study can be used as a basis to assess and improve on the newly introduced ADR reporting tools, as well as conduct further studies to assess the interest, understanding and factors influencing consumers to report ADRs.

CHAPTER 8

RECOMMENDATIONS AND CONCLUSIONS

The feasibility part contributed to the body of knowledge to incorporate direct consumer reporting that could be fed into the SA PV system. If it had not been for COVID-19 and the implementation of the Med Safety App by SAHPRA this study would have been one of the first to have investigated direct consumer reporting on a larger scale in South Africa. Fostering a close collaboration with SAHPRA to share the knowledge and experience gained by this research will hasten the implementation of processes to improve the PV system in South Africa.

As this was the first ADR tool to allow consumers to report ADRs in South Africa, further assessment on the usability, accessibility, and responsiveness of consumers on safety reporting using the SAHPRA online tools should be carried out. Surveys to assess factors that encourage consumers to report using the newly introduced safety reporting tools as well as barriers should also be conducted. The results could then be incorporated in the recruitment and awareness strategies (as solutions) and rolled out to the broader consumers throughout the country. The use of online reporting tools may be well acceptable and successfully launched in urban areas where almost everyone has access to a mobile device or smartphone and access to the internet. However, in rural areas where mobile network and internet connection coverage as well as access to healthcare services are still a major challenge, the online reporting systems may not be of effective use. For a robust pharmacovigilance system in South Africa, SAHPRA and all relevant stakeholders need to consider and deploy safety reporting and awareness methods suitable for the available infrastructures and settings in these areas. As South Africa is a multilingual country with diverse cultures, the reporting system may also need to be adapted to accommodate this diversity. Lack of ownership by the local stakeholders, poor coordination, low awareness on PV and/or awareness and reporting strategies which are suitable for consumers in certain areas and lack of access to resources to enable reporting have been indicated as some of the major barriers to implementation of a successful PV[145]. Setting up of PV offices in regional government hospitals, expanding the Western Cape project on training and allocating interpreters in major hospitals as well as having at least one to

two health community workers trained on PV processes and reporting in local healthcare facilities would greatly improve on increasing the safety reporting as well as contribute to quick signal detection, thus creating a much safer health system for the consumers in the country. These setups would require to be properly equipped with suitable resources including easy access to internet connection in order to speedily assist consumers. Collaborations with patient network groups, healthcare professionals network groups and tertiary institutions offering healthcare services training would also be crucial for the success of the PV system.

REFERENCES

1. South African Health Products Regulatory Authority. 2021. Post-Marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa, Version 8 dated May 2021. https://www.sahpra.org.za/safety-information-and-updates/
2. South African Health Products Regulatory Authority. 2021. Guideline for Adverse Drug Reactions (ADRs) Reporting for Healthcare Professionals. *SAHPRA Communication to Healthcare Professionals*, May 2021
3. World Health Organisation. 2012. Safety Monitoring of Medicinal Products. Reporting System for the General Public.
4. South African Health Products Regulatory Authority. 2020. Complementary Medicines – Discipline Specific Safety and Efficacy, version 3 January 2020.
5. Mothibe ME and Sibanda M. 2019. African Traditional Medicine: South African Perspective. *Intech Open. Traditional and Complementary Medicine*, doi:10.5772/intechopen.83790
6. Gurmesa LT, Defedo MG. 2016. Factors Affecting Adverse Drug Reaction Reporting of Healthcare Professionals and their Knowledge, Attitude and Practice towards ADR Reporting in Nemkete Town, West Ethopia. *BioMed Res Int*, Article ID 5728462, 6 Pages
7. Golomb BA, McGraw JJ, Evans MA, Dimsdale JE. 2007. Physician Response to Patients Reports of Adverse Drug Effects. Implications for Patient-Targeted Adverse Effect Surveillance. *Drug Saf*, 30 (8): 669 – 675
8. Gäwert L, Hierse F, Zink A, Strangfield A. 2011. How Well Do Patient Reports Reflect Adverse Drug Reactions Reported by Rheumatologists? Agreement of Physician-and Patient-Reported Adverse Events in Patients with Rheumatoid Arthritis Observed in the German Biologics Register. *Rheumatol*, 50: 152 - 160
9. Suleman F. 2010. Pharmacovigilance – Who is Responsible and Why Should We Care? *SA Pharmaceut J*, p56 - 58
10. Van Grootheest K, de Graaf L, de Jong-van den Berg LTW. 2003. Consumer Adverse Drug Reaction Reporting. A New Step in Pharmacovigilance? *Drug Saf,* 26 (4): 211 - 217

11. Mehta U, Kalk E, Boulle A, Nkambule P, Gouws J, Rees H, Cohen K. 2017. Pharmacovigilance: A Public Health Priority for South Africa. *S Afr Health Rev 20th Edition,* p125 – 134
12. Guidance on the Format of the Risk Management Plan (RMP) in the EU – in Integrated Format. *European Medicines Agency, Science Medicines Health*. EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2, Human Medicines Evaluation, 31 October 2018
13. Güner MD and Ekmekci PE. 2019. Healthcare Professionals' Pharmacovigilance Knowledge and Adverse Drug Reaction Reporting Behavior and Factors Determining the Reporting Rates. *J Drug Assessment*, 8 (1): 13 – 20
14. Hazell L, Shakir SAW. 2006. Under-Reporting of Adverse Drug Reactions. A Systemic Review. *Drug Saf*, 29 (5): 385 – 396
15. Varallo FR, de Oliverra Paim Guimarães S, Abjaude SAR, de Carvalho Mastroianni P. 2014. Causes for the Underreporting of Adverse Drug Events by Health Professionals: A Systematic Review. *Rev Esc Enferm USP*, 48 (4): 739 – 747
16. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. 2009. Determinants of Under-Reporting of Adverse Drug Reactions. A Systematic Review. *Drug Saf*, 32 (1): 19 – 31
17. Weigmann K. 2016. Consumer Reporting of Adverse Drug Reactions. *EMBO Reports*, 17 (7): 949 – 952
18. Rolfes L, Van Hunsel F, Wilkes S, van Grootheest K, van Puijenbroek E. 2015. Adverse Drug Reaction Reports of Patients and Healthcare Professionals – Differences in Reported Information. *Pharmacoepidemiol and Drug Saf*, 24: 152 – 158
19. Srba J, Vlcek J. 2014. Position and Processing of Adverse Drug Reactions Directly Submitted by Patients to National Regulatory Authorities in Europe. *J Pharmacovig*, 2 (1): 1 – 5
20. Van Hunsel F, Härmark L, Pal S, Olsson S, van Grootheest K. 2012. Experiences with Adverse Drug Reaction Reporting by Patients. An 11-Country Survey. *Drug Saf*, 35 (1): 45 – 60
21. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. 2004. Adverse Drug Reactions as Cause of

Admission to Hospital: Perspective Analysis of 18 820 Patients. *Br Med J*, 329: 15 – 19

22. Leone R, Moretti U, D'Incau P, Conforti A, Magro L, Lora R, Velo G. 2013. Effect of Pharmacist Involvement on Patients Reporting of Adverse Drug Reactions: First India Study. *Drug Saf*, 36: 267 – 276
23. Blenkinsopp A, Wilkie P, Routiedge PA. 2006. Patient Reporting of Suspected Adverse Drug Reactions: A Review of Published Literature and International Experience. *Br J Clin Pharmacol*, 63 (2): 148 – 156
24. Härmark L, van Hunsel F and Grundmark B. 2015. ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems. *Drug Saf.* 38 (4): 337 – 47. doi:10.1007/s40264-015-0264-1
25. Csoka AB, Bahrick A, Mehtonen OP. 2008. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *J Sex Med*. 5(1):227-33. doi: 10.1111/j.1743-6109.2007.00630.x. Erratum in: J Sex Med. 5(12):2977.. Csoka, A [corrected to Csoka, AB]. PMID: 18173768.
26. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, Leufkens HGM, Dodoo ANO. 2016. Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®. *Drug Saf*, 39: 335 – 345
27. Dowelani N. 2017. A Review of Pharmacovigilance Activities in South Africa and Comparative Analysis of Adverse Drug Reaction Reporting Tools in South Africa. University of Stellenbosch PGDip Thesis
28. Maigetter K, Pollock AM, Kadam A, Ward K, Weiss MG. 2015. Pharmacovigilance in India, Uganda, and South Africa with Reference to WHO's Minimum Requirements. *Int J Health Policy Manag*, 4 (5): 295 – 305
29. Terblanche A, Meyer JC, Godman B, Summers RS. 2017. Knowledge, Attitudes and Perspective on Adverse Drug Reaction Reporting in a Public Sector Hospital in South Africa: Baseline Analysis. *Hosp Pract*, doi: 10.1080/21548331.2017.1381013
30. Harrison R, Walton M, Manias E, Smith-Merry, Kelly P, Iedema R, Robinson L. 2015. The Missing Evidence: A Systematic Review of Patients' Experiences of Adverse Events in Health Care. *Internat J Qual Health Care*, 27 (6): 424 – 442

31. Baron S. Goutard F, Nguon K, Tarantola A. 2013. Use of a Text Message-Based Pharmacovigilance Tool in Cambodia: Pilot Study. *J Med Internet Res*, 15 (4): e68
32. Jobson R. 2003. Pharmacovigilance: A Brief Glimpse. *SA Fam Pract*, 45 (2): 53 – 57
33. Hadi MA, Neoh CF, Zin RM, Elrggal ME, Cheema E. 2017. Pharmacovigilance: Pharmacists' Perspective on Spontaneous Adverse Drug Reactions Reporting. *Intergrat Pharm Res and Pract*, 6: 91 98
34. Jeetu G, Anusha G. 2010. Pharmacovigilance: A Worldwide Master Key for Drug Safety Monitoring. *J Young Pharm*, 2 (3): 315 – 320
35. Rolfes L, Van Hunsel F, Taxis K, van Puijenbroek E. 2016. The Impact of Experiencing Adverse Drug Reactions on the Patient's Quality of Life: A Retrospective Cross-Sectional Study in the Netherlands. *Drug Saf*, 39 (8): 769 – 776
36. Frankenfeld C. 2004. "Serious" and "Severe" Adverse Drug Reactions Need Defining. *Br Med J*, 329: 573
37. Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC. 2011. Evaluation of Patient Reporting of Adverse Drug Reactions to the UK 'Yellow Card Scheme': Literature Review, Descriptive and Qualitative Analyses, and Questionnaire Surveys. *Health Technol Assess*, 15 (20): 1 – iv
38. Watson R. 2012. New EU Drug Safety Committee Ends National Reporting of Drug Reactions. *Br Med J*, 345: e4690
39. Ramakrishnaiah H, Naidu S, Jyothsnya S. 2017. A Comparative Study of Adverse Drug Reactions Reported by Healthcare Professionals and Patients in a Tertiary Care Teaching Hospital. *Int J Br Clin Pharmacol*, 6 (5): 1078 – 1084
40. Mouton JP, Njuguna C, Kramer N, Stewart A, Mehta U, Blockman M, Fortuin-De Smidt M, De Waal R, Parrish AG, Wilson DPK, Igumbor EU, Aynalem G, Dheda M, Maartens G, Cohen K. 2016. Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South Africa. Medicine (Baltimore) 2016 May; 95 (19): e3437. Published online 2016 May 13.
41. Mouton JP, Fortuin-de Smidt MC, Jobanputra N, Mehta U, Stewart A, de Waal R, Technau K, Argent A, Kroon M, Scott C, Cohen K. 2020. Serious Adverse Drug

Reactions at Two Children's Hospitals in South Africa. *BMC Pediatr*, 20 (3). https://doi.org/10.1186/s12887-019-1892-x

42. Mouton JP, Mehta U, Parrish AG, Wilson DPK, Stewart A, Njuguna CW, Kramer N, Maartens G, Blockman M, Cohen K. 2015. Mortality from Adverse Drug Reactions in Adult Medical Inpatients at Four Hospitals in South Africa: A Cross-Sectional Survey. *Br J Clin Pharmacol*. 80(4): 818–826.
43. Lynn RM, Riding K, McIntosh N. 2010. The Use of Electronic Reporting to Aid Surveillance of ADRs in Children: A Proof-of-Concept Study. *Arch Dis Child,* 95:262 - 265
44. Harmark L, Van Hunsel F, Grundmark B. 2015. ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems. *Drug Saf,* 38 (4): 337 – 347
45. Duarte M, Ferreira P, Soares M, Cavaco A, Martins AP. 2015. Community Pharmacists' Attitudes Towards Adverse Drug Reaction Reporting and their Knowledge of the New Pharmacovigilance Legislation in the Southern Region of Portugal: A Mixed Methods. *Drug Ther Perspect*, 31 (7): 316 – 322
46. Arnott J, Hesselgreaves H, Nunn AJ, Peak M, Pirmohamed M, Smyth RL, Turner MA, Young B. 2012. What Can we Learn from Parents about Enhancing Participation in Pharmacovigilance? *Br J Clin Pharmacol*, 75 (4): 1109 – 1117
47. Pal SN, Olsson SI, Brown EG. 2015. The Monitoring Medicines Project: A Multinational Pharmacovigilance and Public Health Project. *Drug Saf*, 38 (4): 319 – 328
48. Ekman E, Bäckström M. 2009. Attitudes Among Hospital Physicians to the Reporting of Adverse Drug Reactions in Sweden. *Eur J Clin Pharmacol*, 65: 43 – 46
49. Kozamernik B. 2010. Spontaneous Adverse Drug Reaction Reporting: Attitudes and Practice of Health Care Professionals and Distributors in Southeast European Region. *Farm Vestn*, 61: 271 – 281
50. Hasford J, Goettler M, Munter K-H, Müller-Oerlinghausen B. 2002. Physicians' Knowledge and Attitudes Regarding the Spontaneous Reporting System for Adverse Drug Reactions. *J Clin Pharmacol*, 55: 945 – 950
51. Belton KJ and The European Pharmacovigilance Research Group. 1997. Attitudes Survey of Adverse Drug Reaction Reporting by Healthcare Professionals across the European Union. *Eur J Clin Pharmacol*, 52: 423 – 427

52. Fadare JO, Enwere OO, Afolabi AO, Chedi BAZ, Musa A. 2011. Knowledge, Needs. *Drug Saf*, 39 (11): 1105 – 1116
53. Inch J, Watson MC, Anakwe-Umeh S, on behalf of the Yellow Card Study Collaboration. 2012. Patient versus Healthcare Professional Spontaneous Adverse Drug Reaction Reporting. *Drug Saf*, 35 (10): 807 – 818
54. Anderson C, Krska J, Murphy E, Avery A on behalf of the Yellow Card Study Collaboration. 2011. The Importance of Direct Patient Reporting of Suspected Adverse Drug Reactions: A Patient Perspective. *Br J Clin Pharmacol*, 72 (5): 806 – 822
55. Van Hunsel F, van der Welle C, Passier A, van Puijenbroek E, van Grootheest K. 2010. Motives for Reporting Adverse Drug Reactions by Patient-Reporters in the Netherlands. *Eur J Clin Pharmacol*, 66 (11): 1143 - 1150
56. Krska J, Jones L, McKinney J, Wilson C. 2011. Medicine Safety: Experiences and Perceptions of the General Public in Liverpool. *Pharmacoepidemiol Drug Saf*, 20: 1098 – 1103
57. Attitude and Practice of Adverse Drug Reaction Reporting Among Healthcare Workers in a Tertiary Centre in Northern Nigeria. *Trop J Pharm Res*, 10 (3): 235 – 242
58. Al Dweik R, Stacey D, Kohen D, Yaya S. 2017. Factors Affecting Patient Reporting of Adverse Drug Reactions: A Systematic Review. *Br J Clin Pharmacol*, 83: 875 – 883
59. Peterson LN. 2009. Barriers to Canadian Physicians Reporting of Adverse Drug Reactions. The University of British Columbia, Thesis
60. Kadhim KA. 2015. Self-Reporting of Adverse Drug Reactions in Iraqi Hospitals: Patient's Perspective. *Pharmacol & Pharmacy,* 6: 566 - 572
61. Edwards IR, Aronson JK. 2000. Adverse Drug Reactions: Definitions, Diagnosis and Management. *The Lancet*, 356: 1255 - 1259
62. Matos C, Hãrmark L, van Hunsel F. 2016. Patient Reporting of Adverse Drug Reactions: An International Survey of National Competent Authorities' Views and
63. Medawar C, Herxheimer A, Bell A, Jofre S. 2002. Paroxetine, *Panorama* and User Reporting of ADRs: Consumer Intelligence Matters in Clinical Practice and Post-Marketing Drug Surveillance. *Int J Risk Saf Med*, 15: 161 – 169

64. Hughes L, Whittlesca C, Luscombe D. 2002. Patients' Knowledge and Perceptions of the Side-Effects of OTC Medication. *J Clin Pharm Ther*, 27: 243 – 248
65. Van Hunsel F, Talsma A, van Puijenbroek E, de Jong-va den L, van Grootheest K. 2011. The Proportion of Patient Reports of Suspected ADRs to Signal Detection in the Netherlands: Case-Control Study. *Pharmacoepidemiol Drug Saf*, 20: 286 – 291
66. Potharaju HR. 2010. Reporting of Adverse Drug Reactions by Consumers: Rationale and Potential. *Pharmbit*, XXII (2): 110 – 114
67. Durrieu G, Palmaro A, Pourcel L, Caillet C, Faucher A, Jacquet A, Ouaret S, Perault-Rochat MC, Kreft-Jais C, Castot A, Lapeyre-Mestre M, Monstastruc J-L, on behalf of the French Network of Pharmacovigilance Centres. 2012. First French Experience of ADR Reporting by Patients After a Mass Immunisation Campaign with Influenza A (H1N1) Pandemic Vaccines. A comparison of Reports Submitted by Patients and Healthcare Professionals. *Drug Saf*, 35 (10): 845 – 854
68. Jarernsiripornkul N, Krska J, Capps PAG, Richards RME, Lee A. 2002. Patients Reporting of Potential Adverse Drug Reactions: A Methodological Study. *Br J Clin Pharmacol*, 53: 318 – 325
69. Krska J, Morecroft C. 2013. Patients' Use of Information about Medicine Side Effects in Relation to Experiences of Suspected Adverse Drug Reactions. *Drug Saf*, 36 (8): 673 – 680
70. Van Hunsel F, de Waal S, Härmark L. 2017. The contribution of Direct Patient Reported ADRs to Drug Safety Signals in the Netherlands from 2010 to 2015. *Pharmacoepidemiol Drug Saf*, p1 – 7
71. Basch E. 2010. The Missing Voice of Patients in Drug-Safety Reporting. *N Engl J Med*, 362 (10): 865 - 869
72. Carlesso LC, Cairney J, Dolovich L, Hoogenes J. 2011. Defining Adverse Events in Manual Therapy: An Exploratory Qualitative Analysis of the Patient Perspective. *Manual Ther*, 16: 440 – 446
73. Van Vorst RF, Araya-Guerra R, Felsien M, Fernald D, Elder N, Dudos C, Westfall JM. 2007. Rural Community Members' Perceptions of Harm from Medical Mistakes: A High Plains Research Network (HPRN) Study. *J Am Board Fam med*, 20: 135 – 143

74. Weingart SN., Pagovich O, Sands DZ, Li JM, Aronson MD, Davis RB, Phillips RS, Bates DW. 2006. Patient-Reported Service Quality on a Medicine Unit. *Internat J Qual Health Care*, 18 (2): 95 – 101
75. Johnstone M-J, Kanitsaki O. 2006. Culture, Language, and Patient Safety: Making the Link. *Internat J Qual Health Care*, 18 (5): 383 - 388
76. World Health Organisation. 2002. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva
77. Dheda M. 2013. Decentralized HIV/AIDS Pharmacovigilance in South Africa: Mpumalanga as Pilot Province for National Roll-Out. *J AIDS HIV Res*, 5 (9): 357 – 365
78. Morley G. 2014. Adverse Event Reporting: A Brief Overview of MedDRA. *Med Writing*. 23 (2): 113 – 116
79. Challenges in Coding Adverse Events in Clinical Trials: A Systematic Review. PLoS ONE 2012; 7 (7): e41174. doi:10.1371/journal.pone.0041174
80. Kempen AV. 2007. Legal Risks of Ineffective Communication. *AMer Medic Assoc J Ethics*, 9 (8): 555 – 558
81. Karmarkar A. 2012. Reporting Adverse Drug Reactions: A View on ADR Dictionaries. *Pharma Utility*, 6 (3)
82. Medical Dictionary for Regulatory Activities. http://www.meddra.org/snomed-meddra-mapping. Accessed 12 March 2022
83. Statistics South Africa: Community Survey, 2016. https://www.statssa.gov.za/?page_id=6283
84. The Medicines and Related Substances Act, 1965 (Act No. 101 of 1965) as Amended
85. Mehta U, Dheda M, Steel G, Blockman M, Ntilivamunda A, Maartens G, Pillay Y, Cohen K. 2014. Strengthening Pharmacovigilance in South Africa. *S Afr Med J*, 2014; 104 (2): 104 - 106
86. Uppsala Monitoring Centre. https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring
87. Joubert MC, Naidoo P. 2016. Knowledge, Perceptions and Practices of Pharmacovigilance Amongst Community and Hospital Pharmacists in a Selected District of Northwest Province, South Africa. *Health SA Gesondheid*, 21: 238 – 244
88. South African Health Regulatory Authority. https://www.sahpra.org.za

89. South African Health Products Regulatory Authority. The Med Safety App. https://medsafety.sahpra.org.za
90. Guidance for Industry. 2009. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health and Human Services, Food and Drug Administration, December 2009
91. Bolarinwa OA. 2015. Principles and Methods of Validity and Reliability Testing of Questionnaires Used in Social and Health Science Research. *Nigerian Postgrad Med J*, 22 (4): 195 - 201
92. Zamanzadeh V, Ghahramanian A, Rassouli M, Abbaszadeh A, Alavi-Majd H, Nikanfar A. 2015. Design and Implementation Content Validity Study: Development of an Instrument for Measuring Patient-Centered Communication. *J Caring Sc*, 4 (2): 165 - 178
93. Taber, K.S. 2018. The Use of Cronbach's Alpha When Developing and Reporting Research Instruments in Science Education. *Res Sci Educ* 48, 1273–1296 https://doi.org/10.1007/s11165-016-9602-2
94. World Health Organisation. 2012. Safety Monitoring of Medicinal Products. Reporting System for the General Public.
95. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1994. ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. E2A. Current *Step 4* version dated 27 October 1994
96. Medical Dictionary for Regulatory Activities. https://www.meddra.org/multiaxiality
97. South African Health Products Regulatory Authority. 2020. The National Vigilance Policy for Health Technologies in South Africa, draft 2020.
98. Nadew SS, Beyene KG/Michael, Beza SW (2020) Adverse drug reaction reporting practice and associated factors among medical doctors in government hospitals in Addis Ababa, Ethiopia. PLoS ONE 15(1): e0227712. https://doi.org/10.1371/journal.pone.0227712
99. Hire RC, Kinage PJ and Gaikwad NW. 2013. Causality Assessment in Pharmacovigilance: A Step towards Quality Care. *Sch J App Med Sci*, 1 (5): 386 - 392
100. Hartwig SC, Siegel J, Scheider PJ. 1992. Preventability and Severity Assessment in Reporting Adverse Drug Reactions. *AM J Hosp Pharm*, 49 (9): 2229 – 2232

101. Agoro OO, Kibira SW, Freeman JV, and Hamish S F Fraser HSF. 2017. Barriers to the Success of an Electronic Pharmacovigilance Reporting System in Kenya: An Evaluation Three Years Post Implementation. *J Am Med Inform Assoc*, 25(6), 2018, 627–634 doi: 10.1093/jamia/ocx102
102. O'Callaghan J, Griffin BT, Morris JM and Bermingham M. 2018. Knowledge of Adverse Drug Reaction Reporting and the Pharmacovigilance of Biological Medicines: A Survey of Healthcare Professionals in Ireland. *BioDrugs*, 32:267–280 https://doi.org/10.1007/s40259-018-0281-6
103. Tull, K. 2018. Drug expiry standards in developing countries. K4D Helpdesk Report. Brighton, UK: Institute of Development Studies.
104. Singh A, Bhatt P. 2012. Comparative Evaluation of Adverse Drug Reaction Reporting Forms for Introduction of a Spontaneous Generic ADR Form. *J Pharmacol Pharmacother*, 3:228-32
105. Watson S, Caster O, Rochonb PA, den Ruijter H. 2019. Reported Adverse Drug Reactions in Women and Men: Aggregated Evidence from Globally Collected Individual Case Reports during Half a Century. EClinicalMedicine 17, 100188
106. Saohatse MC. African Language Varieties at Baragwanath Hospital: A Sociolinguistic Analysis. Report Submitted in Fulfilment of PhD study, UNISA.
107. Hasford J, Bruchmann F, Lutz M, Thürmann P, and Schmiedl S. 2021. A Patient-Centred Web-Based Adverse Drug Reaction Reporting System Identifies Not Yet Labelled Potential Safety Issues. *Eur J Clin Pharmacol*, 77:1697–1704
108. Adedeji-Adenola H and Nlooto M. 2020. Direct Reporting of Adverse Drug Reactions by Healthcare Consumers in Africa: A Narrative Review. *Int J Clin Pharm*, 43(1):11-24. doi: 10.1007/s11096-020-01141-x.
109. Upssala Monitoring Centre. https://who-umc.org
110. NIH U.S. National Library of Medicine. https://clinicaltrials.gov accessed 03 May 2022
111. Eurostat. Statistics Explained, 17 Jan 2022 https://ec.europa.eu/eurostat/statisticsexplained accessed 05 March 2022
112. Elbeddini A, Yeats A, and Lee S. 2020. Amid COVID-19: The Importance of Developing an Positive Adverse Drug Reaction (ADR) and Medical Device Incident (MDI) Reporting Culture for Global Health and Public Safety. *J Pharmaceut Pol Pract*, 13:18 https://doi.org/10.1186/s40545-020-00219-1

113. Kalisch LM, Caughey GE, Roughead EE, and Gilbert AL. 2011. The Prescribing Cascade. *Aust Prescr*; 34:162–6
114. Asiamah M, Akuffo KO, Nortey P, Donkor N, and Danso-Appiah A. 2022. Spontaneous reporting of adverse drug reaction among health professionals in Ghana. *Arch Public Health* **80,** 33. https://doi.org/10.1186/s13690-021-00783-1
115. Kheloufi K, Default A, Rouby F, Laugier-Castellan D, Boyer M, Rodrigues B, Ponte-Astoul J, Jean-Pastor MJ, Blin O, and Micallef J. 2017. Informativeness of patient initial reports of adverse drug reactions. Can it be improved by a pharmacovigilance centre? *Eur J Clin Pharmacol*, 73:1009–1018 DOI 10.1007/s00228-017-2254-y
116. Jacobs TG, Ampadu HH, Hoekman J, Dodoo ANO, and Mantel-Teeuwisse AK. 2018. The contribution of Ghanaian patients to the reporting of adverse drug reactions: a quantitative and qualitative study. *BMC Public Health*, 18:1384 https://doi.org/10.1186/s12889-018-6285-9
117. Hariraj V and Aziz Z. 2018. Direct patient reporting of adverse drug reactions: An analysis of spontaneous reports submitted to Malaysian pharmacovigilance centre. *Trop J Pharm Res*, 17(8): 1674. http://dx.doi.org/10.4314/tjpr.v17i8.29
118. Addo B, Sencherey S, and Babayara MNK. 2018. Medication Noncompliance among Patients with Chronic Diseases Attending a Primary Health Facility in a Periurban District in Ghana. *Int J Chronic Dis*, Article ID 7187284, 10 pages https://doi.org/10.1155/2018/7187284
119. Kumar A, Mohammadnezhad M, and May W. 2021. Patients' Perception of Factors Influencing Noncompliance with Medication among Cardiac Patients in Fiji: A Qualitative Study. *Patient Prefer Adherence*, 15 1843–1852
120. Citenvir Patient Information Leaflet, 2022
121. HEXA-BLOK Patient Information Leaflet, 2022
122. Tiwary A, Rimal A, Paudyal B, Sigdel KR, and Basnyat B. 2019. Poor communication by health care professionals may lead to life-threatening complications: examples from two case reports [version 1; peer review: 2 approved] Wellcome Open Research, 4:7 (https://doi.org/10.12688/wellcomeopenres.15042.1)
123. Mander M, Ntuli L, Diederichs N, and Mavundla K. Economics of the Traditional Medicine Trade in South Africa.

https://www.hst.org.za/Publications/South%20African%20Health%20Reviews/18_SAHR_2006-2007_Section%2013.pdf

124. Mahomoodally MF. 2013. Traditional Medicines in Africa: An Appraisal of Ten Potent African Medicinal Plants. *Evid Based Complement Alternat Med*, Article ID 617459, 14 pages http://dx.doi.org/10.1155/2013/617459
125. Berrewaerts J, Delbecque L, Orban P, and Desseilles M. 2016. Patient Participation and the Use of eHealth Tools for Pharmacovigilance. *Front Pharmacol*. 7:90. doi: 10.3389/fphar.2016.00090
126. Isah AO, Pal SN, Olsson S, Dodoo A, and Bencheikh RS. 2012. Specific Features of Medicines Safety and Pharmacovigilance in Africa. *Ther Adv Drug Saf*, 3(1) 25–34 doi: 10.1177/ 2042098611425695
127. Mabaso M, Makola L, Naidoo I, Mlangeni LL, Jooste S, and Simbayi L. 2019. HIV Prevalence in South Africa through Gender and Racial Lenses: Results from the 2012 Population-Based National Household Survey. *Int J Equity Health*, 18:167 https://doi.org/10.1186/s12939-019-1055-6
128. Berhe DF, Juhlin K, Star K, Beyene KGM, Dheda M, Haaijer-Ruskamp FM, Taxis K, and Mol PGM. 2015. Adverse Drug Reaction reports for cardiometabolic drugs from sub-Saharan Africa: a study in VigiBase. *Trop Med Int Health*, 20 (6): 797–806. doi:10.1111/tmi.12481
129. Partida Y. 2007. Medicine and Society Language Barriers and the Patient Encounter. *Am Med Assoc J Ethics*, Volume 9, Number 8: 566-571.
130. Krampe F, Fabry G, and Langer T. 2022. Overcoming Language Barriers, Enhancing Collaboration with Interpreters – an Interprofessional Learning Intervention (Interpret2Improve). *BMC Med Educ*, 22:170 https://doi.org/10.1186/s12909-022-03213-0
131. Espinoza J and Derrington S. 2021. How Should Clinicians Respond to Language Barriers That Exacerbate Health Inequity? *Am Med Assoc J Ethics*, 23(2):E109-116. DOI 10.1001/amajethics.2021.109
132. Benjamin, E., Swartz, L., Chiliza, B. and Hering, L., 2016. Language barriers in health: lessons from the experiences of trained interpreters working in public sector hospitals in the Western Cape. *S Afr Health Rev*, *2016*(1), pp.73-81.
133. Emuze F & James M. 2013. Exploring Communication Challenges due to Language and Cultural Diversity on South African Construction Sites. *Acta Structilia*, 20(1): 44-65

134. Statistics South Africa, 2018. Mid-Year Statistics Estimates. https://www.statssa.gov.za/
135. Khuluvhe, M. 2021. Adult illiteracy in South Africa, Department of Higher Education and Training, Pretoria
136. Ina´cio P, Airaksinen M, and Cavaco A. 2015. Language does not come “in boxes”: Assessing discrepancies between adverse drug reactions spontaneous reporting and MedDRA® codes in European Portuguese. *Res Soc Adm Pharm*, 11, 664–674
137. Dahm M. 2012. Coming to Terms with Medical Terms – Exploring Insights from Native and Non-native English Speakers in Patient-physician Communication. Hermes – *J Lang Comm Bus* no 49-2012. DOI: 10.7146/hjlcb.v25i49.97739
138. Hadlow and Pitts. 1991. The understanding of common health terms by doctors, nurses, and patients. *Soc Sc Med* 32, 193-196.
139. Fage-Butler MA and Jensen MN. 2015. Medical terminology in online patient–patient communication: evidence of high health literacy? *Health Expect*, 19, pp.643–653. doi: 10.1111/hex.12395
140. Singh S. 2018. Medical Translation Gone Wrong: 7 Devastating Medical Translation Errors. Language Blog, Medical Translations. Medical Translation Gone Wrong: 7 Devastating Medical Translation Errors (k-international.com)
141. Freifeld CC, Brownstein JS, Menone CM, Bao W, Filice R, Kass-Hout T, and Dasgupta N. 2014. Digital Drug Safety Surveillance: Monitoring Pharmaceutical Products in Twitter. *Drug Saf* (2014) 37:343–350 DOI 10.1007/s40264-014-0155-x
142. Bellis JR, Kirkham JJ, Nunn AJ, and Pirmohamed M. 2014. Clinical Coding of Prospectively Identified Paediatric Adverse Drug Reactions – a Retrospective Review of Patient Records. *BMC Pharmacol Toxicol*, 15:72. doi:10.1186/2050-6511-15-72
143. Lee D, Cornet R, Lau F, and de Keizer N. 2013. A survey of SNOMED CT implementations. *J Biomed Informat*, 46, 87–96
144. Schröder S, Zöllner YF, and Schaefer M. 2007. Drug Related Problems with Antiparkinsonian Agents: Consumer Internet Reports Versus Published Data. *Pharmacoepidemiol Drug Saf*, 2007; 16: 1161–1166 DOI: 10.1002/pds

145. Adedeji-Adenola H and Nlooto M. 2021. Direct reporting of adverse drug reactions by healthcare consumers in Africa: a narrative review. *Int J Clin Pharm*, 43:11–24 https://doi.org/10.1007/s11096-020-01141-x

146. Chouhan K and Prsasad SB. 2016. Self-Medication and their Consequences: A Challenge to Health Professional. *As J Pharmaceut Clin Res*, 9 (2): 314-317

APPENDICES

Appendix i. Copy of Email with Survey Link Sent to Healthcare Professionals

Dear Healthcare Professional,

Request for your Participation in my PhD Research Study: Validation of Patient ADR Reporting Tool

I am currently registered for a PhD in Pharmacology with the University of Stellenbosch, Faculty of Medicine and Health Sciences, Division of Clinical Pharmacology. My thesis will be looking at developing a direct ADR reporting tool for patients to address under-reporting of ADRs to the national pharmacovigilance unit in the country.

Currently in South Africa, only healthcare professionals are allowed to report ADRs to Pharmacovigilance (PV) unit at SAHPRA (former MCC, Medicines Control Council). As a result, there is a considerable under-reporting of ADRs which is also observed at a global level. In countries where patients are now allowed to submit their ADR reports directly to the PV unit, it has been noted that patients' direct reports are of the same quality as that of healthcare professionals and provide detailed information relating to the ADR. These patients' reports have also contributed towards early signal detection and have the potential to improve current knowledge of ADRs and drugs in the market, identification of counterfeit drugs, identification of medication errors etc.

My research will comprise of 2 parts: the first part will be looking at developing the tool which patients can use to report their ADRs. The second part will be a field research to assess the feasibility of the developed ADR reporting tool, where I will require participation of the general public patients.

For the tool to be acceptable as a reliable patient tool, it requires validation in line with the US FDA Guidelines for the development of Patient-Reported Outcome Instruments of 2009. The first validation should be done by healthcare professionals with knowledge and experience in ADR causality assessment (content validity). The healthcare professionals need to ascertain if the proposed information to be collected by the tool from the consumers when reporting an ADR would be appropriate, relevant and sufficient to conduct causality assessment.

I therefore request your participation in the content validation phase. Once you have given consent to participate in the study, I will send you a copy of the tool to be validated with instructions on how the validation process should be completed. You can then complete the validation and send me the outcome and your comments. The tool will then be reviewed and amended in line with the received validation comments, where necessary. When content validation has been completed, the tool will be sent to non-healthcare professionals for face validity, to assess the usability of the tool.

I attach for your reference, a copy of the synopsis of my research proposal. The research will be reviewed and approved by the Stellenbosch University Human Research Ethics Committee (US HREC). A copy of the US HREC will be made available to you prior to the start of the study.

With kind regards,

Tirhani Maluleke (MSc. Med)

CONSUMER ADR REPORTING FORM SURVEY - CHECKBOX® 6

Welcome Page

Development of a Consumer Adverse Drug Reaction (ADR) Reporting Form

New drugs are granted marketing authorization based on limited safety data collected during clinical trials. As such, safety information on the long-term effects of these drugs and in diverse conditions is unknown at the time of approval for marketing. An effective pharmacovigilance (PV) system is therefore required to continue monitoring the safety of drugs post-marketing.

However, PV activities are hampered by the global under-reporting of ADRs by healthcare professionals. Under-reporting of ADRs decreases the sensitivity of and causes major delays in the detection of safety signals, with a possible negative impact on patients, their quality of life, increasing the burden on the public health system, as well as the economic burden on the society.

This survey is part of the PhD research to assess the feasibility and impact of including the general public (consumers of medicines) in the ADR reporting system in order to address the under-reporting in South Africa.
This part of the survey is looking at content validation of the developed Consumer ADR Reporting Form by Healthcare Professionals - to assess if the included items are relevant and adequate for the causality assessment of ADRs.

The research study has been reviewed and approved by the University of Stellenbosch Health Research Ethics.

Consent: Responding to the survey will constitute consent for participation.

Confidentiality: Only the researchers directly involved in the study will have access to the responses. No personal data is being collected with this survey and confidentiality will be maintained with all responses.

This survey consists of five pages and an additional page where you can share your overall comments about the form.

It will only take you about 10 minutes to complete the survey.

Introduction Page

Development of a Consumer Adverse Drug Reaction (ADR) Reporting Form

New drugs are granted marketing authorization based on limited safety data collected during clinical trials. As such, safety information on the long-term effects of these drugs and in diverse conditions is unknown at the time of approval for marketing. An effective pharmacovigilance (PV) system is therefore required to continue monitoring the safety of drugs post-marketing.

However, PV activities are hampered by the global under-reporting of ADRs by healthcare professionals. Under-reporting of ADRs decreases the sensitivity of and causes major delays in the detection of safety signals, with a possible negative impact on patients, their quality of life, increasing the burden on the public health system, as well as the economic burden on the society.

This survey is part of the PhD research to assess the feasibility and impact of including the general public (consumers of medicines) in the ADR reporting system in order to address the under-reporting in South Africa.
This part of the survey is looking at content validation of the developed Consumer ADR Reporting Form by Healthcare Professionals - to assess if the included items are relevant and adequate for the causality assessment of ADRs.

The research study has been reviewed and approved by the University of Stellenbosch Health Research Ethics.

Consent: Responding to the survey will constitute consent for participation.

Confidentiality: Only the researchers directly involved in the study will have access to the responses. No personal data is being collected with this survey and confidentiality will be maintained with all responses.

This survey consist of 5 pages and an additional page where you can share your overall comments about the form.

It will only take you about 10 minutes to complete the survey.

Next

*Indicate the Relevance of the following items in the Consumer ADR Reporting Form by selecting the appropriate option for each.

Consumer Initials

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Consumer Date of Birth**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Gender**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Weight (kg)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Height (cm)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***If female, pregnancy at the time of onset of event**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Medical History**

Include allergies, other medical conditions you have and any other treatment you are taking (including over-the-counter medication, herbal medication, medical supplements and/or traditional medication)

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

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Page 2

***Information about the Adverse Event (AE)**

Date and time of onset of AE

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Date AE stopped and/or duration of the AE**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Describe the adverse event/reaction experienced in details, including actions taken in response to the AE/reaction**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

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Page 3

***Suspected Medicine(s)**

Name of the Medicine(s) Suspected of causing the AE, Dosage/quantity and Dosing Frequency (how often the medicine is taken)

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Route of taking the medicine(s)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Duration of taking the suspected medicine(s) (i.e. Date started to Date stopped if no longer taking the medicine)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Reason for taking the medicine(s) (i.e. diagnosis)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Reason for taking the medicine(s) (i.e. diagnosis)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***If you stopped taking the suspected medicine(s), did the AE go away?**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Batch Number and expiry date of the suspected medicine(s)**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

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Page 4

***Other Additional Information**

Share any other information related to the suspected medicine(s) and/or the AE you experienced

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

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Page 5

***Information about the Reporter of the Adverse Event**

Initials of the Reporter

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Contact Details of the Reporter**

Please include your contact details so that we can acknowledge receipt of your report, provide you with a reference number for your report as well as for follow-up for further information if necessary

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

***Profession of the Reporter**

- 1. Not Relevant
- 2. Somewhat Relevant
- 3. Relevant
- 4. Very Relevant

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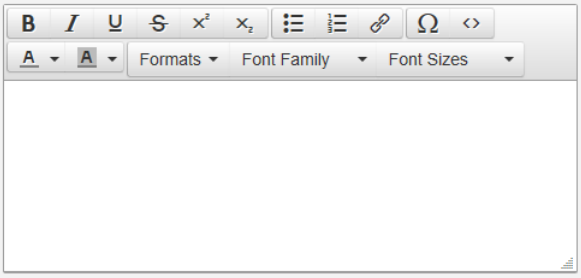
Page 6

Please add any comments you may have with regard to the items included in the Consumer ADR Reporting Form



Back Finish

Final Page

Thank you for taking the survey and assisting in the development of the Consumer ADR Reporting Form.

Appendix ii. Mock Case Scenario

Introduction Page

Development of a Consumer Adverse Drug Reaction (ADR) Reporting Form

New drugs are granted marketing authorization based on limited safety data collected during clinical trials. As such, safety information on the long-term effects of these drugs and in diverse conditions is unknown at the time of approval for marketing. An effective pharmacovigilance (PV) system is therefore required to continue monitoring the safety of drugs post-marketing.

However, PV activities are hampered by the global under-reporting of ADRs by healthcare professionals. Under-reporting of ADRs decreases the sensitivity of and causes major delays in the detection of safety signals, with a possible negative impact on patients, their quality of life, increasing the burden on the public health system, as well as the economic burden on the society.

This survey is part of the PhD research to assess the feasibility and impact of including the general public (consumers of medicines) in the ADR reporting system in order to address the under-reporting in South Africa.
This part of the survey is looking at face validation of the developed Consumer ADR Reporting Form by Non-Healthcare Professionals – to assess the usability of the ADR reporting tool in terms of readability, clearness of the information required as well as clarity of the language used.

The research study has been reviewed and approved by the University of Stellenbosch Health Research Ethics. The ethics committee can be contacted on:
Stellenbosch Health Research Ethics Committee (HREC)
PO Box 19063
Tygerberg
7505
Tel: +27 21 938 9657

The conduct of the validation process within Sanofi has been approved by the relevant internal stakeholders.

Confidentiality: Only the researchers directly involved in the research study will have access to the responses. No personal data is being collected with this survey and confidentiality will be maintained with all responses.

This survey consist of 2 pages and an additional page where you can share your overall comments about the form and a link to the ADR Reporting Tool for completion of the validation.

It will only take you about 10 minutes to complete the survey.

Should you have any questions or concerns regarding the survey, please contact the primary researcher on: Ms TL Maluleke, email: [redacted] , Tel: +27 82 [redacted]

Consent:

I hereby give my consent to participation in the study.
I understand that my participation in this study is voluntary and that I can withdraw participation at any time and not complete the survey.

Should you have any questions or concerns regarding the survey, please contact:

The primary researcher
Ms TL Maluleke
Email:[redacted]
Tel: +27 82 [redacted]

Stellenbosch Health Research Ethics Committee (HREC)
PO Box 19063
Tygerberg
7505
Tel: +27 21 938 9657

Please use the information below to report any ADRs/side effects that the woman has experienced.

https://apps.infoverge.co.za/adr

Case Scenario[1]

A 67-year-old woman, Mrs MV Majola, weighing 82kg had an extensive rash which started on the 29th of August 2019 in the morning, was referred urgently to Dr Bason XY in Midrand. The rash started on the backs of her hands and spread very quickly to the arms, stomach, neck, face, lips and inside her mouth. The rash had some blistering in some areas.

Mrs Majola was started on aspirin 75mg once daily 5 years ago following a stroke. At about the same time (5 years ago), she was diagnosed with type 2 diabetes and has been taking Glucophage 1g twice daily, Altace 10mg once daily, and Zocor 40mg at night since then. She was prescribed Diamicron 40mg each morning during her annual diabetes review 2 months ago (07 August 2019).

Mrs Majola denies taking any over-the-counter medicines or herbal remedies. She has not made any significant changes to her diet and there is no history of recent infection.

[1] Adverse Drug Reactions: A Case Study from the BNF Looking at Adverse Drugs Reactions, BNF e-newsletter, 13 September 2010

Appendix iii. Advertisement

Testing of Side Effects Reporting Tool

Are you taking / have you recently taken any medication (including herbal or supplements) for any condition? Did you experience any unwanted Side effects after taking the medicine?

- A **Side Effect** is any unintended negative effect that you experience after taking a medication. For example; if you take paracetamol for headache and then experience nausea or dizziness.

- A **Safe Medicine** does not imply absence of risk or harm (Side Effects).
  A safe medicine is one in which the nature, severity and frequency of side effects (risk / harm) are outweighed by the benefits.

- All medicines are approved and registered by the Dept. of Health (DoH), using information collected during clinical trial research. After the medicine is registered, DoH continues monitoring the safety of medicine. Therefore, they need all people taking medicine to continue reporting information on any side effects experienced after taking the medicine.

- As part of a study research, a student has developed a tool to report side effects directly to DoH. Before this tool can be accepted by DoH, it needs to be tested. We therefore request you to start reporting any side effects using this tool. All information provided will be kept confidential and transferred to DoH after completion of the study. This study has been approved by the Stellenbosch Human Research Ethics Committee.
- To report side effect you may have experienced, go to the website and follow the instructions.
  - http://apps.infoverge.co.za/adrtest
- Additional information and guidance on how to report the side effects can be found on the website under '**General Information**'

PhD Research Advert_Development of Consumer ADR_Reporting Tool_Version 3.5 dated 31 January 2020

Appendix iv. Paper Consumer ADR Reporting Form

Please provide as much information as you can.

Report the side effect even if you are not certain the suspected medicine caused it or you do not have all the details.

Consumer Details
This refers to the details of a person who experienced the side effect and not necessarily the person reporting

Initials:_____ Age (years):____

Gender:_____ Weight (kg):_____ Height (cm)____

If female, pregnancy at the time of experiencing the side effect (first symptoms): Y / N

Medical History

Allergies: _____

Other medical conditions (such as chronic diseases, recent illness, or medical procedure) you have:

_____

Trade names of medicines you are taking or have recently taken as treatment for the other medical conditions (including over-the-counter medication, herbal medication, medical supplements and/or traditional medication): _____

_____

Side Effect

Date and time of onset of side effect:_____

Date side effect stopped (or state "ongoing") and/or duration of the side effect: _____

Describe the side effect experienced in detail, including actions taken in response to the side effect:

_____

_____

_____

Suspected Medicine(s)

Name of the Medicine(s) suspected of causing the side effect:_____

Dosage and frequency of taking medicine (amount taken and how often):_____

How did you take the medicine(s):_____

Reason for taking the medicine (i.e., diagnosis):_____

Duration of taking medicine (i.e., date started to date stopped if no longer taking the medicine):_

_____

If you stopped taking the suspected medicine(s), did the side effect go away? _____

Other Additional Information

Share any other information related to the suspected medicine(s) and/or the side effect you experienced _____

_____

Person Reporting the Side Effect

Initials:_____ Profession:_____

Contact Details:_____

Please include your contact details so that we can acknowledge receipt of the report and follow-up for further information if necessary.

Appendix v. University of Stellenbosch Human Research Ethics Committee Approvals

Initial Study Approval

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Approved with Stipulations

New Application

10/09/2019

Project ID: 8603

HREC Reference No: S18/10/230 (PhD)

Project Title: Development of a Direct ADR Reporting Tool for Patients to Address Under-Reporting of ADRs to the National Pharmacovigilance Unit in South Africa

Dear Miss Tirhani Maluleke

We refer to your **response to modifications** that were requested on your **new application** received on 20/08/2019 15:20. Please be advised that your responses were reviewed by members of the **Health Research Ethics Committee** via Minimal Risk Review procedures on 10/09/2019 and **approved with a stipulation**.

Please note the following information about your approved research protocol:

Protocol Approval Period: **10-September-2019 to 09- September 2020**.

The stipulation of your ethics approval is as follows:

o Please add the contact details of the principal investigator and Stellenbosch University HREC to the consent and survey forms.

Please remember to use your project ID 8603 and ethics reference number S18/10/230 (PhD) on any documents or correspondence with the HREC/UREC concerning your research protocol.

Translation of the consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note that this decision will be ratified at the next HREC full committee meeting. HREC reserves the right to suspend approval and to request changes or clarifications from applicants. The coordinator will notify the applicant (and if applicable, the supervisor) of the changes or suspension within 1 day of receiving the notice of suspension from HREC. HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note you can submit your progress report through the online ethics application process, available at: https://apply.ethics.sun.ac.za and the application should be submitted to the Committee before the year has expired. Please see Forms and Instructions on our HREC website for guidance on how to submit a progress report.

The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website (www.sun.ac.za/healthresearchethics)

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Melody Shana

Coordinator

HREC1

Approval for Amended Recruitment Materials

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Approval Letter
Amendment

21/02/2020

Project ID: 8603

Ethics Reference No: S18/10/230 (PhD)

Project Title: Development of a Direct ADR Reporting Tool for Patients to Address Under-Reporting of ADRs to the National Pharmacovigilance Unit in South Africa

Dear Miss Tirhani Maluleke

We refer to your amendment request received 03/02/2020.

The Health Research Ethics Committee (HREC) reviewed and **approved** the amendment and through an expedited review process.

The following amended documentation was reviewed and approved:

- Recruitment Advert_v3.5 dated 31 January 2020

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your project ID 8603 and ethics reference number S18/10/230 (PhD) on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mrs. Melody Shana

Coordinator

Health Research Ethics Committee 1

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)•IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the
World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African *Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition)*; as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

Appendix vi. Ekurhuleni Health District Research Committee Approval

City of Ekurhuleni

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

EKURHULENI HEALTH DISTRICT
RESEARCH PERMISSION

Research Project Title: Development of a Direct Adverse Drug Reactions Reporting Tool for Patients to Address Under-Reporting of ADRs to the National Pharmacovigilance Unit in South Africa

NHRD No: Gp_202007-025

Research Project Number: 30/06/2020-08

Name of Researcher(s): Ms Tirhani Lineth Maluleke

Division/Institution/Company: University of Stellenbosch

Date of review by the EHDRC: 11 June 2020

DECISION TAKEN BY THE EKURHULENI HEALTH DISTRICT RESEARCH COMMITTEE (EHDRC)

- This document certifies that the above research project has been reviewed by the EHDRC and permission is granted for the researcher(s) to commence with the intended research project.
- Facilities approved for the research: City of Ekurhuleni – Tembisa clinics.
- Participants' rights and confidentiality must be maintained throughout the study period and when disseminating the findings.
- No resources (financial, material and human resources) from the health facilities will be used for the study. Neither the district nor the health facilities will incur any additional cost for the study.
- The study will comply with Publicly Financed Research and Development Act 2008 (Act 51 of 2008) and its related regulations.

- The EHDRC must be informed in writing before publication or presentation of research findings and a copy of the report/publications/presentation must be submitted to the EHDRC
- The district must be acknowledged in all the reports/publications generated from the research.
- The researcher will be expected to provide the EHDRC with
  - Six monthly progress updates including any adverse events
  - The final study report in electronic format
  - Present the final research findings at the annual Ekurhuleni research conference if possible.

- The EDHRC reserves the right to withdraw the approval, if any of the conditions mentioned above have being breached
- The research committee wishes the researcher(s) the best of success.

DR. J. SEPUYA

DEPUTY CHAIRPERSON: CITY OF EKURHULENI

Dated: 30/06/2020