A cross-sectional study to investigate the knowledge, attitudes, and current practices of pharmacovigilance, among medical doctors and pharmacists in South Africa

by

Nyeleti Portia Rikhotso

This thesis is submitted in fulfilment of the requirements for the degree of

Master of sciences in Pharmacology

Division of Clinical Pharmacology

Faculty of Medicine and Health Sciences

Stellenbosch University

Supervisor: Dr Carine Page

(Division of Clinical Pharmacology, Faculty of Medicine and Health Sciences, Stellenbosch University)

Co-supervisor: Prof Helmuth Reuter

(Division of Clinical Pharmacology, Faculty of Medicine and Health Sciences, Stellenbosch University)

DECEMBER 2021

Declaration

I declare that the thesis entitled, **A cross-sectional study to investigate the knowledge, attitudes, and current practices of pharmacovigilance, among medical doctors & pharmacists in South Africa**, which I hereby submit for the degree, Master of Science in Clinical Pharmacology at Stellenbosch University, is my own work. I also declare that this thesis has not previously been submitted by me for a degree at this or any other tertiary institution and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

_____

Nyeleti Portia Rikhotso

Date: December 2021

Abstract

Background: Pharmacovigilance pertains to activities aimed at monitoring medicines for related safety concerns, thereby ensuring patient safety and wellbeing. The primary method of pharmacovigilance is spontaneous reporting of adverse drug reactions (ADRs). ADRs have a socio-economic impact when they are not reported and mitigated appropriately. This impact is even more apparent in low-to-middle income countries (LMICs), an economic category encompassing all African countries. The World Health Organisation (WHO) has developed a global pharmacovigilance database (Vigibase®) for countries which are members of the Programme for International Drug Monitoring (PIDM), which includes many African countries. ADR reporting levels however remains low across Africa. This is also true for South Africa, despite being the first African country to become a member of the PIDM in 1992.

Therefore, this research study was conducted to investigate the knowledge, attitudes, and practices of pharmacovigilance among medical doctors and pharmacists in South Africa. The aim of this study is to investigate the factors influencing the low adverse drug reporting levels by healthcare professionals in South Africa.

Methodology: A cross-sectional survey was conducted in the form of a knowledge, attitudes, and practices (KAP) study design. The targeted sample population was 384 study participants. The questionnaire consisted of closed-ended questions, designed to assess the demographics, knowledge, attitudes, practices of healthcare professionals nationally. The survey also served to obtain suggestions from healthcare professionals to improve ADR reporting in SA. An online survey was created in the survey platform, SurveyMonkey® and the e-link to the survey was shared with the South African Medical Association (SAMA) and the South African Clinical Research Association (SACRA), two professional associations hosting memberships of registered medical doctors and pharmacists in South Africa. Both associations distributed the e-link to their members via email. The obtained data was analysed using IBM SPSS® Statistics version 27.

Results: A total of 325 responses were received, accounting for 85% of the target sample population. Most (252; 77.5%) of the study participants on this study received an average score for their knowledge on pharmacovigilance, despite extremely low reported levels (91;

28%) of training. Most of the respondents (269; 82.8%,) thought that awareness regarding pharmacovigilance in their professional environment is inadequate. Although the majority (310; 95.4%) of respondents agreed that ADR reporting is their professional obligation, (119; 36.6%) had never seen a reporting form and only (172; 52.9%) had ever participated in ADR reporting. The major factors discouraging respondents from participating in ADR reporting were lack of knowledge on the reporting process and lack of access to the ADR reporting form. The topmost suggestions selected by the respondents to improve ADR reporting in South Africa were to include pharmacovigilance training in the undergraduate curricula of South African universities (266; 81.8%) as well as implementation of on-line or telephonic reporting platforms (235; 72.3%).

Conclusion: This study indicates that there is an average level of knowledge of pharmacovigilance amongst medical doctors and pharmacists in South Africa and that they mostly have a positive attitude towards pharmacovigilance. However, this does not translate into acceptable levels of participation in ADR reporting, most likely due to inadequate pharmacovigilance training provided to medical doctors and pharmacists in South Africa.

KEYWORDS: Pharmacovigilance (PV); adverse drug reaction (ADR), knowledge, attitudes, and practices (KAP), ADR reporting, PV in South Africa

Opsomming

Agtergrond: Farmakowaaksaamheid bestaan uit aktiwiteite wat daarop gemik is om medisyne te monitor vir veiligheidsprobleme wat daarmee verband hou ten einde die pasiënt se veiligheid en welstand te verseker. Die primêre metode van farmakowaaksaamheid is spontane aanmelding van nadelige medisyne reaksies (NMRs). NMRs het 'n sosio-ekonomiese impak as dit nie aangemeld en verminder word nie. Hierdie impak is selfs meer uitgesproke in lae-tot-middel inkomste lande (LMILe), 'n kategorie waarin alle Afrikalande val. Die Wêreldgesondheidsorganisasie (WGO) het 'n wêreldwye farmakowaaksaamheid databasis (Vigibase®) ontwikkel vir lande wat lede is van die Program vir Internasionale Geneesmiddelmonitering (PIGM); hierdie program sluit ook lede uit vele Afrikalande in. Die NMR verslagdoeningsvlakke uit Afrikalande, bly egter laag. Dit blyk ook die geval vir Suid-Afrika te wees, ten spyte van die feit dat Suid-Afrika die eerste Afrikaland was wat in 1992 reeds lid van die PIGM geword het.

Die doel van hierdie studie is dus om die kennis, standpunte en praktyke ten opsigte van farmakowaaksaamheid onder mediese praktisyns en aptekers in Suid-Afrika te ondersoek. Die doel is om die faktore wat die lae vlakke van aanmelding van nadelige medisyne reaksies (NMRs) deur gesondheidswerkers in Suid-Afrika beinvloed, te ontleed.

Metodiek: 'n Dwarsdeursneë-opname is gedoen in die vorm van 'n kennis-, standpunte-, en praktyk-ontwerp (KSP) navorsingstudie. Die geteikende steekproefpopulasie was 384 deelnemers. Die KSP-vraelys het bestaan uit geslote-end vrae, ontwerp om landwyd die demografie, kennis, standpunte en praktyke van gesondheidwerkers te ondersoek. Die vraelys het ook gepoog om voorstelle van gesondheidwerkers te bekom ten einde NMR verslaggewing in Suid-Afrika te verbeter. 'n Aanlynopname is in die SurveyMonkey®-platform opgestel en die e-skakel is deur die Suid-Afrikaanse Mediese Vereniging (SAMV) en die Suid-Afrikaanse Kliniese Navorsingsvereninging (SAKNV) aan hul lede versprei. Die SAMV en SAKNV is beide professionele vereningings met mediese praktisyns en aptekers as lede. Beide verenigings het die e-skakel per e-pos aan hul lede versprei. Die data wat bekom is, is geanaliseer met behulp van die IBM SPSS® Statistics, weergawe 27.

Resultate: Altesaam 325 response is ontvang, wat 85% van die teiken monsterpopulasie uitmaak. Die meeste (252; 77,5%) van die deelnemers aan hierdie studie het 'n gemiddelde

telling vir kennis oor farmakowaaksaamheid behaal, ondanks 'n lae vlak van opleiding op die gebied (91; 28%). Die meeste van die respondente (269; 82,8%,) het gedink dat die bewustheid van farmakowaaksaamheid in hul professionele omgewing onvoldoende is. Alhoewel die meerderheid (310; 95,4%) van die respondente saamstem dat NMR rapportering hul professionele verpligting is, het (119; 36,6%) nog nooit 'n verslagvorm gesien nie en slegs (172; 52,9%) het al voorheen aan NMR verslaggewing deelgeneem. Die belangrikste faktore wat respondente ontmoedig om deel te neem aan NMR verslaggewing, was gebrek aan kennis oor die verslagdoeningsproses en gebrek aan toegang tot die NMR verslagvorms. Voorstelle wat die respondente gekies het om NMR verslagdoening in Suid-Afrika te verbeter, wat die meeste uitgestaan het, was om farmakowaaksaamheid-opleiding in die voorgraadse kursusmateriaal van universiteite (266; 81,8%) sowel as die implementering van aanlyn- of telefoniese verslaggewing (235; 72,3%) in te sluit.

Samevatting: Hierdie studie dui daarop dat daar 'n gemiddelde vlak van kennis oor farmakowaaksaamheid onder mediese praktisyns en aptekers in Suid-Afrika is, maar dat hulle grootliks ‘n baie positiewe standpunt oor die onderwerp toon. Die waarneming strook egter nie met die lae vlakke van NMR rapportering nie; heel moontlik weens onvoldoende farmakowaaksaamheid-opleiding wat aan mediese praktisyns en aptekers in Suid-Afrika gebied word.

Acknowledgements

Firstly, I wish to thank my family and friends for their support throughout my studies and for believing in me. My kids for being so understanding that they must give mommy some quiet space to work. To Dr Simba Takuva for going the extra mile of ensuring that I understand the statistical methods applied during my analysis of the study results and to Dr Moleen Dzikiti for jumping in where she was able to. To Ms Lejandra Hanekom for the administrative support and to my Supervisors, Dr Carine Page and Prof Helmuth Reuter for giving me the opportunity to pursue my MSc degree and for holding my hand and encouraging me even when I doubted that we would get here. Finally, I thank myself for committing to my dreams and putting in the hard work.

Table of content

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

List of Tables

Chapter 1

Chapter 2

Chapter 3

None

Chapter 4

Chapter 5

None

Chapter 6

None

List of abbreviations

ACE	Angiotensin-converting enzyme
ACSoMP	Advisory Committee on Safety of Medicinal Products
ADR	Adverse drug reaction
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ASoP	African Society of Pharmacovigilance
ATC	Anatomical Therapeutic Chemical
AVR	Adverse vaccine reactions
BCG	Bacillus Calmette-Guerin
BMGF	Bill and Melinda Gates Foundation
BRAVATO	Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology
CAPA	Correct and preventative actions
CDER	Centre for Drug Evaluation and Research
CEM	Cohort event monitoring
CEM	Cohort event monitoring
CEO	Chief Operating Officer
CFDA	China Food and Drug Administration
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMDh	Mutual and Decentralized procedure- Human
Covid-19	Coronavirus disease
DEG	Diethylene glycol
DILI	Drug-induced liver injury
DSB	Drug Safety Oversight Board
EAC	East African Community
EEA	European Economic Area
EFDA	Ethiopian Food and Drugs Authority
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization

EU	European Union
EVDS	Electronic Vaccination Data System
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act
FMHACA	Ethiopian Food, Medicine and Health Care Administration and Control Authority
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GCP	Good Clinical Practice
GF	Global Fund
GPRD	General Practice Research Database
GVP	Good Pharmacovigilance Practices
HCP	Healthcare professional
HCW	Healthcare worker
Hep B	Hepatitis B
HIV/AIDS	Human immunodeficiency virus, acquired immunodeficiency syndrome
HPV	Human papillomavirus
HR	Human Resource
IC	Informed consent
ICH	International Council for Harmonisation
ICSR	Individual Case Report Forms
IMPACT	International Medical Products Anti-Counterfeit Taskforce
INTERPOL	International Criminal Police Organization
IPAT	Indicator-based Pharmacovigilance Assessment Tool
ISoP	International Society of Pharmacovigilance
J&J	Johnson and Johnson
KAP	Knowledge, attitudes, and practices
LMIC	Low-to-middle income countries
MAH	Marketing-authorization holders
MAS	Mobile Authentication Services
MCC	Medicines Control Council
MedDRA	Medical Dictionary for Regulatory Activities
MEDQUARG	Medicine Quality Assessment Reporting Guidelines

MHRA	Medicines and Healthcare products Regulatory Agency
MMR	Measles, mumps, and rubella.
MQCL	Medicine Quality Control Labs
mRNA	Messenger Ribonucleic acid
MSc	Master of Science
MSM	Member State Mechanism
NADEMC	Adverse Drug Event Monitoring Centre
NDoH	National Department of Health
NGO	Non-Governmental Organisation
NIP	National Immunization Programme (NIP
NRA	National Regulatory Authority
NSAIDs	Non-steroidal anti-inflammatory drugs
NZ	New Zealand
ORA	Office of Regulatory Affairs
OTC	Over the counter
OUD	Opioid-use disorder
PASS	Post-authorisation safety studies
PBRER	Periodic Benefit Risk Evaluation Report
PD	Pharmacodynamics
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PhD	Doctor of Philosophy
PHP	Public Health Programmes
PIDM	Programme for International Drug Monitoring
PK	Pharmacokinetics
PPB	Kenya Pharmacy and Poisons Board
PR	Prevalence ratios
PRAC	Pharmacovigilance Risk Assessment Committee
PSRT	Protocol Safety and Risk Team
PSUR	Periodic safety update reports
PV	Pharmacovigilance
QC	Quality Control
RA	Regulatory Authority
RFDA	Rwanda Food and Drugs Authority
RFID	Radio frequency identification

RMA	Risk minimization action
RR	Relative Risk
SA	South Africa
SACRA	Clinical Research Association
SAHPRA	South African Health Products Regulator
SAMA	South African Medical Association
SAMRC	South African Medical Research Council
SCID	Severe combined immunodeficiency
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SIVRA	Shoulder injury related to vaccine administration
SJS	Stevens Johnson Syndrome
SmPC	Summaries of Product Characteristics
SMS	Short message service
SPS	Strengthening Pharmaceutical Systems
SRS	Spontaneous reporting systems
SSFFC	Substandard / spurious / falsely labelled / falsified / counterfeit
SU-HREC	Stellenbosch University Health Research Ethics Committee
SUPPORT	Substance Use–Disorder Prevention
TB	Tuberculosis
TEN	Toxic Epidermal Necrolysis
TFDA	Tanzania Food and Drugs Authority
TMDA	Tanzania Medicines and Medical Devices Authority
TSR	Targeted Spontaneous Reporting
TT	Tetanus toxoid
UK	United Kingdom
ULN	Upper Limit of Normal
UMC	Uppsala Monitoring Centre
USA	United States of America
USAID	U.S. Agency for International Development
WHA	World Health Assembly
WHO	World Health Organisation
WHO–CC	World Health Organisation Collaborating Centre

CHAPTER 1
Introduction and project overview

1.1 Brief chapter overview

This chapter provides the background and rationale of the study. It describes the aims and objectives, significance, limitations, assumptions, a brief overview of the methodology as well as an outline of the thesis.

1.2 Background to research problem

In a small north England town of Winlaton, in January of 1848 15-year-old Hannah Greener, died while undergoing removal of an ingrowing toenail. Prior to the procedure, Physician Dr Thomas Nathaniel Meggison administered an anaesthetic, containing chloroform (Paul, 2002). The anaesthetic effects of chloroform had just been discovered less than a year prior by Dr James Simpson, professor of midwifery at Edinburgh (Routledge, 1998) (Fornasier, 2018). Due to the continuing concerns of the public and profession about the safety of anaesthesia, *The Lancet* journal set up a commission, which invited doctors in Britain and its colonies to report anaesthesia-related deaths. The findings were subsequently published in the journal in 1893 (Lancet, 1893). They concluded that death under chloroform anaesthesia was 8.7 times more likely than death under ether anaesthesia (Lancet, 1893). The real cause of Hannah's death was debated, and theories formed among physicians in the anaesthesiology field to date, with lethal arrhythmia and pulmonary aspiration appearing to be equally valid hypotheses (Paul, 2002). Approximately 100 year later in 1954, Henry K. Beecher, the Professor of Anaesthesia at Harvard University, entered the historical debate. Using a well-designed and executed survey was reported by Beecher and associates, they collected data on 600 000 patients from 10 university hospitals over a 5-year period. The report caused considerable controversy; in that it reported a considerably higher mortality in patients that had received the newly introduced muscle relaxant drugs compared with those that did not (Jones, 2001).

The story of Hannah Greener initiated the basic principles of a spontaneous reporting system for suspected adverse drug reactions (ADRs). The US Federal Food and Drug Act was formed on June 30, 1906, and it established that drugs must be pure and free of any contamination and the presence and amount of eleven dangerous ingredients, including alcohol, heroin, and cocaine, had to be listed (FDA, 2019).

In 1937, there were 107 deaths in the USA, because of the use of sulphanilamide elixir, containing diethyl glycol (DEG) as the solvent, which was considered the cause of these deaths (Ballentine, 1981). DEG is a colourless, practically odourless, poisonous, and hygroscopic liquid with a sweetish taste, widely used in manufacturing as a solvent for nitrocellulose, resins, dyes, oils, and other organic compounds (Ballentine, 1981). Sulphanilamide, a drug used to treat streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form. In June 1937, however, a salesman for the manufacturing company reported a demand for the drug in liquid form. The company's chief chemist and pharmacist, Harold Cole Watkins, experimented and found that sulphanilamide would dissolve in diethylene glycol and the mixture was only tested for flavour, appearance, and fragrance and found to be satisfactory and not tested for toxicity

(Ballentine, 1981). At the time the food and drugs law did not require that safety studies be done on new drugs. The incident hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products (FDA, 2018).

In December 1961, Dr William Griffith McBride published a letter in The Lancet, a weekly peer-reviewed general medical journal, reporting a notable number of babies being born with malformations of the arms and legs (phocomelia), specifically in children of patients who were exposed to thalidomide (Fornasier, 2018) (Kim JH, 2011). He noted that he had observed that the incidence of congenital malformations of babies (1.5%) had increased up to 20% in new-borns of women who had taken thalidomide during pregnancy (McBride, 1961). Thalidomide was initially marketed as a sedative and rapidly became popular as it was perceived to be efficient and without toxic effects (Kim JH, 2011). The product was subsequently also prescribed for nausea in pregnant women and was advertised as being completely safe, even during pregnancy, until it was later established that approximately 10 000 babies were seriously affected by congenital abnormalities caused by this drug (Kim JH, 2011). Thalidomide caused serious damage to the unborn child when taken during the first trimester and depending on the timing and level of ingestion, the birth defects referred to as thalidomide embryopathy or thalidomide syndrome (Kim JH, 2011). The thalidomide tragedy marked the start of many processes globally, to improve regulations and attention to the safety of medicines (Fornasier, 2018). This tragedy's impact was an improvement in pharmacovigilance as the spontaneous reporting of adverse drug reactions became systematic, organized, and regulated.

In the United States of America (USA), 1962, the Kefauver-Harris amendment US Food and Drug Administration (FDA) was enacted, requiring safety and efficacy data of drugs before premarketing submission, was approved required that manufacturers prove the effectiveness of drug products before they go on the market, that evidence of effectiveness be based on adequate and well-controlled clinical studies conducted by qualified experts and afterwards, serious side effects are reported and study participants would be required to give their informed consent (FDA, 2012).

In 1964, the yellow card was implemented in the United Kingdom (UK) to compile a spontaneous report of drug toxicity (MHRA, 2021). In Europe (1965), the disaster of thalidomide stimulated the development of a European legislation with the EC Directive 65/65 (Directive, 1965).

Efforts to define and strengthen pharmacovigilance structures ultimately led to the establishment of the World Health Organisation (WHO) Pharmacovigilance pilot programme in 1968 as a resolution from the World Health Assembly in 1963 (Lessa, 2016).

In 1995, the European Medicines Agency (EMA) was set up (EMA, 2015) and improved with amended legislation in 2012 (Directive 2010/84/EU) (EU, 2012).

The figure below depicts a timeline of historical events that have shaped pharmacovigilance:

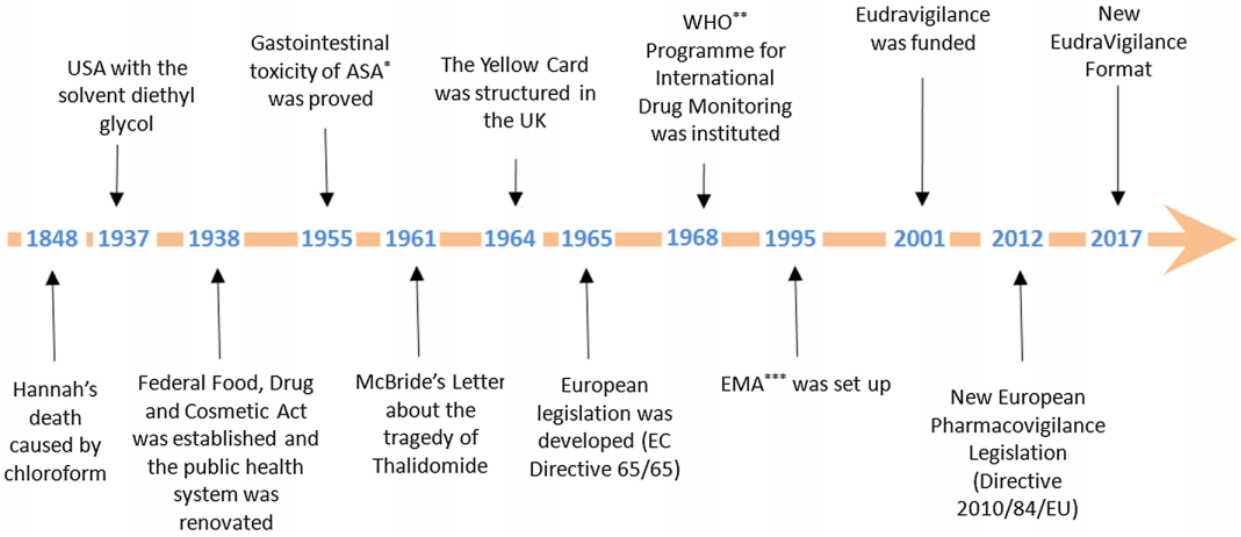


Figure 1-1: Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; **WHO: World Health Organisation; ***EMA: European Medicines Agency (Fornasier, 2018)

1.3 The need for pharmacovigilance

Pharmacovigilance plays a key role in identifying long-term safety information which could not be picked up due to the nature of clinical trials. Once medicines are available on the market, they can be accessed by wider population groups, some of which are usually excluded from clinical trials, due to their vulnerability (e.g., geriatrics, paediatrics, pregnant women, etc.) and some medications are used chronically as well as in combination with other medicines and food (Onakpoya, 2016). Under these diverse circumstances, adverse drug reactions may occur, with differing severities and consequences.

Adverse drug reactions can lead to dire consequences such as complications requiring hospitalization, permanent disability, and death. In the European Union (EU) an estimated 197 000 deaths and 5% of hospital admissions annually can be attributed to ADRs, amounting to an annual cost of €79 billion (EMA, 2017). Pharmacovigilance therefore plays a pivotal role in collecting ongoing post-marketing Drug Safety information.

Regulatory Authorities (RA), healthcare professionals (HCP) and patients each have a role to play in the safety surveillance of medicines. RA must, on an ongoing basis, monitor and ensure the safety, efficacy and quality of registered medicines, and the benefit/risk ratio and rational use of medicines (EMA, 2019).

From the perspective of the HCP, therapeutic tools are ever evolving; and it is, therefore, important to remain abreast of new developments. The HCP must open communication lines with patients, sharing the latest relevant treatment information with the patients and collecting information from patients about their experiences with those medicines. This form of open communication is the basis for spontaneous ADR reporting (Kasliwal, 2012). In principle, a patient's experiences of an undesirable reactions to the medicine, is communicated to the HCP and, the HCP being vigilant, makes a suspected connection

between the reaction and exposure to the medicine., and this suspicion is reported to the pharmacovigilance centre. In most countries spontaneous ADR reporting is the most common method of pharmacovigilance and allows for the collection and systematic analysis of adverse drug reaction reports (Ampadu, *et al.*, 2016). Many medications have been withdrawn from the market by RA or additional safety information was added to the Summaries of Product Characteristics (SmPC) in the form of black box warnings, additional contra-indications, side-effects, or drug interactions, due to the occurrence and reporting of ADRs, not detected during the development of the product.

In 1968, the WHO established the Programme for International Drug Monitoring (PIDM) (PIDM, 2020), with the purpose of developing a central database for collection of information regarding adverse drug reactions from as many sources as possible and affecting a wide variety of population groups. The system ensures communication of changes in risk/benefit balance to member countries with a view of promoting patient safety, including rational and safe use of prescription medicines, including complementary medicines, biologicals, and vaccines. The pilot project was launched in ten countries and from 1968 to 2017, 156 countries globally have gained full membership to the programme and now report individual case reports (ICSR's) into Vigibase® (Juhlin *et al* , 2015). Vigibase® is the WHO global database of ICSR's.

The WHO requires that PIDM member countries have their own National Pharmacovigilance Centre, which manages reports of potential ADRs as received through their National Pharmacovigilance (PV) system (WHO-UMC, 2020). The information gathered within each national PV system then feeds into the WHO PV system known as Vigibase®. The aim of a well-functioning PV system is to improve the quality and safety of medication prescribed, administered, and used by patients. This can be achieved by collaboration among a wide range of local and international partners, organisations, governments, and society at large (Juhlin, 2015).

As the work of the PIDM progressed, it became clear to the WHO that the sharing of information within the PIDM would allow for proactive prevention of future tragedies like those outlined in section 1.2 of this chapter. To carry forward the work of the PIDM, The Uppsala Monitoring Centre (UMC) an independent, non-profit foundation and a centre for international service and scientific research, was established in Uppsala, Sweden in 1978 as the WHO Collaborating Centre for International Drug Monitoring ((UMC), 2020). The UMC provides services and support to national centres worldwide and produces lexicons or nomenclature for the harmonized classifications of medicines and adverse drug reactions, e.g., the WHO Drug Dictionary, the WHO Herbal Dictionary and the WHO Adverse Reaction Terminology. The UMC also provides services to the global pharmaceutical industry, clinical research agencies and academia as partners in the Drug Safety arena. The UMC database, Vigibase®, reflects the world's combined effort in adverse drug reaction reporting. Vigibase® has proven to be an effective tool, containing more than 8 million reports by 2013, dating back since the inception of the PIDM back in 1968 (Uppsala Report 61, 2013) and approximately 15 million reports from 131 countries by 2018 (Watson, 2019). The WHO provides minimum requirements for a functional PV system to assist member countries in setting up national PV systems (WHO-UMC, 2020) and the UMC conducts training to the WHO PIDM member countries on how to set up effective PV systems.

1.4. Under-reporting of ADRs in South Africa and other low-middle income countries

As a continent, Africa has delayed in joining the WHO PIDM; the magnitude of the clinical and economic impact is yet to be established. Published information from Europe indicates that over 1 million ADR reports were submitted in 2013 alone and in total, over 20% between 2008 and 2013 (Uppsala Report 61, 2013). Under-reporting remains low even in Europe, where, unlike in LMICs, more activities are underway to increase awareness and promote pharmacovigilance. A study by Watson and colleagues (Watson, 2019) analysed data collected within Vigibase®, between 1967 to January 2018 and reported a reporting rate of 24,2% for Europe, compared to 49,8% from North America. Table 1-1 below provides a breakdown of ADR reports in Vigibase® per geographical region between 1967 and 2018 (Watson, 2019).

Table 1-1: ADR reports in Vigibase® per geographical region between 1967-2 January 2018 (Watson, 2019).

Geographical region	Number of reports per region	Proportion of reports per region
Africa	140,059	0,9%
Asia	3,022,513	20%
Europe	3,648,727	24,2%
Latin America and the Caribbean	312,279	2%
North America	7,501,871	49,8%
Oceania	427,310	2,8%
Total	15,056,524	100%

In 1992 South Africa was the first African country to gain WHO PIDM membership and by 2000, only five African countries were members. By 2015 there were still 21 African countries which had not yet become members of the programme (Ampadu, 2016). The WHO reported that by September 2016, 35 African countries had become members of the PIDM and at that point collectively submitted 103 499 ICSRs into Vigibase®, which amounts to less than 1% (0.88%) of the total number of global reports (Ampadu, *et al.*, 2016). The Watson study reported that Africa's ADR contribution was 0,93% by 2018 (Watson, 2019). Studies on this topic have identified obstacles to PV growth in Africa, including weak overall national health infrastructure and systems, poor understanding of PV, lack of PV in the formal tertiary education curricula and low levels of interest from healthcare professionals (Olsson S, 2015). Although South Africa established a national PV system in 1987 and joined the WHO PIDM in 1992, under-reporting still a challenge in the country. By 2018 of the 140,059 ICSRs from all African member countries, 39,881 (28%) (Watson, 2019) were received from South Africa, a slight improvement from 24% in 2013 (Ampadu, *et al.*, 2016). Inadequate formal training on ADR reporting processes in South Africa is suspected to be one of the major contributors towards the low levels of ADR reporting (Mouton JP *et al,* 2014).

1.5 Research Question

This project seeks to address the following research question:

"What is the level of knowledge, attitudes and current practices of pharmacovigilance among medical doctors and pharmacists in South Africa?"

1.6 Problem statement

Although medical doctors and pharmacists in South Africa are familiar with the concept of pharmacovigilance, they are not well trained on the process of reporting adverse drug reactions and when they do report, theirs is no feedback received from the national PV unit. Due to their limited knowledge on how to report DRs, medical doctors and pharmacists in South Africa are not always able to identify potential ADRs and thus not motivated to report. Lack of feedback gives a feeling of reporting into a black hole, thus giving the perception that reporting is a futile exercise. Strengthening of the national PV system (to be well-funded and resourced), which is capacitated to perform signal detection and communicate such signals, incorporation of ADR reporting training into undergraduate curricula, as well as ongoing training of healthcare professionals are some interventions that will be effective in promoting ADR reporting in South Africa.

1.7 Research aims and objectives

The aim of this study is to investigate the factors influencing the low ADR levels in South Africa. The results of this study will be used to make recommendations on how to promote post-marketing surveillance of medicines in South Africa.

1. The primary objective of this study is to determine the knowledge on PV among medical doctors and pharmacists in South Africa.
2. To determine the attitude towards practicing PV among medical doctors and pharmacists in South Africa.
3. To determine the current practices of PV, among medical doctors and pharmacists in South Africa.

1.8 Significance of research

This study investigated whether medical doctors and pharmacists are aware of PV and whether they understand the reporting of ADRs to be their professional obligation. This study also investigated the factors contributing to the low rate of ADR reporting among medical doctors and pharmacists. Although nurses were not included in this study, they contribute significantly to patient care and commonly the first to receive patient reports of potential side effects from medication that they themselves administered on the patients. The table below provides a summary of ADR reports submitted globally to Vigibase® per reporter type, since inception in 1967 to 1998 (Watson, 2019). Suggestions will be made on practical methods that could be implemented to promote awareness, enhance reporting rates, and increase communication among all stakeholders.

Table 1-2: ADR reports submitted globally to Vigibase® per reporter type, since inception in 1967 to 1998 (Watson, 2019)

Reporter type	Number of reports per reporter type	Proportion of reports vs total reports received
Physician	5,212,044	34,6%
Pharmacist	979,580	6,5%
Other HCP	1,648,294	10,9%
Patient	4,252,156	28,2%

1.9 Limitations

Questionnaires are a common and useful method to collect data from a large sample of human study participants. Distributing questionnaires electronically as a link to an online survey allows for distribution to a larger sample population compared to using hard copies. Although the link to the survey was distributed to over 7,000 SAMA members and to approximately 650 medical doctors and pharmacists the SACRA database, there was no guarantee that all recipients would indeed have received the email containing the link and if they did receive it, that they would have opened and read it. Having a large database of potential participants and sending of the survey link multiple times increased the chances of receiving responses to meet the targeted sample size of 384.

Laxton (Laxton, 2004) outlines some limitations of administering questionnaires. The biggest challenge is low response rate on questionnaires distributed by email. In addition, respondents may choose not to respond to some of the questions and emailed questionnaires may even allow participants to manipulate the responses as is the case with knowledge related questions, for example. With the latter it is impossible to validate the authenticity and potential source, of responses. Furthermore, and unlike with personal interviews, the context of responses to emailed questionnaires cannot be established and questions can be open to interpretation. Emailed questionnaires may also exclude participants who would potentially provide valuable information but are too busy or uninterested in completing surveys. Such questionnaires may also end up being limited to research-minded participants or to those in favour of the issue.

Medical and pharmaceutical associations were approached to distribute the survey via email to their members; these include SAAHIP (South African Association of Hospital and Institutional Pharmacists), SAAPI (South African Association of Pharmacists in Industry), ICPA (Independent Community Pharmacy Association), South African Medical Association (SAMA) and the South African Clinical Research Association (SACRA), among others. Approval was only received from SAMA and SACRA, while other associations declined the request, citing that they do not distribute surveys for academic purposes. Medical doctors and pharmacists who are not members of SAMA and SACRA and those who do not have access to email, fell outside the scope of this study.

The potential for sampling bias was reduced by including all possible sub-groups of the sample population. Participants of all genders, professional levels, all racial groups, working across all facility types in South Africa, having achieved an undergraduate qualification from any university globally, were provided with an opportunity in this study, on provision that they had a membership with SAMA and SACRA.

Due to the participant sources only being SAMA and SACRA membership databases, it was likely that the largest number of respondents would be medical doctors than pharmacists. It is important though, to collect data from both these groups as the HCPs who prescribe and dispense medications to patients. Pharmacists are well positioned to educate patients about medication that is being dispensed in terms of the correct use of the medicines, common side effects and any notable contra-indications (e.g., use of antibiotics while on hormonal contraceptives). A Portugal study reviewing 36% of the ADR reports submitted to a regional PV centre over a 10-year period, broke down ADRs reported by doctors as 54%, pharmacists 31%, and nurses 15% (Marques, 2013). No local study could be found providing a breakdown of ADRs reported to the national PV unit.

1.10 Assumptions

This study assumed that only the intended participants would complete the survey and each respondent would only complete it once. Some of the answers for the questions related to knowledge of PV could be found on internet search engines. To avoid this, some of the questions were phrased in a complex manner and verified by doing a quick internet search, to ensure that the answers are not readily available. It is assumed that the study participants would find it too time-consuming to search for answers on the internet, especially when the search leads to documents that must first be read to get the required information. It was assumed that the study participants would respond truthfully to the survey questions. This study assumed that responses would be received from both medical doctors and pharmacist, even though the ratio would be unequal.

1.11 Overview of the methodological approach and ethics

The research method applied on this study was quantitative data collection by means of an electronic questionnaire. The study population were medical doctors and pharmacists working in South Africa. The sample size was 384 medical doctors and pharmacists combined. There was no allocated ratio of medical doctors to pharmacists to complete the survey.

The study protocol, informed consent form and questionnaire were approved by the Stellenbosch University Health Research Ethics Committee (SU-HREC) on 11 Feb 2019 [**HREC Ref # S18/10/231**]. Medical and pharmaceutical associations were approached with a request to distribute the questionnaire via email to their members. Approval was received from SAMA and SACRA The questionnaire was entered into SurveyMonkey® online portal and the link was sent to SAMA and SACRA for distribution. SAMA distributed the survey link via email to 17,500 members (doctors) and SACRA sent the link to 650 email respondents (doctors and pharmacists).

1.12 Thesis structure

This thesis consists of six chapters.

1. Chapter 1 is an introductory chapter, providing the background and rationale of the study. The significance of the study together with its limitations are also outlined. A brief overview of the research methodology used in this study is also included.
2. Chapter 2 is the literature review, which starts by outlining the drug development process, the events leading to the development of the WHO-UMC, defining pharmacovigilance, its scope, and common methods. The process of ADR reporting and management by the WHO-UMC is also outlined, as well as consideration for other types of medications such as vaccines, traditional medicines, etc. The chapter ends off by exploring global PV developments as well as developments on the African continent and in South Africa.
3. Chapter 3 discusses the research methodology used in this study. It elaborates on the selected study population, development of the questionnaire used, data collection and analysis. Ethical considerations and limitations are also discussed.
4. Chapter 4 presents the results of the study in a descriptive format, followed by,
5. Chapter 5 discusses the results in a narrative.
6. Chapter 6 concludes the thesis, including recommendations for future studies.

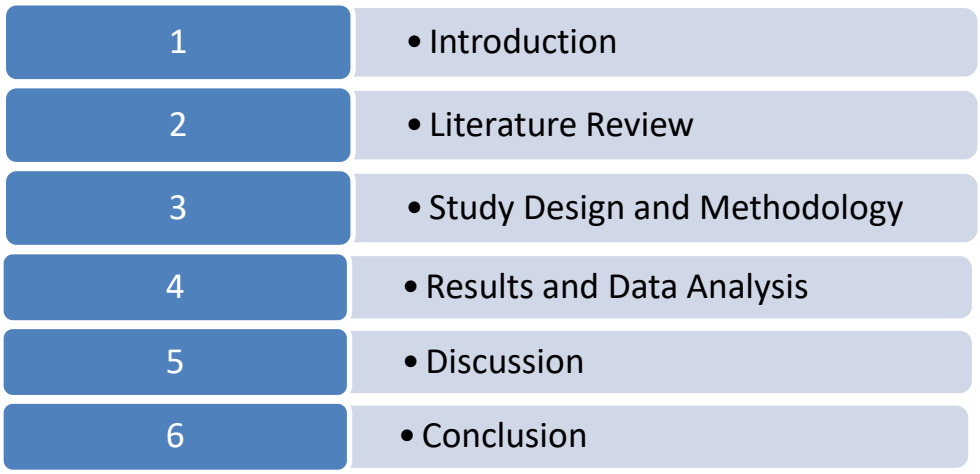


Figure 1-2: Outline of thesis

CHAPTER 2
Review of Literature

2.1 Introduction

This chapter provides an overview of the review conducted on available published literature. To establish a theoretical and contextual foundation for this research study, a general search was initially conducted to assess the extent of published literature available. Search engines and databases such as PubMed®, Science Direct®, Scopus® and Cochrane Library® were used. The focus was mainly on published journal articles, textbooks, websites, and other official publications such as reports, conference proceedings, training presentations, guidelines, and regulations, published by organizations such as the WHO, WHO-UMC, USA- FDA, EMA, the SAHPRA, and others. Themes and key words used in the online search included *pharmacovigilance* (PV), *adverse drug reaction* (ADR), *knowledge, attitudes, and practices* (KAP), *ADR reporting*, *PV in South Africa*, *PV in LMICs*, *spontaneous reporting, quantitative research methods, causality assessment, signal detection, vaccine safety, AEFI reporting, PV training, PV awareness, PV funding*, among others. A literature review matrix was utilised to screen and summarize the selected literature in a manner that facilitated the synthesis and narrative of the literature. The matrix arranged the literature in terms of study objectives, study design, geographical location of study, type of healthcare facility, sample population, and main findings. Through this process, key opinion leaders in the field of study were identified and additional searches were conducted for additional literature, lectures and other works published by them.

The chapter begins with the background into the drug development process, and the historical events leading to the development of the WHO-UMC. Pharmacovigilance processes employed by the WHO-UMC are explored, including the dynamic scope and methods of PV, the tools used for ADR reporting and the management of ADRs received from WHO-PIDM member countries. Special considerations and PV for vaccines are also outlined. The chapter furthermore explores global PV activities as well as the efforts of the WHO-UMC to mentor and support the development of fully functional PV systems in African countries as well as other similar studies to the current study, conducted in other African countries. Finally, the chapter concludes with PV activities currently underway in South Africa, inter alia outlining gaps and challenges that were reported by other researchers.

2.2 Drug Development

A pharmaceutical drug, also called a medication, medicine, or medicinal product, is a chemical substance used to mitigate, treat, cure, prevent, or diagnose a disease or to promote well-being. The development processes typically consist of a drug discovery phase followed by a drug development phase. The development process consists of pre-clinical (*in-vivo and in-vitro*) testing, formulation, and clinical trials (phase I to III). Over the years it has become apparent that the life cycle of a drug continues beyond phase III clinical trials; this has led to post-marketing surveillance and phase IV clinical trials (FDA, 2021).

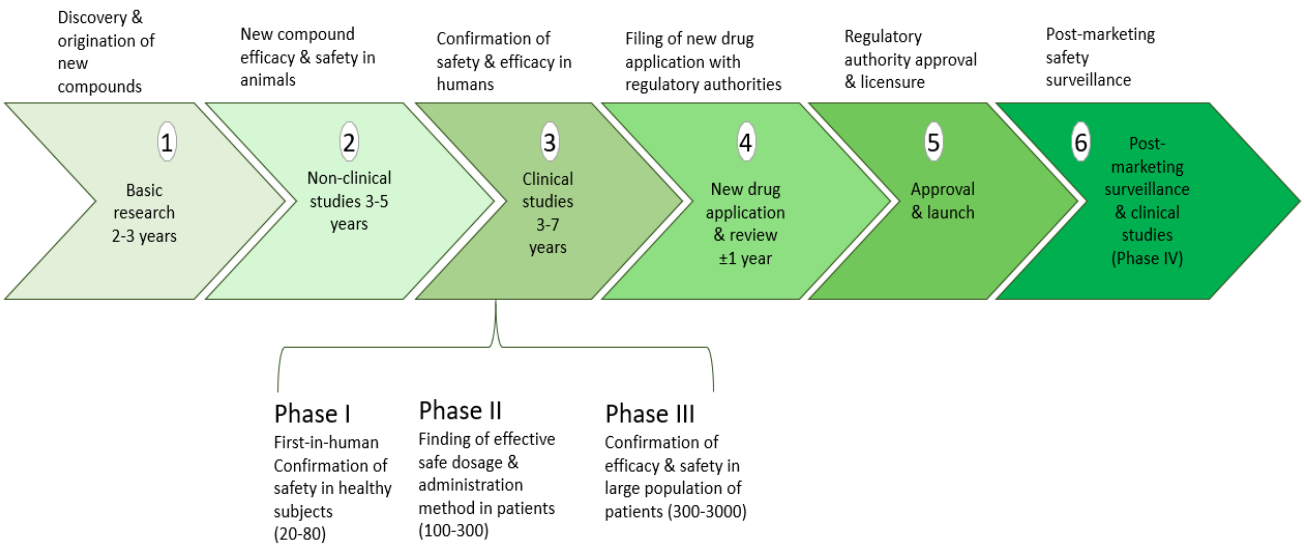


Figure 2-1: Drug Development Process (FDA, 2021)

2.3 Risk-Benefit Assessment

Medicines may under most circumstances be effective and beneficial to human lives; however, they also present a risk of side effects. Throughout the life cycle of a drug, it is important for regulators to continuously monitor the benefit-risk balance to ensure the protection of the rights and wellbeing of people exposed to the drug. The benefit-risk assessment aims to measure the usefulness of a medicine, administered for a certain indication, at a certain dose, in a specific population. This assessment supports the approval of a drug to enter the pharmaceutical market after completion of phase III clinical trials and on a continuous basis afterwards, it supports the decision for the drug to remain on the market, or not. At each point of the assessment, the reliance is on the currently available information. For instance, once the drug is available on the market and available to more people, there may be newly found side effects which may lower the benefit-risk balance. Alternatively, there could be favourable data from phase IV trials, showing that the drug is more effective than shown in phase III trials, this brings the benefit-risk balance up. An external factor can be the availability of safer, more effective alternatives becoming available on the market; this may dramatically drop the benefit-risk balance of a drug (Caster, 2017).

2.4 Adverse Drug Reactions

2.4.1 Definition

The WHO defines an adverse drug reaction as *a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function* (Health, 2007). A side effect is defined as *any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine. Such effect may be either positive or negative. Such effects may be well-known and even expected and may require little or no change in patient management* (Health, 2007). An adverse drug event, otherwise known as an adverse event refers to *any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal*

relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it (Health, 2007). Post-marketing monitoring plays a critical role in identifying rare ADRs which could not have been identified during clinical trials.

2.4.2 Classification of ADRs

Adverse drug reactions were originally classified by the WHO into types A and B. It was, however, noted that not all ADRs fit into these two categories and additional categories were therefore developed. About 80% of ADRs in the hospital setting or causing admission to a hospital are type A (Pirmohamed, 1998). These ADRs are potentially avoidable and often predictable.

Table 2-1: ADR Classification (Pirmohamed, 1998) (Health, 2007)

ADR Type	Description
A	Dose-dependent and predictable from the known pharmacology of the drug, e.g., orthostatic hypotension with antihypertensive medications
B	Uncommon and unpredictable, depending on the known pharmacology of the drug; they are independent of dose and affect a small population. e.g., hypersensitivity (allergic) reactions to drugs
C	Chronic reactions, which relates to both dose and time
D	Delayed reactions
E	End of use / withdrawal reactions
F	Unexpected failure of therapy

2.5 Pharmacovigilance

2.5.1 History and Development of WHO-UMC

The thalidomide tragedy demonstrated the danger of marketing drugs that had not been put through a development programme of rigorous testing for efficacy and safety. It also highlighted the importance of careful post-marketing monitoring of medicines. This led to the establishment of the Programme for International Drug Monitoring (PIDM) by the WHO in 1968. By 1978, all operational responsibilities of the PIDM were transferred to the Uppsala Monitoring Centre (UMC). The WHO-UMC manages the global ADR database (VigiBase®), which is at the centre of the continuous research conducted on signal detection. The UMC undertakes multiple activities to promote PV, including the support and mentorship of PIDM member countries in the development of functional PV systems (WHO, 1999). The process of post-marketing surveillance starts with ADR reports being submitted to the national PV centre. The PV centre then performs data entry, coding, assessment, signal detection. If a signal is detected, the PV centre is responsible for informing the stakeholders of the potential ADR. Confirmation of signals can lead to several regulatory implications, such as the mandatory adding of additional safety measures for the medicine (change in schedule, black box in package inserts) or even complete withdrawal of the medicine from the market.

2.5.2 Scope of pharmacovigilance

According to the WHO, Pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" (WHO, 1999). The scope of pharmacovigilance is ever evolving, and an extended scope has developed to include the following. See Figure 2-2 below:

- Types of medicines: regular medicines, vaccines, traditional/herbal remedies, biologicals
- Substandard/spurious/falsely labelled/falsified/counterfeit (SSFFC)
- When assessing adverse effects, a consideration of the properties of the drug ingredients and the characteristics of the patient.
- Unexpected lack of efficacy, due to product quality (inadequate GCP, distribution, storage, counterfeiting, etc.).
- Inappropriate use (medication errors, dependence and abuse, poisoning).
- Safety challenges of mass treatment campaigns, e.g., rumours and stigma (immunization and public health programmes).

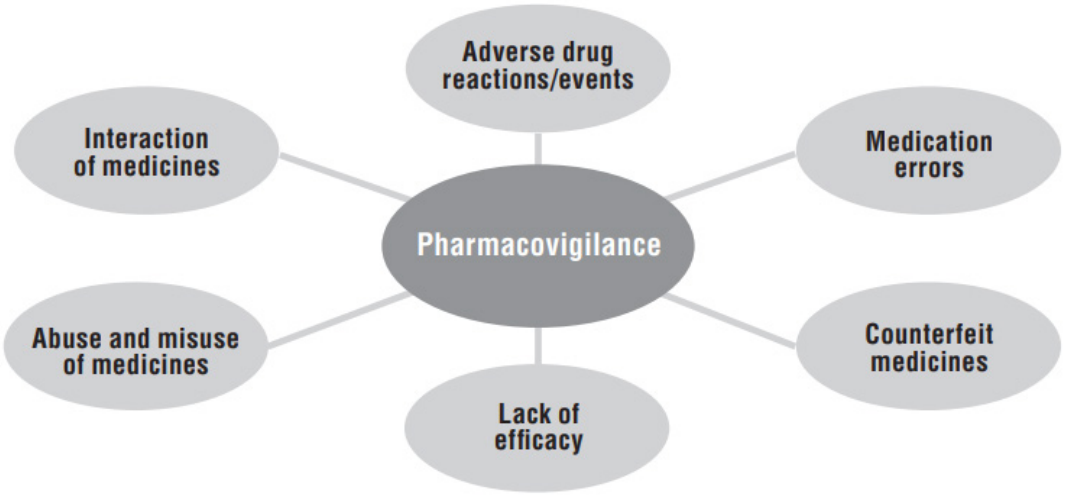


Figure 2-2: Scope of pharmacovigilance (WHO, 2006)

Pharmacovigilance activities include collecting individual case report forms, analysis of data to identify new signals and communication of those signals to stakeholders (Fornasier, 2018). These activities are important for promoting rational use of medicines and ensuring public confidence. Before medicines are put on the market, safety information is gathered through animal studies (pre-clinical) and clinical trials, conducted in humans. Animal studies are key in understanding the potential toxic effects that medicines can cause. Types of animal studies include acute toxicity, carcinogenicity, metabolism, organ damage, dose dependence, teratogenicity, kinetics, mutagenicity, etc. (WHO, 2006). Data gathered through these studies is critical for the next phase of the drug development process. The products under consideration go beyond conventional medicines, and include herbal medicines, other traditional and complementary products, biologicals, vaccines, and medical devices; as summarised below in figure 2-3:

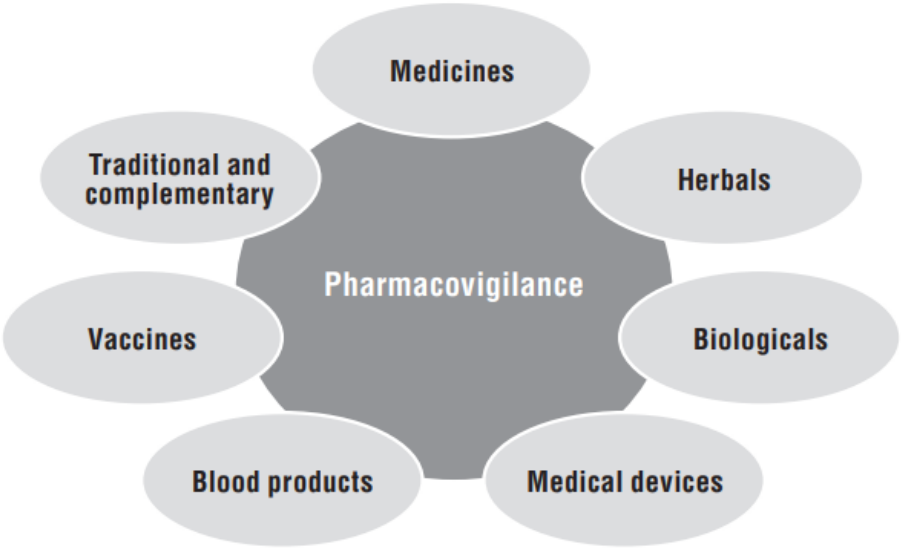


Figure 2-3: Types of medicines included in PV practices (WHO, 2006)

2.5.3 Pharmacovigilance Methods

Studies conducted at post-marketing phase can be descriptive or analytical. Descriptive studies include spontaneous reporting systems (SRS) and intensive monitoring studies. These are useful in generating hypotheses, which are then tested through analytical studies. Analytical studies include cohort and case-control studies (WHO, 2006).

2.5.3.1 Spontaneous Reporting System (SRS)

Spontaneous reporting is a system to monitor the safety of all medicines on the market, throughout the entire lifecycle of the medicine. It covers the global population and detects signals of new, rare, and serious ADRs. This is the most common PV method, consisting of voluntary ADR reporting by HCPs, pharmaceutical companies and in some countries, including patients. An Individual Case Safety Report (ICSR) is the tool used for this method of PV and this is submitted to the national PV centre. Although country requirements may vary, reporting is generally expected for serious ADRs, new medicines (less than 5 years on the market), unknows reactions (even if not serious/severe) and ADRs occurring in vulnerable groups (children, pregnant women, and elderly patients) (Hazell , 2006). The WHO definition of a serious adverse reaction is: “disability or any untoward medical occurrence that at any dose; results in death, life threatening, requires inpatient hospitalisation/prolongation of existing hospitalisation or results in persistent of significant incapacity” (WHO, 2012). The main criticism of this system is its voluntary nature which can easily lead to under reporting. A systemic review of ADR reporting in 2006 identified that more than 94% of all ADRs remained unreported (Hazell , 2006). Another limitation of SRS is that it does not allow for assessment of incidence rates and risk factors of ADRs. Although limitations exist, SRS has proven to be effective when stakeholders are

compliant in reporting suspected ADRs to the relevant PV centres. A study of the signals discussed by the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) found that in 62% of the cases where regulatory decisions were made, the basis of those decisions was data from spontaneous reports (Clarke, 2006). Evidence from data collected through SRS led to the withdrawal of 11 medicines from US and UK markets between 1999 and 2001 (Clarke, 2006). A systematic review of 18 medicines which were withdrawn or suspended in the EU between June 2012 and December 2016, found that the decision affecting 17 of those medicines, was based on evidence from spontaneous ADR reports. A spontaneous reporting system is the easiest PV system to implement, the least labour intensive and relatively inexpensive to maintain, making it a good starting point for most countries.

2.5.3.2 Intensified ADR Reporting

The aim of intensified monitoring is to gather additional information about ADRs, such as risk factors, type, frequency, time course and the impact of those ADRs on the quality of life of patients for medicines at early post-marketing phase. Intensified monitoring is like spontaneous reporting; however, HCPs are prompted to collect additional information from patients. The United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) introduced a concept of additional monitoring by placing a black triangle on label of new medication on the market, to prompt HCPs to be more alert when prescribing and dispensing those medicines. The EMA maintains an extensive list of medicines that require additional monitoring on their website, making it available not only to HCPs but to the public as well (EMA, 2021).

Additional monitoring status is always applied to a medicine in the following cases (EMA, 2021):

- it contains a new active substance authorized in the EU after 1 January 2011.
- it is a biological medicine, such as a vaccine or a medicine derived from plasma (blood), authorized in the EU after 1 January 2011.
- it has been given a conditional approval (where the company that markets the medicine must provide more data about it) or approved under exceptional circumstances (where there are specific reasons why the company cannot provide a comprehensive set of data).
- the company that markets the medicine is required to carry out additional studies, for instance, to provide more data on long-term use of the medicine or on a rare side effect seen during clinical trials.
- it is authorized with specific obligations on the recording of suspected adverse drug reactions.
- Other medicines can also be placed under additional monitoring, based on advice from the Agency's Pharmacovigilance Risk Assessment Committee (PRAC).

2.5.3.3 Targeted Spontaneous Reporting (TSR)

TSR is an ideal PV method for collecting ADR data for targeted population groups such as children, pregnant women, specific clinics, ADRs and/or medicines (e.g., National Tuberculosis (TB) programmes, monitoring the safety of bedaquiline, as it is relatively new on the market) (WHO, 2006). In Uganda, the National PV Centre, in collaboration with the HIV control programme implemented a TSR of suspected renal toxicity at two government facilities, monitoring tenofovir-based regimens from April 2012 to March 2014. It was found that the reporting rate for suspected ADRs had increased five-fold during the period of the TSR; with the incidence of renal toxicity occurring in 1:200 patients. It was also found that with a treatment period of over 4 years, an increase was noted in creatinine levels (Ndagije, 2015). The benefit of TSR is that it can use already developed infrastructure, it targets specific medicines or interest, and it captures all useful information. The limitation is that reports are focused on specific ADRs and some ADRs can be missed.

2.5.3.4 Cohort event monitoring (CEM)

The aim of cohort event monitoring is to gather additional information about a medicine at early post-marketing phase; also referred to as Phase IV observational trials. The benefit of CEM is that all adverse events are recorded, whether related to the medicine or not, and not just suspected ADRs. CEM also identifies interactions when the medicine in question is taken along with other medicines (WHO, 2006).

2.5.3.5 Electronic health records (EHR) mining

Analysis of existing health records available in a database, to identify potential ADRs. This allows collection of all ADRs and all medicines. The UK established the General Practice Research Database (GPRD), which captures useful data including patient demographics, medical histories, hospital referrals, drug-dispensing, vaccination records and lab results. Analysis of such databases can support the development of hypotheses, which are then tested in case-control and cohort studies. A study conducted to review the UK's GPRD found that this data also contributes towards research studies conducted within other science disciplines including pharmacoepidemiology (56%), epidemiology (30%) (Gelfand, 2005).

2.5.3.6 Record Linkage

This is a concept of linking available databases and registries for the purposes of data analysis. In the Netherlands, the PHARMO Database Network, a population-based network of electronic healthcare databases, was established to link community pharmacy and hospital data. It contains information of more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. Over the years, the system has been linked to other databases such as population surveys, doctor's consultations, hospitalization, pharmacy,

pathology, mortality, perinatal, laboratory and genetic data, cancer, and accident registries, etc. Through linkages with various healthcare databases, a complete profile of an individual's medical history throughout life can be created. This linkage makes the system useful in case-control studies, epidemiology, and analytical studies (Leufkens, 2005).

2.6 ADR Reporting and Processing

2.6.1 Individual Case Report Forms (ICSRs)

A one-size-fits-all approach is not appropriate in creating a standard ADR reporting form which is able to accommodate the wide scope of reports required to be received by a national PV centre; however, there is standard information that is required in all cases. Standard information includes patient demographics, drug use, event, reporter (in case additional information is required). For patient demographics, no personal identifying information is collected, only age, gender, ethnicity, medical history. For drug use, it is good to have the suspected drug, indication, dosage, action taken, concomitant medications, how was suspected ADR treated. At times, a medicine may cause an undesired reaction if taken for the incorrect indication or at the incorrect dose. Concomitant medication may also reveal comorbidities. For the event, it is good to have information on the type of event, start and stop dates, treatment, circumstances (to be able to detect possible medication errors, counterfeit medicines, etc.). ADRs can be reported by a wide variety of stakeholders. In some countries, the HCPs who are required to report include physicians, pharmacists, nurses, etc. and patients themselves. ICSR's can be available in paper (NDoH, 2021) or web-based (MHRA, 2021) format. For vaccines, even telephonic reporting is possible. An advantage of a web-based format can be to allow for attachments to be uploaded into the web portal. For example, the easiest way for a physician in a busy hospital to submit a suspected ADR may be to submit a scanned copy of the anonymised hospital records with all the notes directly as they are written. The national PV centre would then have to enter that information into the ICSR format in the database, but this addresses the concern that ADR reporting is time-consuming (WHO, 2006). Web-based forms can be linked to the national PV centre's database, thus avoiding the need for manual data entry. The designing process for the web-based form is costly; however, afterwards the costs to maintain it are low as there is a saving on printing costs. Web-based forms can be formatted such that for events where additional information is required, the reporter can be prompted to provide such information. Reporters can also pre-populate their information (such as name, practice number, hospital, etc.) to save time by not needing to enter this each time they submit a report. The layout and design of the form is also important to consider when designing an ICSR. The form must be user-friendly and not use jargon, especially in countries where patients also report ADRs. It is also important to remain abreast with new developments, technology advances and continuously improve the ICSRs on a regular basis (WHO, 2020).

2.6.2 Identification of ADRs

Adverse drug reactions present the same way and follow the same course as natural disease; therefore, the diagnostic methods applied are the same. The only difference is that ADRs are drug induced. The drug classes most commonly responsible for ADRs in adults are adrenal corticosteroids, antibiotics, anticoagulants, antineoplastic and immunosuppressive drugs, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, and opiates. For children, the

most prevalent drug classes for ADRs are anti-infective drugs, respiratory drugs, and vaccines (Kongkaew, 2008). The following sub-headings outline examples of the type of drug induced ADRs that have been identified.

2.6.2.1 Hepatotoxicity

Hepatotoxicity is a potential reaction for all medicines, due to the multiple functions of the liver, including drug metabolism, excretion, and protein synthesis. Hepatotoxicity is the cause for premature termination of approximately 30% of clinical trials (Friedman, 1999). Researchers reported hepatotoxicity as the leading cause of medicines being withdrawn from the market between 1975 and 2005 (Friedman, 1999). Hepatotoxicity also referred to as drug-induced liver injury (DILI) is classified as hepatocellular liver injury (ALT $\geq$ 2 ULN), cholestatic liver injury (AP $\geq$ 2 ULN) or mixed liver injury (ALT/AP) between 2 and 5 ULN) (CIOMS, 1999). Medicines affect the liver in different ways, by identifying which type of injury occurs most frequently with the use of a particular medicine, it can facilitate the causality assessment.

Example: Hepatic Steatosis (Fatty Liver)

This occurs when fatty acids accumulate in the liver due to the impairment of oxidation processes in the mitochondria. Medicines that have been found to cause this include steroids, methotrexate, tetracyclines, perhexiline and amiodarone.

2.6.2.2 Allergic reactions

Allergic reactions make up 5-10% of all reported ADRs (American Academy of Allergy, 2013). Drug-induced allergic reactions are triggered by any one of the four types (I – IV) of hypersensitivity immune response to the medication, causing symptoms in the nose, lungs, throat, sinuses, ears, mucosal lining and/or skin. Time to onset can range from immediate or up to two weeks after taking the medicine. Anaphylaxis is the most severe form of allergic reaction, with the onset usually being immediate or within one hour of taking the medicine and it can result in death. Clinical features of anaphylaxis include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock. Suspected medications for anaphylactic reactions include monoclonal antibodies, antibiotics, and chemotherapy medication.

The most frequently drug-targeted organ is the skin; most commonly presenting as benign drug eruptions, which can be mild, severe, and sometimes even life-threatening or fatal. Rash is the most common type of drug eruption, with a higher risk with antibiotics, antiepileptics and allopurinol. It usually starts from the trunk and spreads to lower extremities and responds well to conservative treatment. It usually occurs within 4-14 days of drug intake, sometimes even after discontinuation. The time to onset can be a challenge in assessing the causality of the rash, because if it commonly starts after the medicine has been stopped and is therefore not easily attributable to that medicine. Unintentional re-challenge often occurs when the rash could not be attributed to the drug initially until the patient is given the same drug again and it causes an even more severe reaction, thereby elucidating the possible link between the rash and the culprit drug (Raujeau, 1995).

Example: Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Rare but severe skin reaction (blistering and detachment), 70% of cases are drug induced, although it can occur naturally (Raujeau, 1995). SJS and TEN are both life-threatening, with a 10% mortality rate for SJS and 30% for TEN (Raujeau, 1995). The symptoms of SJS and TEN may include high fever and usually mucosal involvement (eyes, mouth, and digestive tract). Hepatic and pulmonary involvement is also possible. Time to onset is less than 4 weeks; usually between week 3 and 4 of treatment. Commonly associated drugs include allopurinol, anticonvulsants, sulphonamides, oxicams and pyrazolone non-steroidal anti-inflammatory drugs (NSAIDs) (Raujeau, 1995).

2.6.2.3 Nephrotoxicity

Drug-associated nephrotoxicity is any injury to the kidney which is directly or indirectly caused by medication. Drug-associated acute kidney injury (AKI) accounts for 18 – 27% of acute kidney failure cases in USA hospitals (Taber, 2008). Haemodynamic renal failure may result from drugs that reduce renal prostaglandins and hence renal blood flow and glomerular filtration rate commonly associated with nonsteroidal anti-inflammatories (NSAIDs) and the relatively newer group cyclooxygenase-2 selective inhibitors (Coxibs) (Taber, 2008). Drug-induced tubulointerstitial nephritis and acute tubular necrosis are also frequent causes of AKI, often caused by antibiotics and less frequently by NSAIDs. Drug-induced glomerular and renal vascular disease is relatively rare. Direct renal tubular toxicity has also been described with medications with unique effects on the epithelial cells of the kidney, including the antiviral agents cidofovir, adefovir, and tenofovir as well as the bisphosphonate pamidronate (Raujeau, 1995) (Taber, 2008). Additionally, crystal deposition in the kidney may promote the development of renal failure. Several different drugs have been described to induce crystal nephropathy, including the antiparasitic drug sulfadiazine, the antiviral agent acyclovir, and the protease inhibitor indinavir (Raujeau, 1995). Finally, an unusual form of renal failure characterized by swollen, vacuolated proximal tubular cells can develop from hyperosmolar substances, such as antibacterial drugs, antifungal agents, antimalaria agents' antivirals, NSAIDs and anticancer drugs (Raujeau, 1995). Knowing the high-risk populations is essential for the prevention and early diagnosis of nephrotoxicity. The main risk factors are related to the reduction of the renal functional reserve (glomeruli without the ability to increase the filtration rate), a larger concentration of drugs on the tubules, and synergistic injury mechanisms (Raujeau, 1995). Some examples are drugs with vasoconstrictor effect associated with diuretics and drugs that compete for the transporter responsible for tubular secretion, increasing the cytoplasm concentration, such as in the combination of cisplatin and aminoglycoside (Raujeau, 1995).

2.6.2.4 Hematological

Myelosuppression occurs when the production and maturation of bone marrow is affected, causing anaemia, leucopoenia, granulocytopoenia, low platelet count. These reactions can be both type A and B ADRs, depending on the causal drug.

For example, most oncology drugs act on fast replicating cells and if blood cells or the gut mucosa are exposed to such a drug, that same drug can cause pancytopenia or oral ulcers by affecting the bone marrow or oral mucosa, respectively. This is a predictable adverse effect explicable by the known pharmacology of the drug, they are dose dependent and common; therefore, the ADR classification is type A. With type B reactions, there is a genetic predisposition for some reactions with the use of drugs such as methotrexate, 6-mercaptopurine, clozapine, or chloramphenicol (Parchment, 1998).

Example: Aplastic anaemia and agranulocytosis

Aplastic anaemia can occur naturally, but it may also be associated with use of medicines, exposure to chemicals, radiation, infections, and auto-immune disorders. A bone marrow examination may be needed to confirm the diagnosis aplastic anaemia characterised a sparsity of cells produced, across all cell lines (red blood cells, platelets, and white blood cells, including neutrophil granulocytes). Medicines classically associated with aplastic anaemia and agranulocytosis include anticonvulsants (phenytoin, carbamazepine), antimicrobials (sulphonamides, mebendazole, zidovudine), antirheumatics (phenylbutazone, piroxicam, indomethacin), ACE-inhibitors (captopril) and immunomodulators (alpha-interferon) (Parchment, 1998). Agranulocytosis is in addition, also strongly associated with clozapine and antithyroid medicines. It should be noted that anticonvulsants and sulphonamides are also often associated with SJS and TEN (Parchment, 1998).

2.6.3 Causality assessment of suspected ADRs

Causality assessment aims to provide answers as to whether a specific drug exposure caused the ADR and ultimately whether the implied drug increases the risk of the observed ADR (User manual for the revised WHO classification, 2018). The assessment of whether a drug has caused a particular ADR is not always straight forward; however, causality assessment can classify the relationship between suspected ADR and drug, using available evidence. Assessing causality on individual cases is limiting, due to challenges such as inadequate information, selection bias and lack of knowledge. A case series of suspected ADRs may supply additional information and confirmatory evidence.

Several methods for assessing causality of ADRs have been developed; however, no system has been able to direct assessors to a definite conclusion of causality. The available systems are, however, useful guides and with accumulating evidence available and continuous analysis of available data, a strong suggestion of likelihood can be made with greater confidence.

A. WHO-UMC Causality Assessment System

The WHO-UMC has developed a causality assessment system in consultation with WHO-PIDM member countries. This system is used to assess case reports and it considers the quality of the data reported as well as the clinical-pharmacological aspects of the case history. The system consists of causality categories as shown in Table 2-2 (WHO-UMC, 2013)

Table 2-2: WHO-UMC Causality Assessment Categories (WHO-UMC, 2013)

Category	Description	Comment
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also, is the consideration of confounding features, but due weight must be placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g., penicillin anaphylaxis.
Probable/ Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no re-challenge information is needed, but confounding drug administration underlying disease must be absent.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provides plausible explanations.	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.
Conditional/ Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more	

	data is essential for a proper assessment or the additional data are under examination.	
Unassessable /Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

B. Naranjo Algorithm

In addition to systems, there are algorithms that can be used to assess causality. These include the Jones algorithm (Jones, 1982), Kramer algorithm (Kramer, 1979), the Begaud algorithm (Bégaud, 1985), among others. The most common algorithm is the Naranjo ADR probability scale. It consists of ten questions about the ADR; a numeric score is assigned as presented in Table 2-3 (Naranjo, 1981). This is often used in clinical trials.

Table 2-3: Naranjo ADR Probability Scale (Naranjo, 1981)

Question	Yes	No	No not known
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was given?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given?	+1	0	0
4. Did the adverse reaction appear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes that could have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Scoring
- > 9 = definite ADR
- 5-8 = probable ADR
- 1-4 = possible ADR
- 0 = doubtful ADR

C. Bradford Hill Criteria

The Bradford Hill criteria developed by Sir Austin Bradford Hill for the assessment of causality in a case series are summarised depicted in Table 2-4. (Robyn, 2005).

Table 2-4: Bradford Hill Criteria (Robyn, 2005)

Criteria	Description
Strength of association	Qualitative (disproportionality) measure of the association between a drug and an ADR

Specificity of event	- There are many common ADRs that can be caused by multiple drugs, e.g., headache, nausea, renal failure, abdominal pain. Generally affecting physical systems that are responsible for metabolism and excretion of the drug. At the same time, these are common symptoms of a wide range of diseases across multiple severities. - Considering the pharmacokinetics (PK) and Pharmacodynamics (PD) of the drugs, it is easier to narrow down the suspected drug out of all that the patient has been exposed to within a reasonable time to onset. The less the number of drugs, the more likely the association.
Temporal relationship	Reasonable time to onset of ADR, post drug administration
Dose response	- ADR occurs above a certain dose and not for lower doses - Presence of risk factors, e.g., rhabdomyolysis with statins - Must compare dosage in reports with dosage on package insert
Consistency of reporting	- Reports received from a range of countries with similar observations. - Multiple risk factors e.g., Rhabdomyolysis with statins (age, dose, interacting drugs, hyperkalaemia, renal/hepatic/thyroid dysfunction) - Case series can establish if a reaction also occurs in the absence of other risk factors or combination of common risk factors - Clustered reporting (one type of clinic, research study, etc.) creates selection bias, which is challenging for signal detection - Geographical consistency, e.g., reports from two or more countries
Biological Plausibility	Fits with what is known about the drug's actions
Experimental Evidence	Supporting evidence found by other researchers, e.g., prolonged QTc interval
Coherence	Fits with existing knowledge, e.g., drugs that are not absorbed are likely to cause organ damage
Analogy	Common reactions observed within the same Anatomical Therapeutic Chemical (**ATC**) group of drugs, e.g., combined oral contraceptives containing oestrogen and venous thrombosis

Example: Causality assessment of omeprazole and acute renal failure as conducted by the New Zealand PV Centre in 1996 (User manual for the revised WHO classification, 2018)

Omeprazole came into the market in 1988. By 1996, the New Zealand (NZ) National PV centre had received 3 reports of acute renal failure with omeprazole as the suspected cause, the first report was received in 1994.

Gender: 2 male, 1 female

Age: 67-78 years

Outcome: One death, no evidence of rheumatoid vasculitis which could cause a possible effect on kidneys, other not yet recovered and the other was unknown.

Step 1: Search all NZ reports for omeprazole in the urinary tract:

- Abnormal renal function – search result 0
- Interstitial Nephritis – search result 2
- Males 2, Age 59-72 years, omeprazole suspect cause in both
- Time to onset 8 months and 4 months
- One recovered with sequelae, one unknown

Step 2: Search for Evidence

- Literature – published case reports of interstitial nephritis and omeprazole since 1992
- National database and VigiBase® search principles
  - Use substance name to search for a drug e.g., omeprazole instead of Losec. Prilosec, etc.
- UMC-VigiBase® search
  - 15 reports found
  - 5 males and 9 females
  - Age range 51-87
  - Indication treated with Omeprazole: gastrointestinal disorders; no co-morbidities
  - Omeprazole was the sole suspect medicine in 12 of the reports
  - Time to onset: 14 days to 42 months; mostly between 1-7 months – information only available for 10 of the 15 reports
  - Concomitant or co-suspect drugs: 4 patients were taking 5 medicines that can cause interstitial nephritis (diclofenac, azathioprine, dicloxacillin, bendrofluazide and indomethacin). Two patients recovered when Omeprazole was stopped, while the other medicines continued.
  - Reported outcomes on de-challenge: 7 recovered, 1 recovered with sequelae, 3 not yet recovered, 4 unknowns

Step 3: Application of Bradford Hill Criteria:

#	**Bradford Hill Criteria**	**Case Series Assessment**
1.	Strength of association	Statistically disproportionate
2	Consistent time to onset	Time to onset mostly between 1 to 7 months of starting treatment
3.	Specificity of event	No comorbidities and concomitant medicines that could have been an alternative cause. Omeprazole was the sole suspect in most of the reports
4.	Reasonable time to recovery	Recoveries on de-challenge
5.	Biological plausibility	Interstitial nephritis is a typical ADR
6.	Consistency of reporting	Reports from 7 countries

2.6.4 Signal Detection

The WHO defines a signal as "a hypothesis of a risk with a medicine with data and arguments that support it, derived from data from one or more of many possible sources" (WHO-UMC, 2021). As new developments occur in pharmacovigilance, this definition has also evolved. A definition presented at the 1991 meeting of national centres participating in the WHO Programme for International Drug Monitoring was "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information" (WHO-UMC, 2021). In their systematic review, Hauben and Aronson (Hauben, 2009). recommended this definition: "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal

or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions" From all these definitions, it can be deduced that a signal is basically information that arises from one or multiple sources, which suggests a new potential causal association or a new aspect of a known association between an intervention (e.g., administration of a medicine) and an event.

The primary global tool used for signal detection is disproportionality analysis. Disproportionality calculations can be viewed through the VigiLyze® system. It can be applied to small databases such as national and regional PV centres as well as large databases such as VigiBase®. This analysis generates a hypothesis on possible drug-ADR associations. The hypotheses are further investigated with a clinical assessment of each ICSR. In their study, Caster *et al.* (Caster, 2020) suggested that there is no increased risk of generating large numbers of false-positive associations when applying disproportionality analysis to small databases. They further emphasized that this does not suggest that this analysis will be equally effective across all database sizes as well as the importance of manual clinical review of ICSRs.

The WHO-UMC regularly screens ICSRs reported into VigiBase® by performing disproportionality analysis using VigiLyze®, until 2014 when they developed a statistical signal detection system, VigiRank® (Caster, 2020). VigiRank® routinely adds additional selection criteria such as the reports must be from two or more countries, quality of data available in the ICSRs, serious ADRs, specific groups of medicines or populations of interest. The selected reports are then assessed by members of a multi-disciplinary team, consisting of physicians, pharmacists, nurses, statisticians, and data scientists. The initial assessment includes whether the reported ADR is already listed in the medicine's package insert and review of the case series to rule out any other possible causes. This is followed by an in-depth assessment of drug-ADR associations which have been selected for further review. The UMC Signal Review Panel reviews the individual report together with scientific literature for additional evidence. A decision is made as to the strength of the available evidence to suggest that a signal should be formulated and communicated.

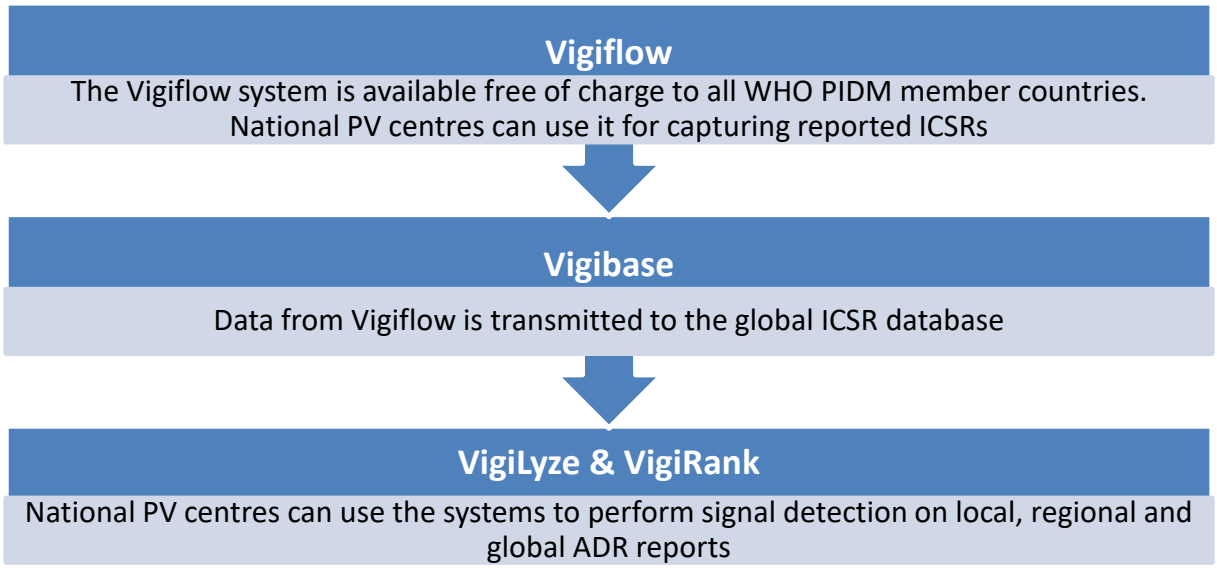


Figure 2-4: Flow of ICSRs in the WHO-UMC PV systems (Caster, 2020)

2.6.5 Signal Communication

One of the advantages of being a PIDM member country is access to VigiLyze® where the signal is made available as a summary report (WHO, 2020). Signals are also published in the WHO Pharmaceuticals Newsletter, which is available to the public on the WHO website. The global research fraternity also refers to published signals and conduct further scientific research into them.

A survey was conducted with 71 countries participating in the WHO Programme. The recipients were asked about the usefulness of the signals published in 26 WHO Pharmaceutical newsletters. Responses were received from 45 out of 71 countries (63%) (WHO-UMC, 2021). The content of newsletters in general was always or often useful in 63.5% of the respondents. In 2001, 17 countries took actions on at least one signal. Actions were rarely taken without considering the published signals. This shows that signal detection and communication plays an important role and has a direct impact on Drug Safety issues handled by members of the WHO Programme for International Drug Monitoring (WHO-UMC, 2021).

2.7 Special Considerations

Additional considerations must be accounted for when identifying and reporting ADRs as not all ADRs are of a pharmacokinetic or pharmacodynamic nature.

2.7.1 Medication Errors

Ferner and Aronson proposed that a medication error is defined as "*a failure in the treatment process that leads to, or has potential to lead to, harm to the patient*" (Ferner, 2006). In May 2016, stakeholders, and experts in the field of pharmacology engaged on the issue of medication errors and made a recommendation to include the word "unintended" before the word failure, to emphasize the non-intentional aspect of medication errors. It was further agreed that the word "failure" in the definition indicates that the intended process fell below expectation and the word "treatment" clarifies that all forms of treatment, not only medicines. "Treatment process" includes manufacturing of the medicine and all the activities that occur until treatment monitoring (Ferner, 2006).

The global cost related to medication errors is estimated at $42 billion annually. This equates to approximately 1% of total global health expenditure (WHO , 2016). It is believed that the impact of unsafe medication practices in low-and middle-income countries is grossly underestimated due to lack of research in this area. To address this global concern, in 2016, the WHO launched the Global Patient Safety Challenge, consisting of 5 working groups. The objectives of the challenge include the development of guidelines, tools and promote collaboration among stakeholders to improve medication safety (WHO , 2016).

The realization that some ICSRs contain evidence of medication errors which are sometimes reported as ADRs has led to the widening of the scope of PV as well as the WHO updating their definition of pharmacovigilance to include the terms: "any other drug-related problem" [41]. The definition for adverse drug reactions has been updated to include not only medical products at normal doses, but also medication errors, off-label use, misuse, and abuse of the medicinal product (Ferner, 2006).

Latent Factors: Aronson describes factors that are outside the control of HCPs which can affect them and cause them to make mistakes. These factors include exhaustion from being overworked, inadequate work resources/tools, management, or human resource (HR) related issues (Aronson, 2009). Errors that occur because of these factors can be prevented with good induction and training as well as improved working conditions.

Active Factors: Aronson associates an error with the intention to perform an action, but the action is not performed (Aronson, 2009). He further distinguishes between errors resulting from pure mistakes, meaning the error was made at planning phase and errors which are skill-based, which means the plan was correct, but the error occurred with execution (Aronson, 2009).

1. Mistakes

- **Knowledge-based errors:** occurring due to a lack of knowledge, for instance prescribing antibiotics without establishing if the patient is currently using hormonal contraceptives. These errors can be avoided with improved drug knowledge, the patient being treated and clear communication among HCPs who are involved in treating the patient.
- **Rule-based errors:** occurring due to deviations from procedural practices, e.g., wrong dose preparation. This can be prevented with proper training and automated reminders when certain medications are dispensed.

2. Skill-based

- **Action-based errors:** also referred to as slips and they occur due to inadequate attention or distractions, e.g., picking up clarithromycin from the shelf when intending on picking up ciprofloxacin. This can be avoided by avoiding distractions and by implementing a QC process.
- **Memory-based errors:** also referred to as lapses and occur due to the inability to recall important information which is known. E.g., forgetting to inform a patient to take the full course of antibiotics. These can be prevented by implementing a QC process and with automated alerts during dispensing.

Reporting of Medication Errors

Spontaneous reporting is the primary method of collecting data on medication errors. The ICSR must be improved to optimize detection of medication errors by soliciting reports on medication errors that cause harm (ADR) and those that do not cause harm. Those that do not cause harm often to remain unreported as they may not be considered to pose any risk. At the same time, there is a hesitation to report those that cause harm as well, due to fear of getting into potential trouble or getting blamed. Education is a key element for preventing medication errors. Some hospitals perform an analysis of medication errors occurring within the facility and provide feedback to the reporter either on a case-by-case basis or in the case of recurrent errors, correspondence and training are across all HCPs within the hospital. National PV centres disseminate alerts resulting from reported medical errors though Dear Doctor letters. Medication errors that cause harm are essentially ADRs; therefore, can result in the same regulatory consequences as other ADRs (WHO, 2014).

Analysis of Medication Errors

A quantitative analysis of the ICSRs containing medication errors is performed where the medical reports requiring action are summarised and prioritized. Followed by a qualitative analysis, consisting of a root cause analysis, to identify the underlying causes of the error and establishment of a corrective action, preventative action (CAPA) plan. During quantitative analysis at the WHO-UMC (see Figure 2.5), medication errors in VigiBase® are analysed according to their level of achievement, the stage in the treatment process, type of medication error or seriousness. Medication error terms are also included in the UMC medical terms dictionary MedDRA (WHO, 2014).

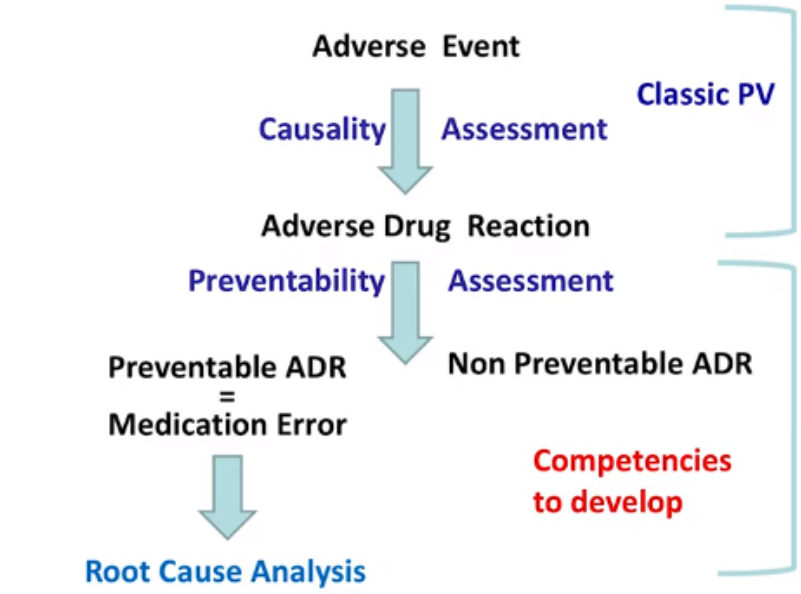


Figure 2-5: WHO-UMC assessment of medication errors (WHO, 2014)

Qualitative analysis is performed to improve systems to reduce the likelihood of medication errors. Root cause analyses are for medication errors which have caused or have the potential to cause serious harm. The James Reason concept states "*we cannot change the human condition, but we can change the conditions under which humans work*" (Reason, 2000). This concept propelled a move from the individual approach, which focused on the errors caused by humans to a systemic approach, focusing on the circumstances under which humans operate. The James Reason model distinguishes between latent errors (e.g., healthcare system errors) and active errors (e.g., frontline healthcare providers). To identify underlying causes and contributing factors that lead to medication errors, the Ishikawa diagram is used. Finally, risk minimization actions (RMAs) or CAPA are implemented and followed up. Public health RMAs can include educational tools such as awareness and training programs. The WHO-UMC can collaborate with national regulatory authorities and pharmaceutical industry to implement RMAs including changes in the medicine's package insert, labelling, controlled distribution, etc.

As a result of pilot projects conducted by the WHO-UMC in collaboration with national PV centres, guidelines were published with title: reporting and learning systems for medication errors: the role of pharmacovigilance centres (WHO, 2014). The guidelines are intended not only

for national PV centres, but also for medication and patient safety organizations to provide guidance on the identification and analysis of medical errors. Another lesson learned from the pilot studies is the need to improve ICSR's to optimize detection of medication errors. The items proposed for improvement include patient weight, current medical conditions, previous history of allergy, suspected and concomitant medications (drug-drug interactions), relevant laboratory test results, narrative describing the circumstances. The guidelines also promote stakeholder collaboration between four levels of partnerships to create a synergistic result for the early detection and prevention of medication errors.

Level 1: PV centres, poison control centres, patient safety organizations
Level 2: Academia, media, professional associations, consumer organizations
Level 3: Patients, HCPs
Level 4: Regulatory Authorities, pharmaceutical industry, hospitals

Examples of Medication Errors

- **Medication errors that have resulted Dear Doctor Letters**

Methotrexate: Incorrect frequency of administration

Methotrexate must be taken once per week, but reports received of patients taking it once every day and experiencing ADRs due to this. A part of the WHO-UMC risk minimization actions, recommendations were outlined in the "Dear Doctor letters" to avoid future occurrences. Recommendations include providing patients with clear handwritten dosing instructions on the drug label. Also, specifying the day of the week when medication should be taken and avoid "Monday" as it can be confused with "morning" (Grissinger, 2018).

- **Medication errors that have resulted in amendment of public health program**

Multiple reports of nephrocalcinosis in infants, including two deaths received by the Moroccan national PV centre because of vitamin D supplements given to infants as part of the national program for preventing rickets. Two doses of vitamin D were given at 600 000 IU at birth and at 6 months. Investigations of the reports concluded that the dose was inappropriate for infants; therefore, it was reduced to 200 00IU and a special paediatric formulation was introduced at this dose (Porter, 2006).

2.7.2 Counterfeit Medicines

The WHO defines counterfeit medicines as "one which is deliberately, and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient (inadequate quantities) of active ingredient(s) or with fake packaging" (WHO, 2017). A term that was collectively used for substandard and counterfeit products is 'SSFFCs' (substandard/spurious/falsely labelled/falsified/counterfeit medical products). On 29 May 2017 at the Seventieth World Health Assembly, it was agreed to replace the use of "substandard/spurious/falsely labelled/falsified/counterfeit medical products" (SSFFC) with "substandard and falsified medical products" (SF), as the term to be used and in all future documentation on the subject of medical products of this type (WHO, 2017).

Counterfeit medications are a public health problem globally and have caused more than 100 000 deaths to date. It is estimated that 10% of medicines worldwide are counterfeit (Berkrot, 2012). The WHO estimates that counterfeit medicines make up 30% of all medicines sold in Asia, Africa, and Latin America, with China being the main culprit as a source of counterfeits (Berkrot, 2012). In 2010 worldwide sales of counterfeit medicines were estimated at $75 billion (WHO, 2010). In 2011, 64% of antimalaria medicines sold in Nigeria were found to be counterfeit (Anon., 2012). In 2013 an estimated 122 350 (3.75%) deaths in children under 5 years old across sub-Saharan Africa were attributed to poor quality antimalaria medicines (Renschler, 2015). The health impact of counterfeit medicines depends on the ingredients that are used in making the counterfeit medicine. At times, the medicine contains no active ingredients and does not cause any direct harm; however, the medicine does not provide a health benefit to the patient, which can ultimately harm the patient. In the case of antibiotics, this can result in antibiotic resistance. In other cases, the counterfeit medicine may contain harmful ingredients, including bacteria-laced water, antifreeze, dye, and boric acid (Rentz, 008). Counterfeit paediatric cough syrup which was found to contain diethylene glycol (DEG), a substance commonly used in commercial products such as resins, antifreeze, inks, and glues, has resulted in the deaths of more than 500 children worldwide (Rentz, 008). In 2012, the FDA distributed warning letters to physicians to alert them about a counterfeit version of their anti-cancer drug Avastin (bevacizumab), in which the active ingredient was replaced with starch and salt (Mackey, 2015). Falsified artemether-lumefantrine has also been described across central and west Africa (WHO, 2017). Such products will inevitably cause increased morbidity, mortality, and transmission, and can create the impression that artemisinin resistance has developed. Additionally, modelling strongly suggests that underdosing is an important contributor to resistance. Therefore, if patients consume co-circulating falsified and substandard medicines, so that underdosing persists, the risks of patients developing resistance to the drug are high.

In high income countries, the primary source of counterfeit medicines are online pharmacies, which are mostly not registered in any country and operate under false pretence (e.g., claiming to be registered in a neighbouring country). Most people purchase drugs online because they are not aware of the potential dangers. At a global level, counterfeit medicines can enter the market through legitimate supply chain processes, from the supply of counterfeit ingredients at manufacturing, to subsequent stages including storage, transportation, and distribution. Factors which promote the entry of counterfeit medicines into the supply chain process include shortages of medicines in the country as well as corruption. In their survey conducted in Nigeria, Garuba *et al.* found that Nigeria's pharmaceutical industry is vulnerable to corruption, particularly at points of entry and drug registration into the country (Garuba, 2009). Cohen *et al.* support this analogy with their argument that direct government involvement in drug registration, procurement and inspection processes creates opportunities for corrupt practices (Cohen, 2007).

A global reporting system for counterfeit medicines is yet to be developed; however, in 2011 the WHO-UMC constructed an algorithm that allows for the identification of substandard products from ICSRs in VigiBase®. The counterfeit medicines identified through this method are likely to be those that have caused harm and end up being reported as suspected ADRs. A similar algorithm was used by the Monitoring Medicines project which ran from 2009 to 2013. One key challenge encountered on both occasions is inadequate information in the ICSRs, which led to inconclusive findings. Both algorithms did lead to the identification of 8 confirmed, and 12 potential counterfeit medicines. This is evidence of the effectiveness of factors such as detailed information within individual reports and agility with processing of

reports submitted into VigiBase®. An awareness must be created to ADR reporters to provide their contact details in case of any queries and not to discard the suspected counterfeit medicine in case testing of the medicines is required (Juhlin, 2015) (Pal, 2015).

(Erwin, 2014) and (Hamilton, 2016), in their systematic reviews agree on the following strategies to combat the scourge of counterfeit medicines:

A. Cooperation among stakeholders

In 2006, IMPACT (International Medical Products Anti-Counterfeit Taskforce) was established, with the mandate to promote collaboration stakeholders including national medicines regulatory authorities, INTERPOL, NGOs, pharmaceutical companies, etc. (WHO, 2016).

The 65th WHO World Health Assembly (WHA) in 2012 established the Member State Mechanism (MSM) on SSFFCs, to promote collaboration and information sharing among WHO member countries (Garuba, 2009).

B. Increase public awareness

The FDA launched an awareness campaign titled "Be Safe; Know your online pharmacy" to educate customers about the dangers of buying medicines online (US, FDA, 2021).

C. Strengthen criminal justice systems

There have been calls for stringent consequences to be applied to punish those involved in the counterfeit medicine (Newton, 2014.) (Nayyar, 2015) (Attaran, 2015). In the United States, the penalties for crimes related to counterfeit medicines are regulated by the Federal Food, Drug and Cosmetics Act; however, the penalties have remained the same since the initial promulgation of the act in 1938. For example, one person involved in the Avastin case was only penalised to 6 months house arrest and 5 years' probation (Mackey, 2015).

D. Improve Management of Supply Chain

A good example for low-to-middle income countries is the successful implementation of stringent regulations for tackling counterfeit anti-TB drugs is Rwanda. Rwanda's strategy includes the distribution of reporting forms to patients and HCPs to report suspected counterfeit medicines to the national PV centre. They also conduct quality control testing at ports of entry, regular sampling and testing of anti-malaria and anti-TB drugs, which are the most counterfeited medicines in the country (Binagwaho, 2013).

Taylor suggests the application of product identifiers to the packaging of the medicine, which may be difficult to falsify (Taylor, 2014.). These include 2D barcodes and radio frequency identification (RFID). These can be used to manage the inventory by tracking and tracing batches of correctly manufactured batches.

Latest technologies such as GPHF-Minilab™ can be used at ports of entry. The usefulness of this equipment was demonstrated in the detection of 1.4 million counterfeit artemether-lumefantrine, mebendazole and anthelminthic which arrived in Angola from China. This also evidence of the ability of this equipment to screen large batches of medicines. A checklist of Medicine Quality Assessment Reporting Guidelines (MEDQUARG) proposed by Newton *et al.* can be used to report drug assessments performed at national ports of entry (Newton, 2014.).

South Africa, Algeria, Kenya, Uganda, and Zimbabwe house the six WHO prequalified Medicine Quality Control Labs (MQCL), meeting the standards as set out by the WHO for testing of medicines. The high-tech equipment available at these labs can be used to test specific medicines which are commonly counterfeited or those that are suspected to be counterfeit through initial screening with GPHF-Minilab^{TM} (WHO, 2015).

E. Increase diligence of HCPs

- Regular training and remaining abreast with latest developments in Drug Safety alerts
- Purchase medicines from reputable sources and confirm registration with the national regulatory authority
- Use WHO checklist to examine product packaging
- Report suspicious medicines to the national PV centre
- Educate patients when dispensing medication to them

F. Point of purchase verification

- The WHO checklist can also be used by consumers, in addition to HCPs
- Mobile Authentication Services (MAS) – a scratch code is affixed on the medicine packaging. When the consumer buys the medication, they scratch the packaging to reveal the barcode and they SMS it to a secure hotline. The consumer then receives a confirmation SMS, verifying the authenticity of the medicine. Examples of this technology include mPedigree GoldKeys, Sproxil and Pharmacure. Currently in Africa, Kenya, Ghana, and Nigeria are embracing this technology (PREVENT, 2016).

2.7.3. Misuse of prescribed drugs - U.S.A

Opioids are analgesics, commonly used when other pain medications do not provide sufficient pain relief or other medications cannot be used due to safety concerns. In 2016 alone, more than 60 million patients in the USA had at least one prescription for opioid analgesics filled or refilled (Dowell, 2016). Examples include prescription medicines such as codeine, morphine, oxycodone, hydrocodone, etc. Careful management due to serious risks, which can extend to others who came to contact with them is crucial in the management of the safety of such products. Misuse of prescription opioids occurs when they are not used as directed at the correct dose, frequency, duration, and administration method; whereas abuse occurs when opioids are used for non-therapeutic reasons or for known psychological effects (e.g., euphoria) (Harding, 2019).

Opioid-use disorder (OUD) is the medical term used for the abuse of opioids and the consequences thereof, such as addiction and dependence. Symptoms of OUD include a strong desire for opioids, the inability to control or reduce use, continued use despite interference with major obligations or social functioning, the use of larger amounts over time, and a great deal of time spent obtaining and using opioids. Since the 1990s, the use of cough syrup (containing codeine) to create a recreational drink popularly referred to as 'Lean', 'sizzurp', 'purple drank', was popularized by American hip hop musicians. By 2016, 11.5 million Americans were misusing prescription opioids, 2.1 million had opioid use disorder (OUD), and more than 64,000 died from overdosing on opioids. In October 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency (HHS, 2017). The American Medical Association estimated an increase in mortality from OUD since

the beginning of the Covid-19 pandemic, although it is too soon to get definitive data (HHS, 2017). In general, the effects of the pandemic include anxiety, grief, isolation, economical and health changes as well as decreased access to medical treatment (HHS, 2017).

Professional organizations, states, and federal agencies (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; the Washington Agency Medical Directors Group, 2015; and the U.S. Department of Veterans Affairs/Department of Defense, 2010) have developed guidelines for opioid prescribing. Existing guidelines share some common elements, including dosing thresholds, cautious titration, and risk mitigation strategies such as using risk assessment tools, treatment agreements, and urine drug testing (Dowell, 2016).

The FDA has developed a strategy to combat opioid abuse, by focusing on 4 main domains (FDA , 2021):

- Decreasing public / patient exposure to opioids
- Stopping and treating those with OUD
- Promoting the development of other types of pain medications, to reduce the need for opioid use
- Acting against illegal sale of opioids

Actions implemented by the FDA include the following:

- Promulgation of the *SUPPORT for Patients and Communities Act*, also known as *Substance Use–Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act* took place in 2018. This act allows for the implementation of the strategies outlined above (Dept of Health and Human Services, 2020).
- In June 2020, the FDA and the Department of Commerce started to collaborate with Internet Domain Name Registries to combat online sale of opioids (FDA , 2021):
- In July 2020, the FDA informed opioid manufacturers and manufacturers of medicines used to treat opioid overdose to update their package inserts to include warning information regarding naloxone. Nalaxone is indicated for the complete or partial reversal of opioid-associated adverse effects caused by both natural and synthetic opioids (RXList, 2020). The updates will be effective as of 2021. They also mandate prescribers to discuss carefully assess the patient's risk factors and the need for opioid treatment, considering available alternatives.

2.8 Vaccine Pharmacovigilance

Based on the emerging success of the smallpox programme, in 1974, the World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI). The initial EPI goals were to ensure that every child received protection against six childhood diseases (i.e., tuberculosis, polio, diphtheria, pertussis, tetanus, and measles) by the time they were one year of age and to give tetanus toxoid vaccinations. When given to women of childbearing age, vaccines that contain tetanus toxoid (TT or Td) not only protect women against tetanus, but also prevent neonatal tetanus in their new-born infants. By 1990, vaccination was protecting over 80% of the world's children from the six main EPI diseases, and other new vaccines are continually being added to the EPI programmes in many

countries. In 1999, the Global Alliance for Vaccines and Immunization (GAVI) was created to extend the reach of the EPI and to help the poorest countries introduce new and under-used life-saving vaccines into their national programmes (WHO, 2020).

Each year, vaccines prevent more than 2.5 million child deaths globally. Between 2000 and 2008, vaccination reduced global deaths from measles by 78% (from 750 000 deaths to 164 000 deaths per year) (WHO, 2008). This shows the important health contribution made by vaccines; however, they are not completely risk-free. A recent example of the influenza vaccine, Pandemrix highlighted vaccine safety and pharmacovigilance (Doshi, 2018).

An AEFI is defined as "*any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine*" (WHO, 2012). Typically, AEFIs are those adverse events which are injection-process related and a direct effect of the vaccine component, but also include patient or host genetics. Adverse vaccine reactions (AVRs) are those for which causality has been determined to be associated with the vaccine. AVRs can result in local reactions, systemic reactions and may include allergic reactions. Local reactions occur at the injection site, including pain, erythema, induration, etc. Fever is the most common systemic reaction. Allergic reactions include wheezing, generalized urticaria, swelling of the mouth and throat, difficulty breathing and in severe cases, anaphylaxis (WHO, 2012).

2.8.1 Adverse Events Following Immunization (AEFIs)

The WHO classifies AEFIs into five categories as listed and described below (WHO, 2020):

A. Vaccine quality defect induced (WHO, 2020):

- Based on factors such as the manufacturing process, adjuvants, preservatives, concomitant vaccines administered.
- Example: Influenza vaccine administered in children in Australia during 2010-2011. It was observed that children < 5 years had an increased risk of fever and febrile seizures. Investigations concluded that the cause was from the manufacturing process (Wood, 2012).

B. Injection process (WHO, 2020):

- Reactogenicity (bleeding, redness, swelling, pain, etc.)
- Inappropriate diluents used; shoulder injury related to vaccine administration (SIVRA)
- Contamination on the surface of the vial
- Errors occurring during administration, e.g., lymphadenitis from the BCG vaccine,
- The routes of administration of vaccines (oral, intramuscular, subcutaneous, intradermal, intranasal) contribute to the occurrence of AEFIs. For example, Bell's palsy (facial muscle paralysis) was noted after some intranasal immunization with the influenza vaccine, resulting in a change in the vaccine route of administration.

C. Immunization anxiety induced (WHO, 2020):

- Resulting from anxiety about the immunization, e.g., syncope before or after vaccination.

D. Coincidental events (WHO, 2020):

- AEFI caused by an underlying condition and not by the vaccine itself or the injection process, e.g., fever occurs at the time of vaccination can easily be associated with the vaccine but when confirming patient's comorbidities, it might be caused by another illness such as onset of malaria.

E. Vaccine product induced (WHO, 2020)

- An AEFI resulting from inherent properties of the vaccine product. Example: Vaccine-acquired rotavirus in infants with severe combined immunodeficiency (SCID). Attenuated vaccines are typically contraindicated in patients with known severe immunodeficiency; however, the rotavirus-vaccine series is recommended at 2 months of age. At this age, SCID cannot yet be identified in infants with no family history of immunodeficiency. Administration of the rotavirus vaccine is what revealed the immunodeficiency. A case series of five infants was reported with these findings [91]. This occurrence gave rise to the hypothesis that ADRs might not be random but rather be genetically predetermined. This phenomenon is referred to as adversomics; which is an emerging field of study of immunogenetics and immunogenomics of vaccine adverse events at the individual and population level, respectively (Poland, 2009). Further studies in adversomics may reveal the need for population-based vaccination programmes to be adapted to incorporate exclusion of certain individuals based on genetic profiles.

- Examples of genetically predetermined AEFIs:
  - Adjuvanted influenza-H1N1 vaccine causing age-dependent myeloid and lymphoid cellular responses (Sobolev, 2016).
  - MMR vaccine causing febrile seizures – children with AEFI found to have similar genetic presentations (Svanström, 2014).
  - Smallpox vaccine causing reactogenicity at injection site due genetic polymorphisms in genes expressing an immunological transcription factor (Reif, 2008).
  - Live vaccines cause infections and is therefore contra-indicated in immunocompromised patients or patients receiving immunosuppressive agents such as methotrexate for the treatment of tumours or auto-immune diseases such as rheumatoid arthritis or psoriasis (Arvas, 2014)

2.8.2 Types of Vaccines (CDC, 2019) (Pardi, 2018)

A. Live attenuated vaccines, e.g., Tuberculosis [Bacillus Calmette-Guérin (BCG) vaccine], oral polio, measles, rotavirus, yellow fever

- Live form of the pathogen, which causes a mild form of the disease; thereby stimulating the body's own immune response.
- There is a potential to revert to the fully pathogenic form of the microorganism and cause the disease.
- Immunocompromised patients at high risk for developing the pathogenic form of the disease.
- Risk of contamination during manufacturing and cold chain processes
- Increased risk for immunization errors (e.g., during reconstitution)
    - Examples of known AEFIs:
        - BCG vaccine: Disseminated BCG
        - Oral Polio vaccine: vaccine-associated paralytic poliomyelitis
        - Measles vaccine: febrile seizures, anaphylaxis
        - Yellow fever vaccine: hypersensitivity reactions

B. Inactivated whole cell vaccines (killed antigen), e.g., whole cell pertussis

- Made from pathogens which have been killed through physical or chemical processes and cannot cause disease; may be considered safer than live attenuated vaccines.
- Vaccine may be ineffective, or the immune response may be short lived. Booster dose might be necessary.
- Examples of known AEFIs:
- Pertussis vaccines: seizures, hypotonic-hyporesponsive episode

C. Subunit vaccines (purified antigen), e.g., Hep B, HPV, Meningococcal vaccine

- Contain only the antigenic parts (proteins or polysaccharides) of the pathogen which are necessary to causes an immune response.
- Conjugate vaccines incorporate polysaccharides to a carrier protein.
    - Examples of known AEFIs:
        - Hepatitis B vaccine: anaphylaxis
        - Conjugated meningococcal vaccines (e.g., MenAfriVac): fever, urticaria and bronchospasm.

D. Toxoid vaccines (inactivated toxins), e.g., Tetanus, diphtheria toxoid

- Made from a non-pathogenic form of a bacterial toxin which are harmless, called toxoids.
- This requires an adjuvant to enhance the immune response and booster doses are necessary.
    - Examples of known AEFIs:
        - Tetanus toxoid: anaphylaxis and brachial neuritis

E. RNA Vaccines, e.g., Covid-19 messenger (mRNA) vaccine candidates developed by Pfizer and AstraZeneca pharmaceutical companies (Pardi, 2018)

- Novel vaccines developed as a response of the global Covid-19 pandemic.
- Works by introducing a sequence which is coded for a disease-specific antigen.
- The antigen is the recognized by the immune system.
- In the case of the Covid-19 vaccine candidates, the mRNA instructs the production of harmless spike proteins on the cell surfaces.
- The immune system detects the spike protein as being foreign to the body and develops an immune response by developing antibodies against the spike proteins.
- The same antibodies are effective against Covid-19 infection.

2.8.3 Vaccines Ingredients (WHO, 2020):

Listed below are some of the components, both active- and inactive ingredients of vaccines. AEFIs may result from any of these ingredients and not necessarily from the active ingredient or vaccine itself.

- Pathogen, antigen, or epitope – the pathogen or a component of the pathogen
- Stabilizers - ensures vaccine effectiveness during storage, e.g., lactose-sorbitol, sorbitol-gelatine.
- Adjuvants - stimulate production of antibodies against the antigen when only a part of the pathogen is used in the vaccine, e.g., aluminium (most used), monophosphoryl lipid A, AS03 (used in Pandemrix vaccine), Freud's adjuvant.
- Antibiotics - often used during manufacturing of live attenuated vaccines to prevent bacterial contamination of tissue culture cells in which vaccines are produced. neomycin is commonly used; however, it has a risk of allergies
- Preservatives - used in multidose vials during manufacturing to prevent contamination, e.g., phenol derivatives, formaldehyde, thiomersal (contains ethyl mercury)

Vaccines' safety cannot be managed according to the same algorithms as other medicines as they are administered to healthy individuals, mostly children and to exponentially large populations, most often to prevent disease or alleviate symptoms of disease. The benefit/risk profile of a vaccine changes with circumstances and across different regions and countries. For example, a vaccine for Ebola Virus would be more beneficial in West African countries than in many other parts of the world; whereas, currently in 2020, a vaccine for the SARS-CoV-2 virus is required and will be beneficial worldwide (WHO, 2020).

They are often given concomitantly with other vaccines, which makes it difficult to investigate causality. Vaccines are complex biological compounds, usually consisting of a mixture of multiple antigens or live organisms, adjuvants, and preservatives. Due to their biological nature, vaccine storage, handling and administration are extremely specific; particularly the live attenuated vaccines and if not adhered to, can result in AEFIs (WHO, 2020).

The WHO defines vaccine pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, prevention and communication of AEFIs (adverse events following immunization), or of other vaccine- or immunization-related issues" (Health, 2007).

Spontaneous reporting is the primary PV method of AEFI reporting globally. The WHO recommends that AEFI surveillance must be tightly integrated with the public health system coordinating the delivery of vaccines on a national level. This requires a collaboration between the National Immunization Programme (NIP) and the National Regulatory Authority (NRA).

Historically, vaccines have been made available to LMICs after years of use in US, Europe, and other EU countries. Lately, there has been a need for introduction of newly developed vaccines directly to LMICs (e.g., MenAfriVac®, Dengvaxia®) (Trotter, 2017). This puts the responsibility of safety surveillance of these vaccines from early post-marketing phase, squarely on the LMIC's regulatory authorities and NIP's.

With the current global Covid-19 pandemic, multiple vaccine candidates are undergoing concurrent clinical trials and it remains unknown which of these will successfully enter the market (Wellcome, 2021). Most likely, more than one vaccine candidate will be introduced into the global healthcare system at the same time, due to the presence of different viral variants as well as known scale up and manufacturing constraints. Due to the novel nature of the various Covid-19 vaccines, the importance of robust pharmacovigilance cannot be emphasized enough. The risk of AEFIs occurring and not being detected and reported is remarkably high in most LMICs.

The WHO has created a reporting form specifically for AEFIs, with a set of "core variables" to collect essential information to facilitate for safety review. For serious AEFIs, there is an AEFI investigation form, which contains information to be collected to facilitate the investigation of causality. This includes, among other data, information about the patient's family, other patients who received the same vaccine. Other WHO forms to be completed during the investigation include the laboratory request form for collection of specimens from the patient, vaccine, syringe, and needle used during the vaccination. Finally, there is also a causality assessment form for performing an individual level causality assessment (brightoncollaboration, 2021).

Brighton collaboration is a group of scientists who have come together with the joint effort to harmonise definitions of events or clinical syndromes which are often reported in association with vaccines (brightoncollaboration, 2021). When performing the individual level causality assessment according to the WHO method, the clinical diagnosis of the adverse event is defined according to the Brighton collaboration. This can be a challenge for national PV centres where AEFI reports are received but they only contain one symptom, such as vomiting or weakness, which are general and can be associated with multiple diagnoses.

The WHO process and forms required to be completed by PV centres at a national level, have been criticised for being cumbersome and challenging; particularly in LMIC due to resource and staff limitations. The number of forms and information to be gathered for investigation of reported AEFIs can be time consuming when there are issues of inadequate staff, lack of electronic health records, inadequate knowledge/training of reporters regarding information to be included when submitting an AEFI report to the national PV centre, etc.

At times it can be difficult for the national PV centre to confirm a certain diagnosis which is suspected by the reporter due to resource limitation, for example, a report is received with meningitis as the AEFI. As part of the investigation, the reporter is contacted for additional information on how the diagnosis was confirmed and the reported notes that this was based on a clinical assessment alone due to lack of facilities to perform a lumbar puncture.

These are common LMIC challenges which must be taken into consideration when national PV centres construct their PV framework. Another time and resource demanding task are literature search for similar AEFIs reported elsewhere or available data on the vaccine. This is typically done at a later stage with regular medicines, but with vaccines, it is part of early investigations to see how commonly it occurs, typical triggers and assess any similarities with known data.

Figure 2-6 depicts the surveillance cycle followed by Figure 2-7, which illustrates the WHO-UMC upon investigation of an individual AEFI and the algorithm recommended by WHO-UMC for investigating causality cluster of AEFIs at local/national level, (WHO, 2013):

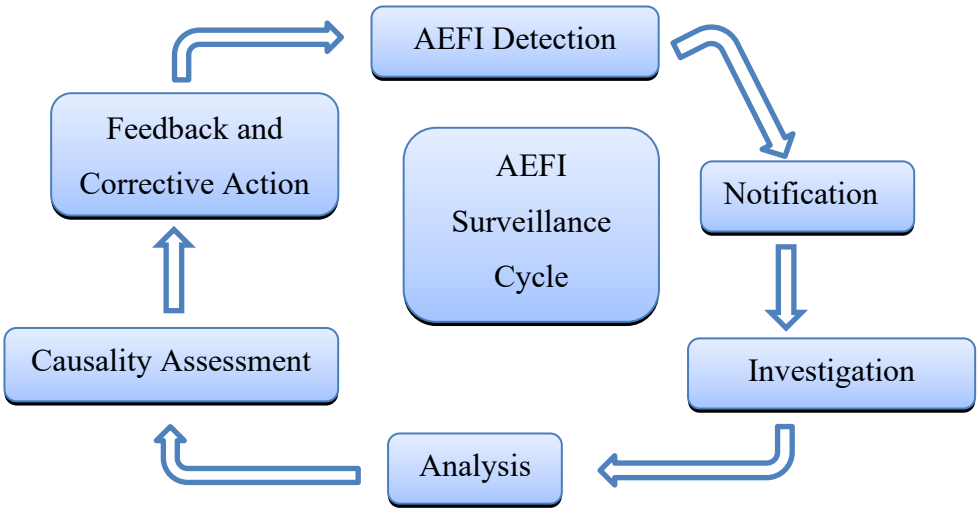


Figure 2-6: AEFI Surveillance Cycle (WHO, 2013)

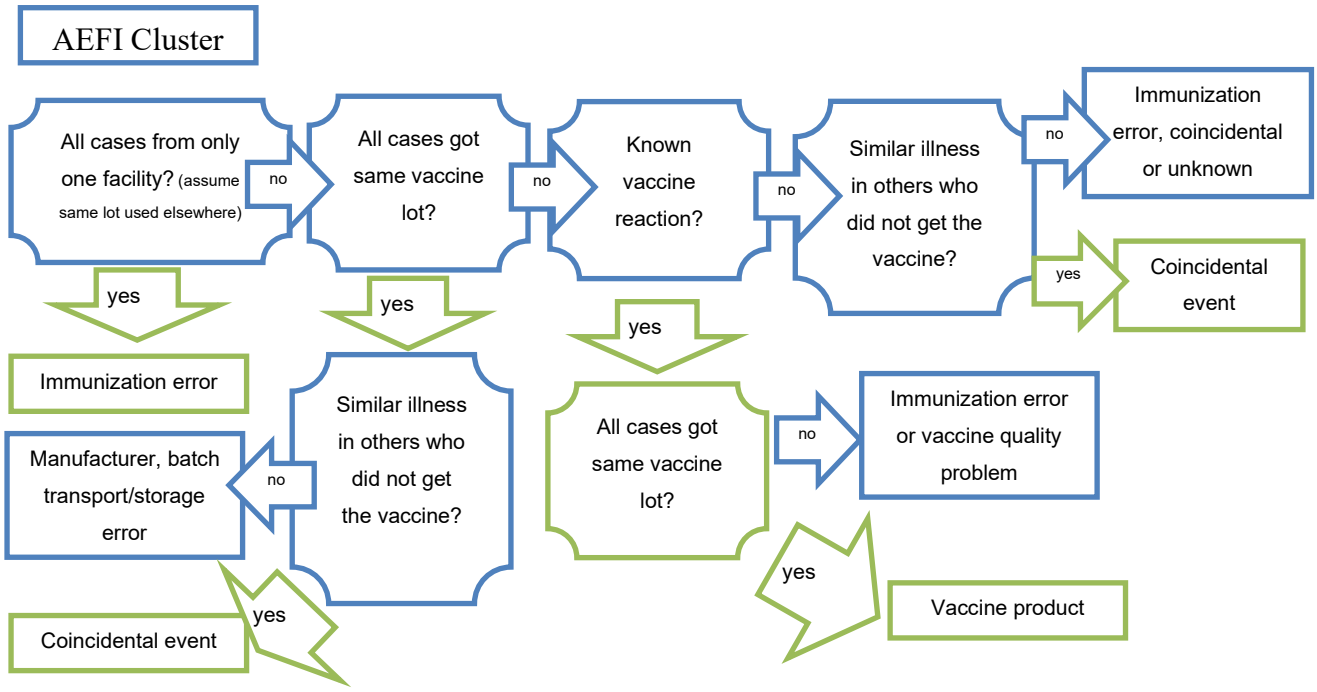


Figure 2-7: WHO AEFI cluster investigation (WHO, 2013)

Observed vs expected analysis is a comparison of how many cases of common reactions are expected to be identified vs those identified post-vaccination. The estimates are typically based on data from pre- and post-marketing clinical trials as well as clinical practice. For instance, if an NPI normally receives one case of fever during seasonal influenza vaccinations, but suddenly they receive five cases in a season, this is a trigger for further investigation. In some countries, prior to introducing a new vaccine into the national vaccination programme, an estimate the expected frequency of common vaccine related effects and compare that to the effects observed during the vaccination programme, to see if the observed frequency is higher than the expected. This was done with the influenza virus vaccine during the 2009 novel H1N1 pandemic and it was an effective method to distinguish events that are temporarily associated with, but not caused by, vaccination from those caused by vaccination in mass immunization (Wang, 2013). Countries can learn from this and implement the same strategy for the upcoming SARS-CoV-2 vaccine.

For AEFI case series, like regular ADRs, the WHO-UMC applies the Bradford Hill criteria for the causality assessment. The signal detection at the WHO-UMC involves the identification of patterns across multiple case reports, received from multiple countries. The patterns include similarities in patients, clinical presentations, time to onset, outcomes, etc (WHO, 2013). The WHO-UMC communicates potential signals in their Signal publication, which is distributed to PIDM member countries. This is not necessarily done to confirm that causality is established; however, it is mostly to alert national PV centres and HCPs to look out for similar occurrences and to submit them into VigiBase® for further analysis as well as to minimize the risks, where possible.

2.9 Global Pharmacovigilance Awareness

Global efforts to promote health education are undertaken by the WHO and other stakeholders. The WHO-UMC provides methods, tools and training that empowers stakeholders, including patients, healthcare professionals, researchers, WHO PIDM member countries, etc. with the aim of strengthening PV communication and awareness (UMC, 2021).

The WHO-UMC uses the following platforms for this purpose:

A. Website (UMC, 2021)

In the first year of the website's implementation in 2017, the website had attracted over 82 000 users. On the website, users are directed to other awareness projects such as the following:

- Online Magazine (Uppsala Reports that contains latest PV-related news and activities of the WHO PIDM (UMC, 2021).
- Podcast (Drug Safety Matters) on latest trends and challenges in medicines safety (UMC, 2020).
- Patient-centred communication, translated into multiple languages.
    - Take & Tell with theme music and brochures targeted at educating patients on how adverse drug reactions occur and how to report them.

- Annie & Mac's Adventures using a comic book which teaches children about medicine e.g., special campaign package for world antibiotic resistance week.
- Drugs and Bugs, an academic book for young readers.
-

B. Social Media – active accounts on Twitter, LinkedIn, Facebook, and YouTube

The MHRA collaborated with the WHO-UMC to pilot the Scope campaign, the first EU-wide PV awareness campaign (Jadeja, 2016). EU member states participated in the campaign to increase awareness of their national level ADR reporting system for spontaneous reporting. This requirement is included in the updated EV PV legislation Directive 2010/84 – Article 102 which states "The Member States shall take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate" (Union, 2010). The entire project timeline from planning to reporting phase took place between February 2014 and April 2017; however, the campaign itself was ran for 5 days (form the 7th to the 11th of Nov 2016).

The strategy employed by the Scope campaign was to make ADR reporting easy and accessible, raise an understanding of the value of reporting, encouraging patients to participate in reporting and to develop communication strategies for ongoing promotion. Animations (MHRAgovuk, 2016) and infographics (MHRA, 2021), were distributed, using social media platforms to the public and 165 relevant stakeholder groups (patient organizations, advocacy groups, etc.). The campaign reached 2,562,071 people, mostly through stakeholders disseminating to their networks. As a result of the campaign, there was a 13% increase in suspected ADR reporting (1,056 reports) between 15 NCAs in the campaign week (Jadeja, 2016). With this campaign having run for a week, the recommendations resulting from the campaign include the consideration of more frequent social media use and further collaboration between NCAs and stakeholders to make this an annual ADR awareness week at a global level.

As a result, toolkits containing good practices, together with the infographics and animations, have been made available for adaptation, translation, and future implementation. A CPD/CME accredited e-learning course has also been launched, targeting HCPs at any stage of their careers and it can be part of a curriculum for students.

2.10. Global Pharmacovigilance activities during the Covid-19 pandemic

The International Society of Pharmacovigilance (ISoP) is a global, professional, independent, not-for-profit society founded in 1992, aiming to promote pharmacovigilance globally (ISoP, 1992). ISoP has coverage in more than 60 countries. A key initiative for Africa is the establishment of ASop, the African subsidiary of ISoP, launched in November 2010 at the 10th ISoP Annual Meeting in Accra, Ghana to play an educational role with the objective to develop and foster pharmacovigilance in African countries. ASoP's objectives include regular exchange of information on pharmacovigilance by means of meetings, workshops, bulletins, trainings, and specifically organised congresses as well as seeking funds, and awarding grants, fellowships, and other contracts to promote pharmacovigilance in African countries (ISoP, 1992).

The current novel Covid-19 pandemic provides a challenge with limited timelines within which solutions in terms of prevention and treatment protocols have had to be explored to combat the virus rapidly and effectively (WHO, 2020). Not only does the pandemic necessitate an extensive shortening of timelines for the conduct of clinical trials, but multiple phase II and III clinical trials are implemented in parallel and data analysis performed in a staggered manner as key clinical endpoints are achieved (WHO, 2020).

Several recent vaccine related safety concerns which have received substantial public attention, *viz* Pandemrix® causing narcolepsy, Dengvaxia® causing severe dengue, have suggested the presence of patient specific risk factors associated with the occurrence of these adverse outcomes. In addition, a new study field of systems immunology has emerged to describe the complexity of the immune system which may allow us to further understand the pharmacodynamic principles of adverse events associated with vaccination and the subsequent process of developing immunity (WHO, 2020).

Like with any other medication, the risk extends to safety matters arising from counterfeit vaccines as well as quality concerns throughout the life cycle of a vaccine, including formulation, manufacturing, packaging, storage conditions, handling, dispensing, and administration. Recent surveys have furthermore documented concerning decreases in public confidence in vaccine safety, further escalated by several rumours and stigma within specific communities and amongst different cultures and religions. In 2019, the WHO has declared vaccine hesitancy as one of the ten threats to global public health (WHO, 2020).

The International Society of Pharmacovigilance (ISoP) and the WHO UMC have a common interest to promote scientific research and practice through the mutual exchange of information on adverse events and risks related to medicinal products. The 42nd Global Advisory Committee on Vaccine Safety (GACVS) held on 27–28 May 2020, addressed pharmacovigilance preparedness for the launch of the future Covid-19 vaccines (ISoP, 1992). In collaboration, the WHO global manual (WHO, 2020) was developed in 2020 to provide guidance on how the stakeholders could collaborate to ensure the efficient handling of Covid-19 vaccine safety, surveillance, and pharmacovigilance. Prior to vaccine roll-out, each country should include safety surveillance as part of their preparedness plans. For the successful and effective roll-out of Covid-19 vaccines, stakeholder collaboration must include national health departments, regulatory authorities, immunization programmes, pharmaceutical companies, and NGOs. The manual contains several chapters and modules spanning from safety considerations for different types of vaccines, resource-sharing at regional level and across industries, to establish adverse event following immunization (AEFI) & adverse event of special interest (AESI) reporting platforms, how to perform causality assessments using the Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) safety templates and provision of practical tools such the AEFI reporting and investigation forms (WHO, 2020).

2.11. Region-specific Pharmacovigilance Developments

2.11.1 FDA Pharmacovigilance Activities and Funding

The United States (US) Food and Drug Administration (FDA) consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical

Products and Tobacco, Foods, Global Regulatory Operations and Policy, and Operations. (Ofir, 2017).

The Centre for Drug Evaluation and Research (CDER) provides safety oversight on drugs within the authority of the FDA. The Drug Safety Oversight Board (DSB), created in 2005 and mandated by law in the, advises the CDER Centre Director on the handling and communicating of important and often emerging Drug Safety issues. The DSB meets monthly and provides a forum for discussion and input about how to address potential Drug Safety issues (Ofir, 2017).

The FDA's Human Drugs Program is responsible for ensuring the safety and efficacy of new, generic, and over the counter (OTC) medicines, monitoring marketed medicines to ensure patient safety, and monitoring medicine quality. The Centre for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) field drugs program are the components of FDA's Human Drugs Program, which operates with funding from budget authority and user fees.

In 2007, the FDA introduced the FDA Amendments Act (FDAAA). As a response, the Sentinel Initiative was launched in 2008 (sentinelinitiative, 2016). Over time, Sentinel has developed the largest multisite distributed database in the world dedicated to medical product safety. It is constantly growing and improving from the pilot version to the version with advanced capabilities. In 2016, the full version of the Sentinel System was launched (sentinelinitiative, 2016).

Other initiatives of the CDER include the FDA Adverse Event Reporting System (FAERS); a spontaneous reporting system for submitting ADRs, medication error reports and product quality complaints resulting in adverse events; to the FDA. Under 21 CFR 314.80 post-marketing safety reports which are serious and unexpected adverse from all sources (domestic and foreign) must be submitted within 15 days (Ofir, 2017). The reports in FAERS are evaluated by clinical reviewers, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), to monitor the safety of products after they are approved by FDA. The Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Guidelines were published in March 2005 for the purpose of providing guidance to the pharmaceutical industry (CDER, 2005).

If a potential safety concern is identified in FAERS, further evaluation is performed. Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labelling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

Healthcare professionals, consumers, and manufacturers submit reports to FAERS. FDA receives voluntary reports directly from healthcare professionals (such as physicians, pharmacists, nurses, and others) and consumers (such as patients, family members, lawyers, and others). Healthcare professionals and consumers may also report to the products' manufacturers as depicted in Figure 7. If a manufacturer receives a report from a healthcare professional or consumer, it is required to send the report to FDA as specified by regulations. Over 13 million reports have been submitted into FAERS since 1969, averaging at approximately 1.69 million new reports in 2016 (Ofir, 2017).

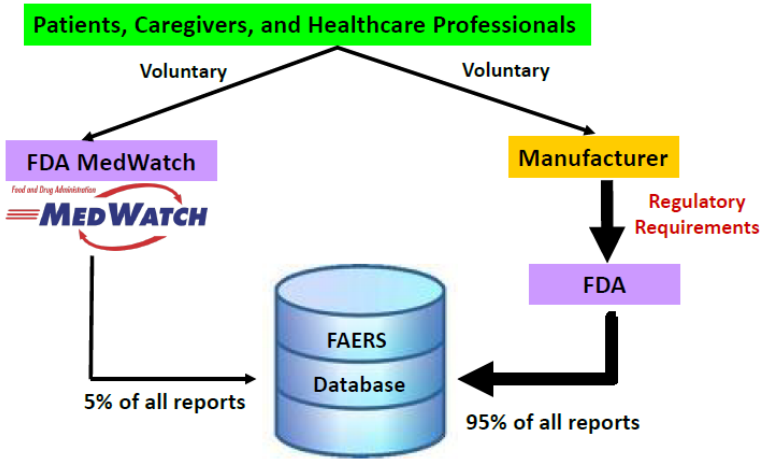


Figure 2-8: FDA post-marketing safety data reporting process (Ofir, 2017).

2.11.2 EMA Pharmacovigilance Activities and Funding

The European Medicines Agency (EMA), the European Union (EU) Member States and the European Commission are responsible for implementing and operating much of the pharmacovigilance legislation. The Agency plays a key role in coordinating activities relating to the authorisation and supervision of medicines, including safety monitoring, across this network (EU, 2001).

The Agency is working with a wide range of stakeholders including the European Commission, pharmaceutical companies, national medicines regulatory authorities, patients, and healthcare professionals to ensure effective implementation and operation of the pharmacovigilance legislation.

It was noted that ADRs were the cause of 197 000 deaths per year in the EU. As a response to this concern, pharmacovigilance legislation was developed in the form of Directive 2010/84/EU (EU, 2001) and Regulation (EU) No 1235/2010 (EU, 2010). This was accompanied by an implementing regulation: Commission Implementing Regulation No 520/2012 of 19 June 2012 (EU, 2012).

The pharmacovigilance legislation aims to reduce the number of ADRs in the EU. It aims to achieve this through (EU, 2012):

- the collection of better data on medicines and their safety.
- rapid and robust assessment of issues related to the safety of medicines.
- effective regulatory action to deliver safe and effective use of medicines.
- empowerment of patients through reporting and participation.
- increased levels of transparency and better communication.

This new legislation led to the establishment of the Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA. The PRAC was formally established in July 2012 and its membership was completed in spring 2013 with the appointment of patient and health-care professional organization representatives as full voting members. The Committee includes independent experts in pharmacoepidemiology, clinical pharmacology, biologics, signal

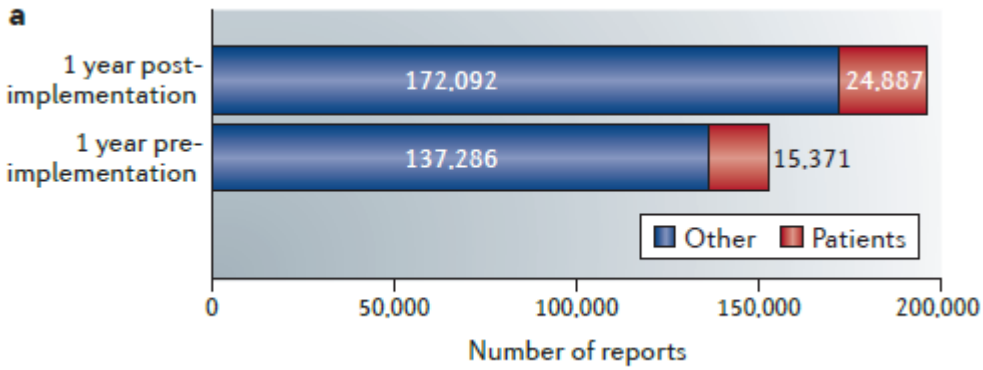
detection, risk communication and vaccine vigilance. The main responsibility of the PRAC is assessing all aspects of the risk management of medicines for human use. This includes the detection, assessment, minimisation, and communication relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account. It also has responsibility for the design and evaluation of post-authorisation safety studies and pharmacovigilance audits. The PRAC generally provides recommendations to the CHMP, the Coordination group for Mutual and Decentralized procedure- Human (CMDh), the EMA secretariat, Management Board and Ethics Committee, as applicable (Arlett, 2014).

In just a year of being in existence, the PRAC achieved the following among many achievements (Arlett, 2014):

- An increase of more than 9,000 in patient reports of suspected adverse drug reactions.
- Product information changes because of assessment of signals of new or changing safety issues with certain medicines.
- Initiation of major public-health reviews, including combined hormonal contraceptives and venous thromboembolism, medicines containing cyproterone acetate / ethinylestradiol and venous thromboembolism, and codeine-containing products used for pain relief and overdose in children.
- Training thousands of individuals in pharmacovigilance.

In the first 18 months of its operation, the PRAC has considered risk management plans for 160 medicinal products. In this work the PRAC has focused on ensuring feasible, evidence-based and risk-proportionate planning.

The collection of individual reports of suspected adverse drug reactions (ADRs) is one of the foundations of drug surveillance, and the reporting rules have been strengthened. These now include the formal introduction of patient reporting in all EU member states (to enable patient engagement), the provision of instructions on reporting in drug leaflets for patients, as well as the labelling of new drugs and those under close safety surveillance with a black triangle symbol indicating the need for enhanced reporting (Arlett, 2014).



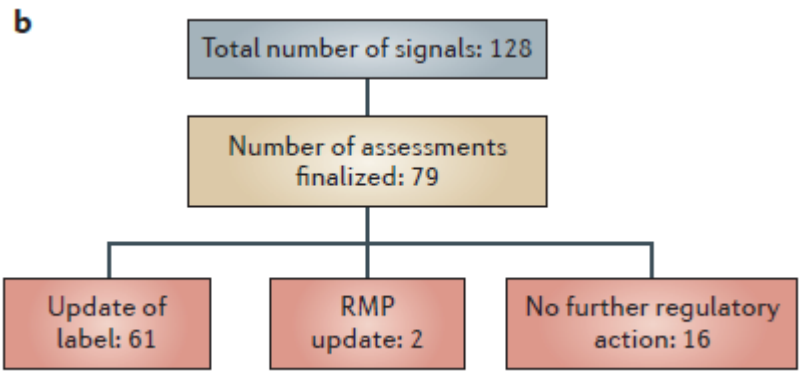


Figure 2-9: Impact of the new European legislation on pharmacovigilance (Arlett, 2014).

a | Number of cases of spontaneous reports of adverse drug reactions within the European Economic Area in the 12-month periods before or after

b | Number of safety signals evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC) in its first 18 months and the outcomes of the finalized evaluations.

In October 2012, the EU pharmacovigilance legislation was further amended following review of the withdrawal of the medicine Benfluorex, sold under the brand name Mediator®. Benfluorex was used as an add-on treatment in patients with diabetes who are overweight. Medicines containing benfluorex were first authorised in 1974. At the time of this review, they were available as tablets containing 150 mg benfluorex hydrochloride in France and Portugal. In 2007, a re-assessment of the benefit–risk balance led to the withdrawal of the indication for the use in patients with high blood levels of triglycerides. In November 2009, following several reports of cardiac valvulopathy (thickening of the heart valves) and pulmonary arterial hypertension (high blood pressure in the artery that leads from the heart to the lungs), the French medicines regulatory authority carried out a review of the safety of benfluorex and decided to suspend its marketing authorization. As a result, benfluorex-containing medicines were taken off the market in France (Frachon, 2011). Shortly after, as a precautionary measure, the Portuguese medicines regulatory authority also decided to recall these medicines from the market. On 18 Dec 2009, the EMA issued a press release announcing its recommendation that the marketing authorisations for products containing benfluorex are to be withdrawn across the EU (EMA, 2009).

Following this, the PV regulations were amended, to further strengthen the protection of patient health. Amended Regulation (EU) No 1027/2012 was effective as of 5 June 2013 and Directive 2012/26/EU was applicable since 28 October 2013 (EU, 2004) (EU, 2012). Practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation are available in the guideline on Good Pharmacovigilance Practices (GVP) (EMA, 2019). GVP apply to marketing-authorization holders (MAH), the EMA and medicines regulatory authorities in EU Member States, and cover medicines authorized centrally via the Agency as well as medicines authorized at national level.

All MAH's across the EU and the European Economic Area (EEA) must submit information to the EMA on authorized medicines and keep this information up to date. The aim of the submission of data is to establish a complete inventory of all medicines authorized for use in the EU and EEA, including medicines authorized centrally via the EMA and those authorized at national level. The Agency uses this information for the following activities (EMA, 2019):

- Data analysis:
  - analysis of data in EudraVigilance and signal detection
  - reporting and coding of individual case safety reports
- Regulatory activities:
  - maintenance of a repository of periodic safety update reports (PSURs) and literature monitoring
  - calculation of PV fees
- Communication with stakeholders:
  - European medicines web portal
  - publishing a complete list of all medicines authorized in the EEA
  - exchanging data within the EU and internationally
  - supporting communication between PRAC and MAH's

Regulation 658/2014 of 15 May 2015 introduced a fee-based funding approach for PV services, paid by MAH's, applicable as of 26 Aug 2014 (EU , 2014). The PV services charged for include Assessment of PSUR/PBRER, post-auth safety studies (PASS) and safety referrals. An annual fee was applicable as of 01 Jul 2015 for maintenance of the IT systems used for PV activities as well as for monitoring relevant scientific literature. Prior to the new 2012 legislation, all MAH's were mandated to remain abreast of all scientific literature containing safety information on their active ingredient. This included information published by manufacturers of generic products. As of 2012, the EMA decided that such monitoring would be done centrally for all EU member countries and MAH's would then pay an annual fee as of July 2015. Fee reductions apply for SME's and manufacturers of herbal and homeopathic medicines are exempt from paying. The annual fees are calculated per chargeable unit, which depends on the number of active substances, products on the market, pharmaceutical form, number of countries the products are sold in, see below Table 2-5. (EMA, 2019).

Table 2-5: Summary of EMA pharmacovigilance fees (EMA, 2019)

Type of procedure/service	**Standard Fee**	**Micro enterprises**	**Small and medium-sized**	**Generics Homeopathic Herbal products**
Single assessments of PSURs	EUR 19 500 per procedure	Exempt	60% of applicable fee or share of fee	Full fee
Assessment of imposed PASS (conducted in more than one-member state)	- EUR 43 000 per procedure to be paid in two instalments: 1. EUR 17 200 assessment of draft protocol 2. EUR 25 800 assessment of final study report			Full fee / share of fee
Assessment of PV referrals	- EUR 179 000 if the referral concerns 1 or 2 active substances and/or combinations - Fee increased by EUR 38 800 for every additional active substance/combination, up to max EUR 295 400			Full fee
Annual Service (PV information technology and monitoring of medical literature)	- EUR 67 per chargeable unit - Due on 01 July every year as of 01 Jul 2015		60% of applicable fee	80% of applicable fee to the chargeable units concerned

2.12 Pharmacovigilance Developments in Africa

2.12.1. Challenges of Pharmacovigilance in Africa

Compared to Africa, the impact of ADRs can more readily be measured in places such as the USA and Europe, because ADRs are relatively well reported in those areas and the information is readily available. Africa is heavily ridden with diseases such as HIV/AIDS, tuberculosis (TB), and malaria. Investments to public health programmes in LMIC by global health initiatives such as PEPFAR, Global Fund (GF), Global Alliance for Vaccines and Immunizations (GAVI), Bill and Melinda Gates Foundation (BMGF) and others against HIV/AIDS, TB and Malaria has resulted in treatments and vaccines becoming rapidly available in many African countries, which also increases the occurrence of ADRs. Due to limited ADR reporting, their exact impact in this region cannot be measured. African drug regulators mainly depend on the FDA and EMA to share information regarding changes in the benefit-risk ratio of drugs registered in those regions as well. It is no doubt that PV is in serious need in all countries, including LMICs and it is gaining traction as countries become aware of the need.

Recent studies have identified several obstacles to PV growth in Africa, including lack of capacity for HCPs, weak overall national health infrastructure and systems, lack of communication/feedback from national PV centres, lack of PV training (Ampadu, 2016) (Olsson S, 2015).

Due to cultural and financial reasons, there is a wide use of traditional medicines; however, these are not well characterised as traditional healers are not willing to share their trade secrets, which are said to be sacred and spiritual. A good example of a non-African country with a wide use of traditional medicines but with well-established systems is China. Because their traditional medicines are well characterised, they can assess causality and identify traditional medicines associated with certain ADRs. A 2012 China Food and Drug Administration (CFDA) report estimated approximately 15-20% of reported ADRs to be associated with traditional medicines (China FDA, 2013). ADR forms are still widely available in paper format across Africa and logistically, the distribution and return of completed ADR forms to the national PV centre from all parts of the country can also pose a challenge. From the time that an ADR form is completed at a healthcare facility for instance, it probably gets filed until a certain time when there are enough reports to be returned to the national PV centre through the postal service. Meanwhile, at the national PV centres, paper ADR reports are received from multiple areas with varying quality of information included. These must be captured into a database by the limited staff available together with follow-up with reporters where key information is missing. In the end, there is a delay in the submission of ADRs to VigiBase® and the quality of the ADRs is not the best. These dynamics limit the activities at the national PV centres to data entry and leaves little time for essential activities such as causality assessments and signal detection (Olsson, 2015).

2.12.2. Improving Pharmacovigilance in Africa

Although the number of African countries establishing national PV systems and gaining membership into the WHO PIDM, only a few African countries (e.g., Nigeria and Eritrea) have well established national PV policies. Politicians and healthcare decision makers need to be convinced of the urgent need to implement legislation and policies that mandate the establishment and budget allocation towards PV activities. To convince governments,

researchers must perform local studies providing evidence of the prevalence, harms, and financial impact of ADRs at country level. National drug regulations should make it mandatory for not only MAH's to report ADRs, but also HCPs as well as patients. Among the HCPs, nurses and pharmacists should be empowered with adequate training, to complete ADR forms; however, the treating physician should remain the official reporter in case of any additional information required or queries. Awareness campaigns must be funded by governments to create a reporting culture within the country (Olsson, 2015).

The international community has explored several strategies to support the African continent in developing structures for safety surveillance of marketed medicines. The WHO as well as the Uppsala Monitoring Centre (UMC) and the WHO Collaborating Centre for PV undertook a focused approach on PV capacity building in Africa, with the UMC alone training 100 HCPs since 1993 in its annual PV course. Furthermore, the WHO has developed PV handbooks addressing specific needs for PV in HIV/AIDS, TB, and malaria, focusing on active PV methods such as targeted spontaneous reporting and of cohort event monitoring (WHO, 2013) (WHO, 2007) (WHO, 2012). Practical implementation of these methods has been successfully demonstrated in pilot studies conducted in Kenya, Tanzania, Ghana, Nigeria, Uganda, and Zimbabwe (Ndagije, 2015) (Bassi, 2013) (Dodoo, 2014) (Suku, 2015). The implementation itself was not without its challenges, considering the existing socio-economic challenges across Africa. The following are some of the common lessons learned from these CEM programmes, which can be expected when implementing similar programmes in other African countries (Suku, 2015):

- The biggest and most common challenge was identified to be inadequate funding. Other challenges such as inadequate data entry staff and study resources (internet, cell phones, etc.) can be avoided with adequate funding being available.
- Community engagement and sensitization starting prior to study commencement.
- Understanding the local disease landscape to inform recruitment strategies and planning (e.g., recruiting for a malaria programme during the rainy season, when malaria is highly prevalent).
- Adequate time and trained site staff to perform effective informed consent (IC), which includes explaining to participants, the purpose of the study. The CEM handbook warns that including these explanations in the IC process can be time consuming and have cost implications; however, also warning that a requirement for formal informed consent could lead to participants refusing to be enrolled. Ethically, however, there is no way around this. There is a high risk of exploitation to occur in study participants coming from poor populations, where participants provide consent but motivated by financial and/or other incentives. This risk is mitigated by national regulatory authorities recommending reimbursement fees for study participation. An additional mitigation is robust informed consent, to ensure that participants are fully aware what the study entails. Other challenges related to IC, which can be reduced with detailed, robust IC, included women requiring permission from their husbands, reluctance to participate and low literacy rates.
- Adequate programme staff training, regular re-training, staff support and onsite monitoring visits and remuneration. This may also reduce issues of high staff turnover, which were found to be prevalent at all studied countries.
- Accurate data entry workload and resource projections.

- Strike action was another common challenge; however, this is usually due to local, socio-economic, and political issues and out of the researchers' control. This can cause unforeseen delays in enrolment and study completion.

In June 2009, the WHO-UMC established an African office (UMC–Africa) with dedicated funding, while the University of Ghana (October 2009) was designated as a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance (WHO–CC), working together with UMC–Africa. The African hub (WHO–CC, UMC–Africa) undertook advocacy, country visits, in-country training, and capacity building in several countries, culminating in most of them becoming full members of the PIDM (Olsson, 2015). Since its inception, the UMC-Ghana has developed a PV Toolkit, among other PV tools (including disease-specific toolkits) intended to support the setting up on PV centres. The PV toolkit provides minimum requirements for a functional PV system, provides basic information regarding the WHO PIDM as well as key concepts on pharmacovigilance (WHO Collaborating Centre Ghana, 2012).

2.12.3. Pharmacovigilance indicators to develop pharmacovigilance systems in African countries

In general, indicators are objective measures that allow an evaluation of baseline situation and progress in healthcare services and interventions. The WHO-UMC uses pharmacovigilance indicators to measure the status of national PV systems within PIDM member countries to determine the extent of support required by that country as well as the measure the impact of the support provided. PV indicators facilitate the ability to identify strengths, weaknesses, achievements, growth, and impact and to assess the return on investment made into pharmacovigilance (WHO-UMC, 2015) (SPS Program, 2009). Effective indicators should be simple to understand, easy to measure and interpret, reproducible, sensitive to detect problems and applicable to any facility engaged in PV. There is also an assessment checklist to be used when performing an assessment of a PV system/program against the indicators (WHO-UMC, 2015). The idea of PV indicators arose during a 2007 meeting of PV consultants and staff from WHO, UMC and WHO African Regional Office in Ghana. The over-riding philosophy was to develop a set of indicators to measure the impact of interventions which are to be developed by the WHO-UMC to support the establishment of PV systems within African countries. The identification of candidate indicators and their categorization was carried out through questionnaires to national pharmacovigilance centres, the results presented and discussed at subsequent meetings of the African Pharmacovigilance Consultant Group and annual meetings of WHO PIDM member countries. The development process was continuously reviewed and finally validated by WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) until publication in 2015. As part of field testing of the PV indicators prior to publication, the WHO-UMC collaborating centre in Ghana, used the indicators to assess the status of PV across African countries during their visits to those countries (WHO-UMC, 2015). Prior to using the pharmacovigilance indicators, it is necessary to obtain some background information covering the demographics, economics, the health-care system, and the pharmaceutical scenario. This will provide the denominator for calculating most of the indicator values.

There is a total of 63 indicators, classified as structural, process and outcome/impact indicators and categorized into *Core* (27) and *Complementary* (36). Core indicators (C) are those considered to be highly relevant, important, and useful in characterizing pharmacovigilance, while Complementary indicators (T) are those additional measurements considered to be relevant and useful (WHO-UMC, 2015) (SPS Program, 2009).

A. Structural indicators assess

- Visibility and magnitude of the PV programme
- Enabling environment
- Legal framework
- Sustenance – are there structures in place

B. Process indicators assess

- Extent of PV activities
- Describe the mechanism of PV (i.e., collection, collation, analysis, and evaluation)
- Extent to which the PV system is operating

C. **Outcome/Impact Indicators (core and complementary), to indicate the following**

- Effects and changes resulting from PV activities
- Advocacy tool
- Trends
- Return on investment

2.12.4. Core PV indicators

There are 27 core pharmacovigilance indicators: 10 structural, 9 process and 8 outcome or impact indicators (WHO-UMC, 2015).

2.12.4.1. Core Structural Indicators (10) check for the existence of (WHO-UMC, 2015):

1. A PV centre with a standard accommodation
2. A statutory provision for PV? (legislation, policy)
3. A drug regulatory authority
4. Regular financial provision for the PV centre
5. Human resources to carry out its functions properly
6. A standard ADR reporting form
7. A process in place for collection, recording and analysis of ADRs
8. Is PV included in national curriculum of schools for healthcare professionals?
9. A newsletter/information bulletin/website for dissemination of PV information
10. A national PV advisory committee

2.12.4.2. Core Process Indicators (9) check for the following (WHO-UMC, 2015):

1. Total number of ADR reports received in the last calendar year (target 200 reports per million inhabitants per year)
2. Total number of reports in national/local database
3. Percentage of total annual reports acknowledged
4. Percentage of reports subjected to causality assessment in the year
5. Percentage of national reports satisfactorily completed and submitted to the national centre last year

5.a) Submitted to WHO
6. Percentage of reports on therapeutic ineffectiveness
7. Percentage of reports on medication errors
8. Percentage of registered pharmaceutical companies having functional PV systems
9. Number of active surveillance activities initiated, ongoing or completed in the last 5 years

2.12.4.3. Core outcome/impact indicators (8) check for the following (WHO-UMC, 2015):

1. No. of signals identified by PV centre in the last 5 years
2. No. of regulatory actions taken last year based on national data, not information/action taken by international RA's.
   - label change
   - safety warning
   - medicine suspension/withdrawal/other restrictions
3. No. of medicine related hospital admissions/1,000 admissions
4. No. of medicine related deaths/1,000 persons served by hospital
5. No. of medicine related deaths/100 000 in the population
6. Average cost of treatment of medicine-related illness
7. Average duration of extension of medicine-related hospital stay
8. Average cost of medicine related hospitalization

In addition, nine pharmacovigilance indicators cutting across the three classes were selected for Public Health Programmes (PHP) to enable the monitoring and evaluation of pharmacovigilance following the large-scale deployment of medicines in a PHP where many people are exposed to medicinal products:

2.12.4.4. Core indicators for Public Health Programmes (PHP) (WHO-UMC, 2015):

1. PV activities in place within the PHP
2. All main treatment guidelines/protocols in use within the PHP systematically considers PV
3. Existence of standard ADR reporting form in the PHP
4. Total no. of ADR reports collected within the PHP in the previous year
5. Total no. of ADR reports/1,000 individuals exposed to medicines in the PHP the previous year
6. Total no of reports on therapeutic ineffectiveness in the previous year
7. Percentage of completed reports submitted to the national PV centre in the previous year

7.a) to WHO
8. No. of medicine-related hospital admissions/1,000 individuals exposed to medicines in the PHP in the previous year
9. No. of medicine-related deaths/1,000 individuals exposed to medicines in the PHP in the previous year

2.12.5. Complementary Indicators (WHO-UMC, 2015):

There are 36 complementary indicators: 11 structural, 13 process and 12 outcome or impact.

1. Existence of a dedicated computer for pharmacovigilance activities
2. Existence of a source of data on consumption and prescription of medicines
3. Existence of functioning and accessible communication facilities in the pharmacovigilance centre
4. Existence of a library or other reference source for Drug Safety information
5. Existence of a computerized case-report management system
6. Existence of a programme (including a laboratory) for monitoring the quality of pharmaceutical products
   6.a) The programme (including a laboratory) for monitoring the quality of pharmaceutical products collaborates with the pharmacovigilance programme
7. Existence of an essential medicines list which is in use
8. Systematic consideration of pharmacovigilance data when developing the main standard treatment guidelines
9. The pharmacovigilance centre organizes training courses
   9.a) for health professionals
   9.b) for the public
10. Availability of web-based pharmacovigilance training tools
    10.a) for health professionals
    10.b) for the public
11. Existence of requirements mandating market authorization holders to submit periodic safety update reports

An older set of the PV indicators is called "Indicator-based Pharmacovigilance Assessment Tool (IPAT) (SPS Program, 2009). It was developed within the Strengthening Pharmaceutical Systems (SPS) and supported by USAID and published in Dec 2009 for conducting PV assessments in developing countries at a national, public health programs and health facility level. The indicators in this tool are remarkably like the WHO PV indicators; however, the outcome/impact indicators in the IPAT tool are not as elaborate. The tool was used in the assessment of PV systems and their performance in 46 African countries in 2010. The report was published in 2011 and the development of PV systems in many of those 46 countries remain inadequate to date (SPS Program, 2009). Such assessments should not be in isolation; after performing the analysis and knowing the status of the PV system, there should be interventions and plans on how to implement them. A follow-up assessment should also be performed after implementation, to measure the impact of the interventions.

The IPAT tool measures performance in each of the following PV components (SPS Program, 2009):

1. Policy, law, and regulation
2. System, structure, and stakeholder coordination
3. Signal generation and data management
4. Risk evaluation and assessment
5. Risk communication and management

A Masters research study conducted in Kenya, assessing the vaccine PV system using the IPAT tool reported that although Kenya had a PV system specifically for vaccines in place, there was no specific legislation guidelines and structural framework for this. Out of 100 %, indicators on law, policy and regulations scored 50%, structures, systems and stakeholder coordination scored 24%, signal detection and data management scored 40% and risk

management and evaluation scoring 25% (Chepkemboi, 2016). These limitations result in poor coordination of vaccine PV activities and are part of the factors contributing to low ADR and AVR reporting.

2.12.6. Pharmacovigilance in practice: lessons learned

The PV indicators were used in a study conducted from July to Dec 2018, to assess the functionality and to identify the strengths and limitations of the national PV systems in four East African countries (Ethiopia, Kenya, Tanzania, Rwanda) (Barry, 2020). The study was conducted as part of the PROFORMA projects, which aims to strengthen the national pharmacovigilance infrastructure and post-marketing surveillance system involving mass drug administration and immunization programmes being deployed under public health programs in the selected East African countries. As a follow-up to the assessment, capacity-building interventions to be carried out by the PROFORMA project. Below is a tabular presentation of the National Medicines Regulatory Authorities (NMRA) in each of the four countries as well as the year in which country joined the WHO PIDM and total number of ICSR's submitted to VigiBase® since joining the PIDM to the time of assessment in 2018 (Barry, 2020).

Table 2-6: NRA name changes and year of joining WHO PIDM (Barry, 2020)

New NMRA Name	Previous NMRA Name	Year of joining WHO PIDM	Total number of ICSR's
Tanzania Medicines and Medical Devices Authority (TMDA)	Tanzania Food and Drugs Authority (TFDA)	1993	1,331
Ethiopian Food and Drugs Authority (EFDA)	Ethiopian Food, Medicine and Health Care Administration and Control Authority (FMHACA)	2008	11,373
Kenya Pharmacy and Poisons Board (PPB)	Same	2010	30
Rwanda Food and Drugs Authority (RFDA)	Rwanda (Ministry of Health)	2013	1,899

The East African Community (EAC) Harmonized Pharmacovigilance Indicators tool was used in this assessment. This tool was derived from the WHO pharmacovigilance indicators and the Indicator-Based Pharmacovigilance Assessment Tool (IPAT).

Table 2-7: Summary of infrastructure structures on the national PV systems (Barry, 2020)

Country	Full time staff	Defined annual budget	Existence of a source of data on medicine consumption	Pre-service training	In-service training	Web-based training	PV information communication plan	Toll-free number	Website
Ethiopia	10	×	×	✓	✓	×	✓	✓	✓
Kenya	5	✓	×	×	✓	×	✓[a]	×	✓
Rwanda	2	×	×	×	×	×	×	×	×
Tanzania	12	✓	×	×	✓	×	✓	✓	✓

✓ present, X missing/not available, NMRA National Medicines Regulatory Authority, PPB Pharmacy and Poisons Board

[a] No specific plan for pharmacovigilance; communication plan available for the NMRA (PPB), but not specific to pharmacovigilance

Table 2-8: Summary of data management structures within the national PV systems (Barry, 2020)

Country	Existence of a national database for pharmacovigilance information	Existence of standard adverse event reporting form	Existence of standard adverse event reporting form for the public	Existence of electronic adverse event reporting system	Process for collection, recording, and analysis of ADR reports
Ethiopia	✓	✓	×	×	✓
Kenya	✓	✓	×	✓	✓
Rwanda	✓ [a]	✓	×	×	×
Tanzania	✓	✓	✓	✓	✓

✓ present, X missing/not available, ADR adverse drug reaction

[a] database was not in use

Table 2-9: Summary of scope of PV within the national PV systems (Barry, 2020)

Country	Adverse events/ reactions	Therapeutic ineffectiveness	Medication errors	Medical devices and diagnostics	Misuse, abuse, and/or dependence	Poor quality	AEFIs
Ethiopia	✓	✓	✓	✓	✓	✓	[a]
Kenya	✓	✓	✓	×	✓	[a]	[a]
Rwanda	✓	✓	×	×	✓	[a]	✓
Tanzania	✓	✓	✓	[a]	✓	[a]	✓

✓ present, X missing/not available, AEFI adverse events following immunization

[a] present in a separate form

It was found that all four countries have policies and legal frameworks defined by laws and regulations and there are guidelines in place for the conduct of pharmacovigilance activities. All countries, excluding Rwanda have systems in place for the conduct of PV activities. All four national PV centres have not initiated any regulatory action based on local information regarding safety issues (Barry, 2020). Olsson and colleagues highlighted that the number of reports received from Africa are inadequate to identify significant safety issues (Olsson, *et al.*, 2015). African countries are therefore, encouraged to increase ADR reporting rates as information from other continents may not always be relevant for the African population. For a more efficient VigiBase® analysis, it is important for safety data from similar geographical, demographic, genetic and nutritional backgrounds to be available and this can only be achieved through ICSR's received from national PV centres. Kenya and Tanzania have acted upon information received from the WHO or individual countries abroad, whereas, Ethiopia and Rwanda have not (Barry, 2020).

Another common challenge at all four national PV centres is inadequate funding and human resources. Ethiopia and Rwanda both do not have a dedicated budget for PV activities. Kenya and Tanzania do have dedicated budgets; however, the budgets do not match the resource and workload requirements, therefore, an improvement is required (Barry, 2020).

Although only Tanzania has adverse event reporting forms for the public, it is encouraging to see that Tanzania, Kenya and Ethiopia have communication plans in place, even if the communication plan in Kenya is not specifically for PV related matters. Only Ethiopia and Tanzania's national PV centres have toll-free numbers. Ethiopia promotes the toll-free number on a national radio program. Tanzania broadcasts public education information

related to the safety of medicines across five television and radio stations, while Kenya also includes newspapers and roadshows (Barry, 2020).

2.12.7. Pharmacovigilance Funding

Historically, pharmacovigilance activities started as a voluntary initiative across different settings, with HCPs to address the growing concern around the risks of medicine use. The reason for spontaneous reporting being the primary method of PV widely used is that it can be done at a low cost. Cost estimates are illustrated in the PV toolkit (WHO Collaborating Centre Ghana, 2012). The costs associated with PV have been summarised in Table 2-10.

Table 2-10: Example of budgetary items for a PV centre (WHO Collaborating Centre Ghana, 2012)

Fixed Costs	**Recurring Costs**
Infrastructure	Salaries
Equipment (Computers, software)	Office costs (rent, electricity, etc.)
Training (Baseline Induction)	Stationery and other office supplies
Research on pharmacovigilance	Travel
Website development and maintenance	Training and Workshops
	Communication (Advocacy and public sensitization using the media e.g., internet, radio, TV, and newspapers

2.12.7.1. Source of PV funding:

- Government (usually DoH) – structured budget allocated annually from fiscus
- Regulatory Authority – fluctuating budget depending on other priorities
- Fees charged to industry for PV services – revenues depend on activities
- Donor funding – Donors generally do not fund national PV centres; however, they fund public health programmes. Primarily for the introduction of new medicines or vaccines in LMIC's (e.g., WHO Global Vaccine Action Plan with Vaccine Safety Blueprint and Global Vaccine Safety Initiative [GVSI]). Funders for public health initiatives and related PV activities include Global Fund, UNITAID (through WHO), PEPFAR (HIV/AIDS), Bill and Melinda Gates Foundation (BMGF), GAVI (vaccines), USAID (SIAPS programme), EU (Horizon 2020, Monitoring Medicines Project) (Kovacs, 2017).

A. Global Fund:

Application to the global fund can be disease focused (e.g., HIV, TB, Malaria) or for general strengthening the health system (focusing on PV) or PV system implementation with the introduction of new medicines/vaccines. The application requires a description of PV activities already in place or planned as part of public health programmes (Xueref, 2013).

B. Bill and Melinda Gates Foundation:

The foundation hosted a series of international meetings throughout 2012 and afterwards published a report in 2014 titled "A report of the Safety and Surveillance Working Group". Their analysis consisted of funded products in the pipeline, to be introduced into the market

between 2012-2015 and this was matched with an analysis of the PV capacity in of the countries where the products will be launched. The only African countries which had the highest capacity were Nigeria and Uganda. The BMGF then embarked on a predictable and sustainable funding model, where funding is shared among stakeholders (Donors, MAH, NMRA), but emphasis on local country ownership of the systems from the outset. Funding must be self-sustaining and long-term, and the system should not be product-specific, but rather allow for entry of other products with time. For this purpose, a trust fund was formed under the World Bank and technical support is sought from regional implementing partners and WHO with the use of indicator-based monitoring and evaluation (BMGF, 2013).

2.12.7.2. Strategies to get funding:

- Researchers must convince Government with research data that shows the burden of ADRs globally and locally
- Apply for donor funding for public health programmes
- Partnerships with Universities, healthcare facilities and WHO/collaboration centres
- Publication of scientific literature on research conducted relating to PV

2.13 Pharmacovigilance Developments in South Africa

2.13.1 South African Pharmacovigilance Structures

The Medicines and Related Substances Control Act 101 (Act 101) was promulgated in South Africa in 1965 (Govt, 2017). The Act mandated the establishment of the Medicines Control Council (MCC), currently called the South African Health Products Regulatory Authority (SAHPRA) and stipulates the standards by which medicines are to be regulated and monitored in South Africa. Regulation 40 of Act 101 stipulates that the holder/applicant of a certificate of registration for a medicine in terms of section 15 of the Act, or a holder of a licence in terms of section 22C(1)(b) must inform the Authority, in the manner and within the time frame as determined by the Authority, of any:

- New or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to ADR, and risk management activities associated with the medicine (Govt, 2017).
- A health care provider, veterinarian or any other person should inform the Authority, in the manner as determined by the Authority, of any suspected adverse drug reactions; or new or existing safety, quality or effectiveness concerns, occurring because of the use of any medicine or scheduled substance (Govt, 2017).

In 1987 the MCC, in collaboration with the University of Cape Town, established the National Adverse Drug Event Monitoring Centre (NADEMC); a unit to collect and perform a causality assessment of ADRs received through spontaneous reporting. ADRs were then submitted from the NADEMC to the MCC. The ADRs were then reviewed by the PV Advisory Committee at the MCC, and recommendations made regarding the registration

status of medicines, including labelling changes or market withdrawal. The PV Advisory Committee consisted of a pharmacist and 6 external experts from various institutions. The small number of committee members and the fact that they are not full-time employed, created a limitation in the committee's ability to perform robust causality assessments and signal detection. Committee members who were not full-time employed may also have had limited capacity to attend technical training and to stay abreast with latest international developments around Drug Safety and pharmacovigilance (SAHPRA, 2020).

In 1992, South Africa became the first African country to gain membership into the WHO Programme for International Drug Monitoring. The Expanded Programme for Immunization (EPI) implemented a targeted spontaneous reporting (TSR) system in 1998, to collect adverse events following immunisation (AEFI). With the launch of the national antiretroviral (ARV) treatment programme in 2003, TSR systems were implemented at provincial level for the collection of ARV-related ADRs. TSR systems were expanded to include not only ARV's but also TB-medicines in 2011, with the National Department of Health (NDoH) programmatic decentralised PV unit. As part of this initiative, provincial training was provided to HCPs and bulletins were published providing updates on national PV activities (Dheda, 2013). A concerning maternal and infant mortality rate in South Africa, resulting from HIV/AIDS (complicated by Tuberculosis and pneumonia), haemorrhage and hypertension led to the WHO 2013 recommendation of ARV treatment for pregnant women diagnosed with HIV during pregnancy being initiated immediately, regardless of CD4 cell count or clinical stage (WHO, 2013). This recommendation led to the establishment of a pregnancy exposure registry and birth defects surveillance (PER/BDS) system the eThekwini District, KwaZulu-Natal (KZN) province (SA NDoH, 2015).

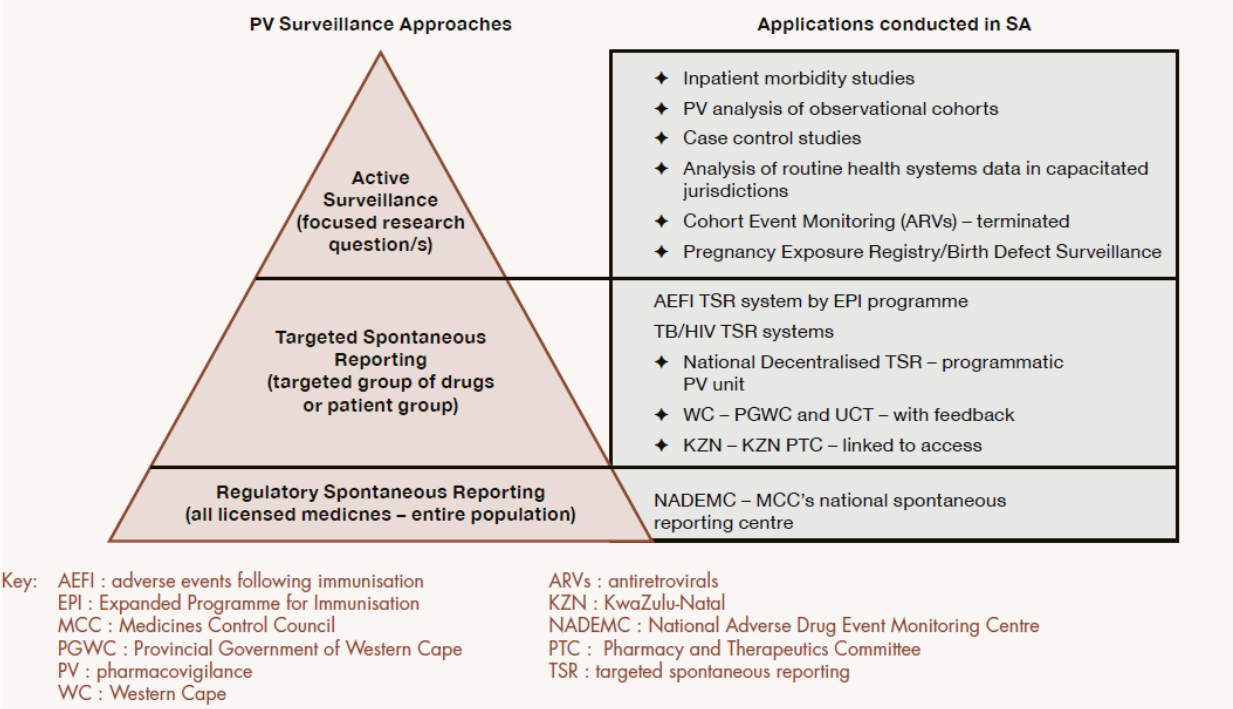


Figure 2-10: Summary of PV activities in South Africa (Mehta, 2014)

From the summary of the PV activities in South Africa (Figure 2-10), with growing access to medicines and vaccines, PV systems are evolving from passive to more active methods. Several targeted spontaneous reporting systems have been implemented to complement the

passive spontaneous reporting to the NADEMC. Multiple efforts are undertaken; however, it appears that these are operated in parallel, which limits their effectiveness. This observation is in keeping with the August 2012 South Africa PV workshop, which resolved that there are multiple existing PV programmes and there is a need for coordination of all databases to feed into the national database (Mehta, 2014). There is a concern as to whether the reports collected through all the programmes in isolation end up making it into the WHO VigiBase® database. The same was acknowledged at the 2012 Africa Pharmacovigilance Meeting, where it was noted that the national database does not include data from all sources (Ouma, 2012). The focus area thus far appears to be on HIV and TB medicines, which is understandable as these are most widely used in this country. Attention also needs to include non-communicable diseases as well such as diabetes, hypertension, and cardiovascular medications as these are also widely used in the country. With the novel Covid-19 pandemic and resulting research into vaccine and treatment options, this further highlights the need to focus the safety of medicines across the board.

In terms of the Act 101, the SAHPRA's objectives are to provide for the monitoring, evaluation, regulation, investigation, inspection, registration, and control of medicines, scheduled substances, medical devices, radiation control, clinical trials, and related matters in the public interest (SAHPRA, 2020). To achieve its objectives, the SAHPRA must ensure that evidence of existing and new adverse events and reactions, interactions, and signals emerging from post-marketing surveillance and vigilance activities are investigated, monitored, analysed, and acted upon; and this is achieved through vigilance. 'vigilance' in relation to a medicine, medical device, means the continuous monitoring and evaluation of its safety, efficacy and performance profile and the management of any risk throughout its life cycle. Currently spontaneous reports can be sent to National Adverse Drug Event Monitoring Centre (Cape Town) or Pharmacovigilance Unit (SAHPRA). The PV teams at NADEMC and the SAHPRA PV unit then manually capture the ICSR into the WHO VigiFlow® system from which they are imported to the WHO VigiBase® database.

In 2003, the MCC published guidelines for post-marketing ADR reporting; these have been updated numerous times with the latest version published by the SAHPRA in September 2020 (SAHPRA, 2020). These guidelines place the obligation of ADR reporting squarely on the holder of the medicine certificate of registration (i.e., pharmaceutical company / marketing authorization). The guidelines stipulate that the company is to appoint a pharmacovigilance officer, who will serve as the main liaison with the NADEMC and the SAHPRA PV unit (SAHPRA, 2020). This is contrary to EMA and FDA regulations, which in addition, allow reporting by HCPs and consumers directly to the national PV centre. For reporting to include HCPs and consumers, online reporting is the most practical method. Currently in South Africa, only manual ADR reporting or CIOMS forms are available. ADR forms are available on the SAHPRA website or at their offices or at the back of the South African Medicines Formulary (SAMF). These can be completed in hard copy or electronically and submitted to the PV centre via email. The guidelines also stipulate those reports can also be submitted in the e2b format using an xml. file. In their survey conducted among HCPs (doctors, nurses, pharmacists, and pharmacist assistants) at a public sector hospital, Terblanche, and colleagues (Terblanche, 2017) found that the factors discouraging ADR reporting included not knowing how to report them (53.8%), lack of time (37.1%), additional workload (22.0%). Most of the respondents also reported that they had never received PV training (Mehta, 2014). Easy access to reporting methods as well as training are the key factors that can improve reporting by HCPs.

At minimum, the following information must be included in an individual ADR report /CIOMS form (SAHPRA, 2020):

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

In latest version of the SAHPRA guidelines, the following items have been removed; however, ideally, the following relevant information must be included as much as possible to facilitate causality assessment. The initial analysis of the pilot National Department of Health (NDoH) programmatic decentralised TSR system revealed that 48% of the reports were unevaluable due to poor quality data (Dheda, 2013). As much as it is important to reduce the workload for reporters by defining the minimum reportable information, it is also important to collect as much information as possible for the data to be useful.

- Treatment starts date and reaction onset date – temporal relation
- Dose and dosing regimen
- Indication
- Concomitant medicines and comorbidities
- Age and gender
- Action taken – de-challenge/re-challenge and outcome
- Other information that may be relevant
- Discharge summaries, post-mortem reports, and relevant laboratory data

The future of pharmacovigilance in South Africa is looking bright. In its Strategic Plan 2018-19 to 2022-23, the SAHPRA has outlined plans to strengthen the existing vigilance framework. Among other things, the SAHPRA endeavours to develop Good Vigilance Practice, like those available for the EMA and FDA (SAHPRA, 2018). The SAHPRA board and leadership realizes the importance of communication in pharmacovigilance and thus plans to develop a framework for feedback and communication of vigilance-related matters to stakeholders. Considering the multiple decentralised PV programmes that have been implemented over the years in South Africa, there is a need to create linkages across all databases, to feed into the VigiFlow system (SAHPRA, 2018). Although these have been focusing on specific therapeutic areas (HIV, TB, malaria) and population groups (pregnant women, children), their contribution to policy decisions on treatment protocols are undoubted. For example, in 2012 the NDoH changed first-line ARV treatment in pregnant women from Nevirapine-based regimen to an Efavirenz-based one due to reported ADRs (Dheda, 2013). Additionally, the SAHPRA recognizes the need to strengthen the vigilance of complementary, veterinary medicines and medical devices with the improvement of regulatory framework. The strategic plan also mentions plans to move to online reporting ICSRs, replacing the current paper-based forms and to include HCPs as required ADR reporters (SAHPRA, 2018). The plan to include HCPs is not reflected on the SAHPRA guidelines although these have been updated twice since the SAHPRA's inception.

2.13.2 Funding

The SAHPRA regulations require post-marketing ADR reporting up to six months after the expiry date of the last marketed batch (SAHPRA, 2020). Unlike the FDA and EMA, the SAHPRA does not charge pharmaceutical companies/license holders for the services provided by the PV unit and NADEMC, yet it has been established that the function of a national PV centre includes data entry into VigiFlow®, correspondence with reporters for queries ad feedback, causality assessment, signal detection as well as communication of signals and any other relevant information. National PV centres also need to work closely with other stakeholders locally and globally to learn and remain abreast with the latest developments. All these activities require funding both from industry and government. Medicines and Related Substances Amendment Act 72 of 2008, section 39 states that funds may be derived from sources including State funds received through the Department of Health; fees raised and interest on overdue fees; as well as money accruing to the RA from any other source (Govt, 2017). The WHO minimum requirements for a functional PV system emphasizes the need for guaranteed funding. A systematic and qualitative review of the PV systems in South Africa, India, and Uganda, reported that the key deficiencies in all three countries included lack of funding, poor coordination of activities, inadequate human resources and poor training for existing staff and HCPs. The study recommends that a PV specific budget must be allocated to address the reported deficiencies (Maigetter, 2015). The fee-based model for PV that has been introduced in the EU per Regulation 658/2014 of 15 May 2015 in South Africa. However, it is important that the government also allocates dedicated funds for PV to ensure steady and sustainable support to PV in the country. Several public health programmes and clinical trials in South Africa are already funded by donors such as PEPFAR, Bill and Melinda Gates Foundation, etc. In the opinion of the author, it would, therefore, be fitting for the national PV centre, through the SAHPRA, to apply for donor funding from existing and other donors.

2.13.3 Other studies on factors affecting ADR in reporting in South Africa

Under-reporting of adverse drug reactions is a global concern and, although South Africa has shown an improvement over the years, reporting rates are still extremely low considering the time since South Africa became a member of the WHO PIDM in 1992. It is reported that since 1992, South Africa had submitted a total of 28, 609 reports into VigiBase® (Olsson, 2015). This amounts to approximately 27 reports per million inhabitants per year, compared to the expected 200 reports per million inhabitants as estimated by the WHO-UMC (SPS Program, 2009).

Several studies have been conducted across different sectors and HCPs in South Africa, to investigate the factors that contribute to low ADR reporting. Terblanche *et al*, Bogolubova *et al,* Gordhon and Padayachee as well as Joubert and Naidoo all found that most HCPs both in public and private hospitals believe that ADR reporting is important although they had previously not received PV training (Terblanche, 2017) (Bogolubova, 2018) (Joubert M, 2016) (Gordhon Y, 2020). Generally, the majority also agreed that they would report ADRs if they receive sufficient training, although in the study conducted by Gordhon and Padayachee in nurses, doctors, and pharmacists, 92% of the respondents noted that they believed that doctors should be responsible for reporting (Gordhon Y, 2020). Hanafi et al had a similar finding with 89% of nurses preferring to refer a suspected ADR to the doctor rather than report it themselves

(Hanafi, 2013). De Angelis *et al.* concluded that this lack of confidence seen in nurses is due to them not being fully aware of their role in ADR reporting (Angelis, 2016). On the other hand, an Australian study among doctors and nurses, found that both doctors and nurses (98.3%) were aware of their hospital's PV system; however, nurses were more likely than doctors to know how to report (88.3% v 43.0%), and have reported previously (89.2% v 64.4%) (Evans, 2006).

A study in several public health facilities in Tshwane Health District, Gauteng Province, among doctors, pharmacists and nurses found that 51.1% of all HCPs combined reported that their clinical knowledge is inadequate to equip them in identifying an ADR [83]. Approximately half of the respondents across all these studies reported that some of the barriers to reporting include lack of knowledge on how and where to report. Factors that discourage ADR reporting are lack of time, concerns that the ADR is wrong and lack of feedback from the national PV centre after reporting (Terblanche, 2017) (Bogolubova, 2018) (Joubert M, 2016) (Gordhon Y, 2020). In the study conducted in 2016 and 2017 by Gordhon and Padayachee, pharmacists were the HCPs who were the most aware of how to report ADRs at 83%, compared to doctors and nurses 54% each group (Gordhon Y, 2020). It is encouraging to see a more recent study, conducted by Haines *et al*.in 2019, indicating higher mean knowledge scores at 91.4% for pharmacists, 82.8% for doctors and 84.0% for nurses. The study also reported that 92% of respondents believe that they should try to prevent ADRs when prescribing and dispensing medicines (Haines, 2020). It is evident that studies conducted in South Africa in recent years, relating to pharmacovigilance practices, has a positive impact on HCPs, by creating an awareness about the concept of PV. This does not; however, replace the impact that purposeful PV and ADR training can have. This only supplements by making HCPs aware of their obligation. To indicate this point, the same study reports that only 12% of the respondents knew where to find ADR forms within their facilities, although they are aware of the requirement to report (Haines, 2020).

This is consistent with Bogolubova et al, who found that Pharmacists were more likely to have received training (p = 0.040685) (Bogolubova, 2018). In the study conducted by Joubert and Naidoo, 44.1% participants indicated that they had previously reported an ADR (Joubert M, 2016). This is a relatively high reporting rate compared to other studies such as Gordhon and Padayachee with 17% and Bogolubova *et al.*at 18.9%. Regarding the relationship between work experience and likelihood of reporting, Gordhon and Padayachee and Bogolubova *et al.* found that respondents with less experience had little knowledge (23% of pharmacist and doctor interns) on ADR reporting than senior level HCPs (Bogolubova, 2018) (Gordhon Y, 2020). This is consistent with findings from a similar, older study conducted in Australia, where senior nurses reported to be more involved in PV activities than their junior counterparts (Evans, 2006).

2.13.4. Pharmacovigilance in South Africa during the Covid-19 pandemic

On 08 Feb 2021, the South African government announced the suspension of AstraZeneca vaccine roll-out, after receiving results of reduced efficacy of the vaccine against the circulating Covid-19 variant (B.1.351). By 17 Feb 2021, in collaboration with the South African Medical Research Council (SAMRC) and other stakeholders, the NDOH, initiated roll-out of the Johnson & Johnson vaccine (Ad26.COV2.S), aiming to vaccinate 500 000 healthcare workers across South African. At that point, no regulatory authority had granted the J&J vaccine a marketing authorisation; it could hence not be procured for use in South Africa under a Section 21 application as per the Regulations to Act 101. An alternative option was to implement the roll-out through a phase IIIb clinical trial named Sisonke (SAMRC, 2021),

meaning “together” in Isizulu and Xhosa). At the time, the development of the functionality to report AEFIs into the EVDS was still underway and the SAHPRA Vigilance Unit was still developing the framework through which AEFI data will be collected in a suitable format to allow for timeous exporting to VigiBase®.

The SAHPRA guidelines for safety reporting during clinical trials (SAHPRA, 2019), mandate safety reporting by the sponsor for unregistered medicines. To comply to the guidelines, the Sisonke study Protocol and Safety Team (PSRT) developed an online ADR reporting tool (Sisonke PSRT, 2021) using the REDCap® system, based on the paper-based NDoH AEFI case report form (NDoH, 2021) (CRF), which was updated on 28 Jan 2021 to include Covid-19 vaccines. Figure 2.11 below displays a summary of the flow of AEFI reported data during the conduct of the Sisonke vaccine roll-out, from the study participant to the WHO VigiBase® database (Sisonke PSRT, 2021).

The Sisonke project provides a great opportunity to serve a pilot initiative for the South African NDoH to identify challenges, lessons learned and good practices that can be utilised in the national roll-out of registered Covid-19 vaccines after completion of the Sisonke study (SAMRC, 2021). By 26 the end of the Sisonke study on 16 May 2021, over 10 000 AEFIs had been reported into the REDCap® system.

On 22 April 2021, SAHPRA announced the launch of the Med Safety App, which is targeted at HCPs and patients, for reporting ADRs. This launch was just in time for the national Covid-19 vaccine roll-out which started on 17 May 2021.

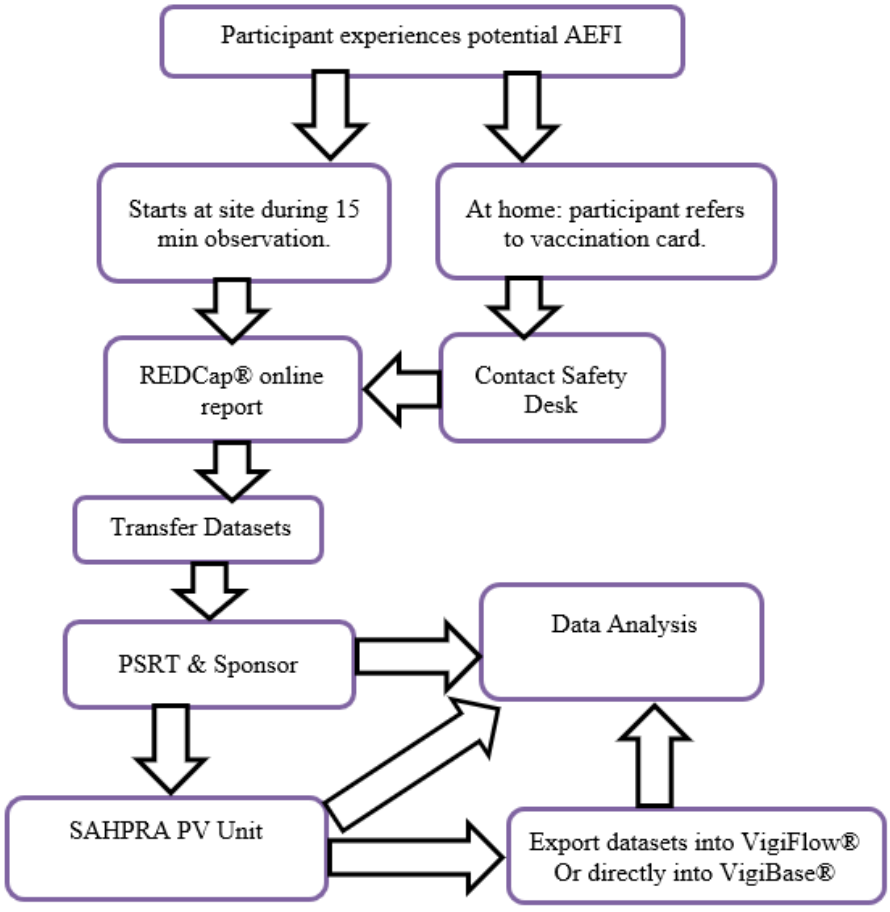


Figure 2-11: Flow of AEFI reports in the Sisonke study J&J vaccine roll-out to Healthcare Workers (Sisonke PSRT, 2021)

2.14 Conclusion

The reviewed literature provides evidence that ADRs pose a significant global public health threat. With further understanding of the shortfalls leading to Drug Safety issues, the scope of PV has evolved to include other types of medicines as well as issues of quality and falsification. The WHO, through the Uppsala Monitoring Centre, has developed several pharmacovigilance structures over the years and many countries have started actively participating in PV activities. The African continent remains behind with ADR reporting to the WHO VigiBase® database; however, with the support of the UMC together with collaborating partners, gradual improvements can be seen. Researchers are becoming more aware of the risks that come with a wider range of medicines becoming increasingly available in LMIC's. The public health and cost implications are not yet well established in resource-limited countries; however, the need for research in these areas is becoming increasingly apparent. Researchers need to produce evidence in terms of research data, to convince politicians of the importance of pharmacovigilance. It is critical for governments to implement legislative frameworks and provide funding for PV systems. National PV centres need to get to a point where they are well capacitated, HCPs need to be well trained and reporting mechanisms need to be functional, to allow for local and regional signal detection to occur. National Regulatory Authorities in Africa must get to a point where regulatory decisions (e.g., market withdrawal, package insert updates, etc.) are made based on local ADR reports instead of only relying on international agencies such as the FDA and EMA.

A systemic review published by Onakpoya and colleagues in 2015 identified 407 medicines withdrawn from the market globally between 1957 and 2011. Of the 407, death was documented as the reason for withdrawal in 95 medicines. Only 27% of the medicines were withdrawn worldwide, whereas 40% were withdrawn in in more than one country. Surprisingly, 16 medicines remained on the market despite being withdrawn in at least two other countries. The longest interval between the first death reported and withdrawal of the attributed medicine was 56 years; this timeframe has not improved in over 60 years (Onakpoya, 2016).

The current Covid-19 pandemic has undoubtedly amplified the urgent need for robust PV systems to be developed. Funding must be directed towards post-marketing surveillance of vaccines and medicines which are being developed much quicker than the typical drug development processes. HCPs must be trained on PV requirements in time for the rolling out of SARS-Cov-2 vaccines and treatments, to notice any adverse effects that are highly likely to be missed during rapid clinical trials. The current pandemic has also created an opportunity for agility in addressing the crisis. Public: private partnerships have been strengthened between pharmaceutical companies, NGO's, Academia, and government institutions; facilitating real-time data analysis and information sharing. The same spirit of agility can be adopted further into the post-marketing phase.

Chapter 3

Research Methodology

3.1 Introduction

This chapter discusses the research methodological considerations and choices that have shaped the conduct of this study. The chapter explores the development of the survey that was used, considerations made during study sample selection as well as other aspects such as sample error and bias as well as data reliability and validity. Ethical aspects and methods of data analysis are also outlined.

3.2 Research design

This was a knowledge, attitudes, and practices (KAP) study design. A quantitative research method was adopted and involved the use of a questionnaire as a data collection tool. The study participants consisted of medical doctors who are affiliated with the South African Medical Association (SAMA) and a combination of medical doctors and pharmacists affiliated with the South African Clinical Research Association (SACRA).

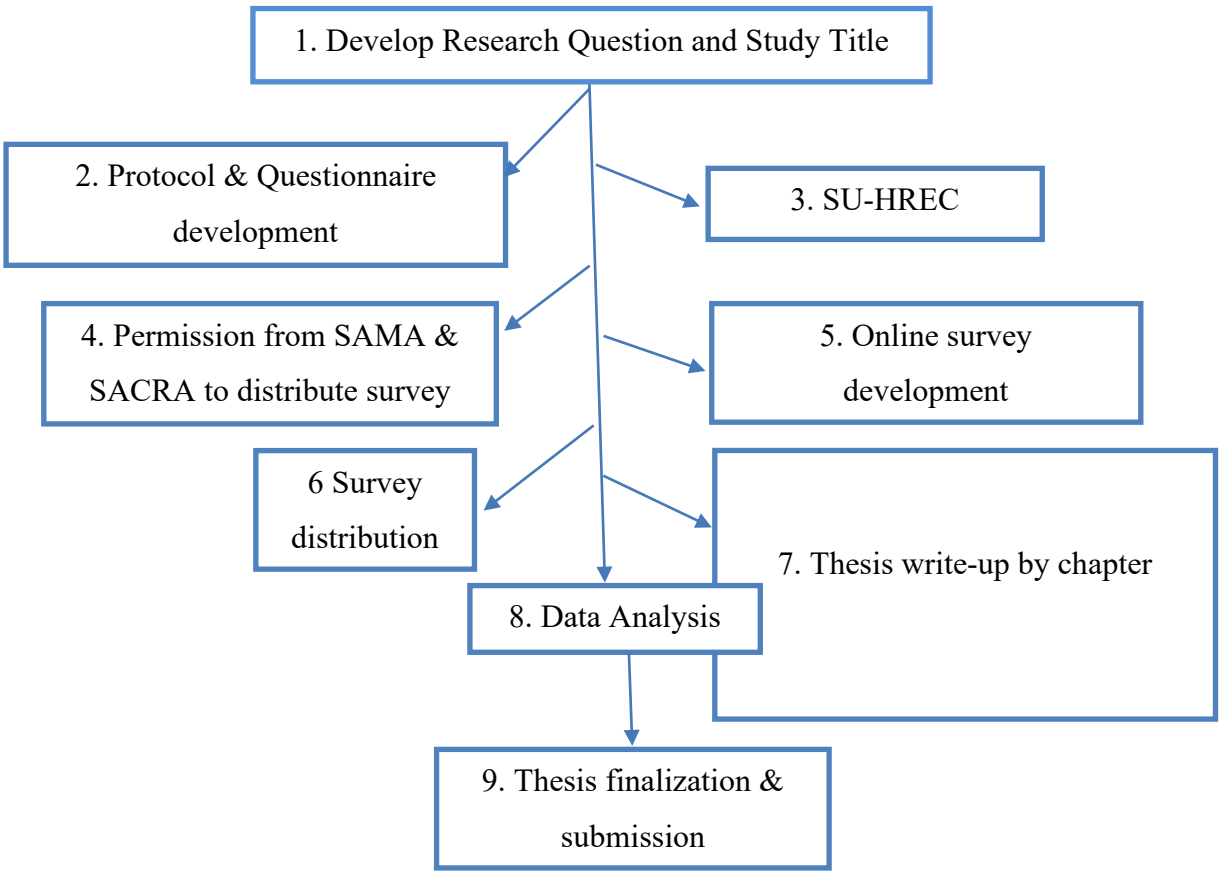


Figure 3-1: Flow Diagram of study conduct

3.3 Questionnaire development

The survey used in this study consisted of a brief description of the study, an informed consent and confidentiality statement, with the option to agree or decline participation, followed by the questionnaire. The informed consent section (Annexure A) of the survey stipulated the purpose of the research study, the size, benefits of participation, potential risks, withdrawal of participation, protection of data privacy and contact details of the researcher and supervisors. The questionnaire contained six (6) demographics-related questions, eight (8) questions to establish knowledge, five (5) attitude-related and five (5) practices-related questions (Annexure B).

3.3.1. Content and face validity

Pilot testing of questionnaires is essential in checking whether individuals from the same sample group as those who will be administered the questionnaire understand the contents of the questionnaire in the manner intended by the researcher (Taherdoost, 2016). Pilot testing is also useful in detecting layout and presentation problems that could contribute to the target group misunderstanding statements or questions and/ or being reluctant to complete the questionnaire. Pilot studies thus play an important role in proactively detecting and correcting errors and ambiguities in questionnaires, as described by Taherdoost (Taherdoost, 2016), Laxton (Laxton, 2004) and others, which could adversely influence the quality of data that will be collected.

To ensure that the questions would be correctly interpreted by the target population, the questionnaire was validated by a combination of ten selected medical doctors and pharmacists who fit the description of the target population. The participants of the pilot study were assured of the anonymity and confidentiality of their feedback and participation in the pilot study. Participants were asked how they interpreted the various questions and sections in the questionnaire, whether the questionnaire was clear and easy to understand, and whether the presentation and format were user-friendly and encouraged completion. Patients were also asked to comment on the appropriateness of questions, and whether they thought that additional questions should be included. The questionnaire was amended based on feedback received from the pilot study prior to initial ethics committee submission. In teams of ease of completing the survey, it was estimated that the study survey would take approximately 5-10 minutes to complete, and this was found to be acceptable for surveys typically used in KAP studies.

3.3.2. Enhancing reliability of data

Reliability refers to the consistency of a measure (whether the results can be reproduced under the same conditions) (Roberta Heale, 2015). To enhance the reliability of study data, sampling error and sampling bias must be minimised. Data may be highly precise and consistently reflect a certain response but may be inaccurate if the data-gathering tool has been incorrectly designed, as described (Taherdoost, 2016) (Laxton, 2004). To enhance the reliability of the data, a large sample size of 384 participants was selected and the questionnaire was distributed to more than 7,000 potential participants. The study was tailored for the target population which consists of medical doctors and pharmacists working in South Africa and thus the questions included in the questionnaire were relevant for the target group. To ensure this, the questionnaire was adapted from similar questionnaires used by other researchers who previously conducted studies to assess the

knowledge, attitudes, and practices of pharmacovigilance in different settings (Bharadwaj, 2016) (Kumari, 2015) (Reddy, 2014).

The questionnaire was distributed to medical doctors and pharmacists who work at public or private healthcare facilities and at all professional levels. This minimised sampling bias and thus improved reliability of the study data.

3.3.3. Enhancing validity of data

Although reliability contributes to data integrity, it does not necessarily always lead to validity (Roberta Heale, 2015). Validity reflects the accuracy of data obtained from a sample and can be classified into two types (Laxton, 2004):

(i) Internal validity, which refers to the accuracy of a specific study's findings and the clear illustration of cause-and-effect relationships (Laxton, 2004). Concerns related to internal validity could include whether each respondent had only completed one questionnaire and whether the survey was conducted in a manner that did not influence respondents to respond in a particular way.

(ii) External validity reflects the extent to which the findings of a study can be extrapolated or applied to other situations (Laxton, 2004). External validity could be undermined by the nature of study participants, the time-period or place at which the study is conducted, which all have the potential to make the data obtained unrepresentative of the target population.

Validity in this current study was improved by minimizing bias, with the increase of sample size and diverse population groups. Distributing the questionnaire in the form of an online survey enabled the distribution to a wide number of potential participants, thereby increasing the response rate as well.

3.4 Sampling

3.4.1. Selection of target population and sample size

The healthcare professionals who typically assess and report ADRs in South Africa are medical doctors and pharmacists. Although nurses are likely the first care givers in a position to collect initial reports of new symptoms from hospitalized patients, the treating doctor, as the prescriber, remains ultimately responsible for ensuring the accuracy of such information prior to submitting a potential ADR report.

Medical and pharmaceutical associations were approached to distribute the survey via email to their members; these include the South African Association of Hospital and Institutional Pharmacists (SAAHIP), the South African Association of Pharmacists in Industry (SAAPI), the Independent Community Pharmacy Association (ICPA), the South African Medical Association (SAMA) and the South African Clinical Research Association (SACRA), among others. Only SAMA and SACRA accepted the request and

both associations have representation of HCPs working in private as well as public healthcare sectors across South Africa.

3.4.2. Determining sample size

A previous study conducted in a Ghana, in medical doctors across the country, similar to the current study, estimated the underlying rate of reporting of ADR to be about 59% respectively (Sabblah, 2014). OpenEpi®, a web-based, operating system-independent series of programs for use in epidemiology, biostatistics, public health, and medicine was used to calculate the sample size. A sample size of 334 healthcare professionals was established to be appropriate to estimate the ADR reporting rate, if ADR reporting rate is estimated at 59% with a desired precision of +-5.5%. The sample size was inflated by 15% (from 334 to 38 4) to account for non-response.

3.4.3. Sampling error and bias

The potential for sampling bias was reduced by including all possible sub-groups of the sample population. Participants of all genders, professional levels, racial groups, and working in all categories of healthcare facilities in South Africa, having achieved an undergraduate qualification from any university in South Africa or abroad, were provided with an opportunity to participate in the study, on provision that they were SAMA and/or SACRA members. The size and diversity of the sample population also had a positive impact on the reliability and validity of the study data.

3.5 Ethical clearance procedures

Initial ethics approval was received from Stellenbosch Health Research Ethics Committee on 11 Feb 2019 [**HREC Ref # S18/10/231**]. The initial protocol planned to conduct the study at all nine (9) Academic Hospitals in South Africa. Additional ethical clearance was sought from the Provincial Departments of Health (DoH) in all nine (9) provinces as well as from the Chief Operating Officer (CEO) or Superintendent from each Academic Hospital. After the declaration of a national lockdown, caused by the global Covid-19 pandemic in March 2020, the protocol was updated to change the format of the questionnaires from hard copy questionnaires delivered to the target facilities, to an online survey. Final SU-HREC approval of the amended protocol was obtained on 09 Jun 2020.

Data confidentiality was maintained by not collecting participant identifiers. In the consenting phase of the survey, participants were informed that the purpose of this study is a component of the researcher's master's in science (MSc) degree and that the study was conducted under ethical approval by SU-HREC. Participants were given an option to decline participation without any explanation and consequences. No coercion was used, no incentives were provided, and no reimbursements were offered to participation.

3.6 Study conduct

The survey was created in the SurveyMonkey® online survey system. The survey was shared with the relevant parties at SAMA and SACRA in the form of a Uniform Resource Locator (URL) link for distribution to their respective members. Data collection occurred over a period of five (5) months.

3.7 Data analysis and reporting

Data was downloaded from the SurveyMonkey® system in Microsoft Excel 2016 ™ format and manually coded. The raw dataset was cleaned, by grouping universities where respondents achieved their undergraduate qualifications into *"local, low-to-middle income and European"* and by categorising knowledge scored into *"good, average, and low"*. The data was then coded with numerical values. Once coded, descriptive data analysis was performed using IBM SPSS® Statistics version 27.

Categorical variables were summarised as count (percent) and presented graphically as bar graphs. To determine factors associated with ADR reporting, a binomial regression was performed. Due to the outcome of ADR reporting being common (>50%) the appropriate measure of association was risk ratio, and this was estimated using a multivariate binomial regression model (Mancl, 2013). A univariate binomial regression was used to confirm if each variable is related to ADR reporting (Smith, 2018). A cut of p=value of $p < 0.1$ was used to select variables to be included in the multivariate binomial regression model. This cut off point was selected to remain conservative in order not to exclude any variables early, that could be significant in the multivariate binomial regression model after adjusting for confounding. Such a cut-off is a standard and typically used when aiming to remain conservative. Although the cut-off p-value was applied, some variables with $p > 0.1$ were also included if they are known to have a potential association with ADR reporting. in the multivariate binomial regression model, a p-value of $p < 0.05$ was considered statistically significant. The estimates were reported with the corresponding 95% confidence intervals.

CHAPTER 4
Data analysis and results

4.1 Introduction

This chapter presents the results obtained from this study. Most of the results are presented in the form of frequencies and appear in either tabular or graphic form. Associations among variables were tested using a binomial regression model. Pearson chi-squared tests were performed to analyse the association between the knowledge category and the baseline characteristics; however, none of the results were significant; therefore, the data was not shown.

4.2 Data collection process

Over 7,000 surveys were emailed to members the South African Medical Association (SAMA) and the South African Clinical Research Association (SACRA), respectively. From these, 325 responses were received within a period of five (5) months, providing for a sample response rate of 85%.

Table 4-1: Summary of data collection process

Month no.	Number of responses received
1	27
2	134
3	132
4	29
5	3
TOTAL	**325**

4.3 Demographics

The majority (164; 50.5%) of the respondents were male, whereas (161; 49.5%) were female, with a mean age of 48 years from 324 respondents who specified their age. The highest proportion of the respondents (157; 48.3%) were employed at private healthcare facilities, followed by public facilities (120; 36.9%), private-public facilities (20; 6.2%) and clinical research sites (16; 4.9%). A small portion of respondents (12; 3.7%) did not specify the type of healthcare facilities where they worked.

The highest number (137; 42.2%) respondents consult less than 14 patients a day, followed by those who consult 15-19 patients (69; 21.2%), 20-25 (47; 14.5%), more than 35 patients (30; 9.2%). Those who consulted 25-35 patients a day ranged from 16-21 (4.9-6.5%). Some respondents did not specify the number of patients they consult per day (5; 1.5%).

Most of the respondents were medical doctors (298; 91.7%), across several professional levels, including medical interns (12; 3.7%), general practitioners (27; 8.3%), medical

officers (126; 38.8%) and medical specialists (133; 40.9%). The total number of pharmacists were (24; 7.4%). Three (3; 0.9%) respondents did not indicate their profession. Most respondents achieved their undergraduate qualifications at South African universities (298; 91.7%). Those who graduated from European universities were (12; 3.7%). Universities within low-to-middle income countries (LMIC's) were grouped to exclude South African universities. Like those who graduated at European universities, a low (10; 3.1%) of respondents had graduated from LMIC universities. A small number (5; 1.5%) of respondents did not specify the university where they achieved their undergraduate qualifications.

Table 4-2: Frequency distributions of demographic characteristics (N = 325)

Demographic Characteristic	**Summary**
Gender, n (%)	
Male	164 (50.5%)
Female	161 (49.5%)
Age (n)	324
Health facility, n (%)	
Public	120 (36.9%)
Private	157 (48.3%)
Private and Public	20 (6.2%)
Research Site	16 (4.9%)
Not specified (NS)	12 (3.7%)
Number of patients served per day n (%)	
< 14	137 (42.2%)
15-19	69 (21.2%)
20-24	47 (14.5%)
25-29	21 (6.5%)
30-34	16 (4.9%)
> 35	30 (9.2%)
Not specified (NS)	5 (1.5%)
Professional level, n (%)	
Medical Intern	12 (3.7%)
General Practitioner	27 (8.3%)
Medical Officer	126 (38.8%)
Pharmacist	13 (4.0%)
Senior Pharmacist	11 (3.4%)
Medical Specialist	133 (40.9%)
Not specified (NS)	3 (0.9%)
University of graduation, n (%)	
Local University	298 (91.7%)
European Union University	12 (3.7%)
Low to Middle Income Country (LMIC) University, excluding South African Universities	10 (3.1%)
Not specified (NS)	5 (1.5%)

Table 4-3: Breakdown of number of patients seen per day by facility type

Characteristic	**Facility**				
Number of patients served per day	**Public n (%) (n =120)**	**Private n (%) (n=157)**	**Public & Private n (%) (n=20)**	**Research Site n (%) (n=16)**	**NS n (%) (n=12)**
< 14	47 (39.2%)	64 (40.8%)	9 (45%)	**12 (75%)**	5 (41.7%)
15-19	17 (14.2%)	42 (26.8%)	5 (25%)	1 (6.25%)	3 (25%)
20-24	23 (19.2%)	19 (12.1%)	5 (25%)	1 (6.25%)	0
25-29	9 (7.5%)	10 (6.4%)	0	1 (6.25%)	0
30-34	6 (5%)	10 (6.4%)	0	0	1 (8.3%)
> 35	**16 (13.3%)**	**10 (6.4%)**	1 (5%)	1 (6.25%)	2 (16.7%)
Not specified (NS)	2 (1.7%)	2 (1.3%)	0	0	1 (8.3%)

Most respondents who consulted less than 14 patients a day were employed at clinical research sites (12; 75%). There was a small difference in the proportion of healthcare practitioners (HCPs) consulting less than 14 patients a day, among those working at private, public or combination private-public facilities. Among HCPs consulting >35 patients a day, a slightly higher proportion (16; 13.3%) worked at public compared to those who worked at private healthcare facilities (10; 6.4%), respectively.

4.4 Knowledge

It was noted during data cleaning that knowledge question no. 7 (what document is used when for ADR reporting in South Africa?) was omitted from the survey erroneously. The knowledge scores ranged between 2-9, with a mean of 6.25. The *good* category was allocated to a score of 8-10, *average* was a score of 5-7 and *poor* was ≤4. Most of the respondents scored *average* for knowledge (252; 77.5%), followed by *good* knowledge (45; 13.8%) and *poor* knowledge at (28; 8.6%). Most of the study participants (310; 95.4%) understood and knew the purpose of pharmacovigilance (PV).

Table 4-4: Summary of knowledge categories

Knowledge Category	**Summary** n (%)
Good (8-10)	45 (13.8)
Average (5-7)	252 (77.5)
Poor (≤4)	28 (8.6)

Table 4-5: Knowledge-related questions and scores

Knowledge Question	**Correct response, n (%)**
1. Select a definition of pharmacovigilance	90 (27.7%)
2. The most important purpose of pharmacovigilance	**278 (85.5%)**
3. Is it your professional obligation to report ADRs?	**310 (95.4%)**
4. Where is the pharmacovigilance unit situated in South Africa?	189 (58.2%)
5. What does NADEMC stand for?	**232 (71.4%)**
6. What is the name of the international centre for ADR monitoring?	88 (27.1%)
8a. Tick all the applicable minimum information required when reporting an ADR: *An identifiable source (reporter) of the information.*	**285 (87.7%)**
8b. Tick all the applicable minimum information required when reporting an ADR: *An identifiable patient.*	**245 (75.4%)**
8c. Tick all the applicable minimum information required when reporting an ADR: *Suspected medicine(s).*	**314 (96.6%)**
8d. Tick all the applicable minimum information required when reporting an ADR: *Patient home address.*	**244 (75.1%)**

Although very few respondents selected the correct definition for PV (90; 27.7%) and provided the correct name of the international centre for ADR monitoring (88; 27.1%), more respondents were familiar with the NADEMC. Over eighty percent (278; 85.5%) knew what the purpose of PV is and the highest proportion (310; 95.4%) agreed that ADR reporting was their professional obligation. Most of the participants were aware of the minimum information required when reporting a suspected ADR, ranging from 244-314 (75.1 – 96.6%).

Table 4-6: Background characteristics for knowledge

Characteristic	**Knowledge, n (%)**		
	Poor (n=28)	Average (n=252)	Good (n=45)
University of graduation, n (%)			
Local university	**28 (100%)**	228 (90.5%)	42 (93.3%)
European Union (EU) University	0	**11 (4.4%)**	1 (2.2%)
Low to Middle Income Country (LMIC) university	0	**9 (3.6%)**	1 (2.2%)
Not specified (NS)	0	4 (1.6%)	1 (2.2%)

Pearson chi-squared tests were performed to analyse the association between the knowledge category and the baseline characteristics summarised in table 4.2 was performed. None of the results were significant (data not shown). None (0; 0%) of the respondents who achieved their undergraduate qualifications at European and / or LMIC universities had poor knowledge. Poor knowledge occurred most frequently with respondents who qualified at South African universities (28; 100%).

4.5 Attitudes

Most respondents (320; 98.5%) agreed that reporting of adverse drug reactions is necessary. Above eighty percent (287; 88.3%) of the respondents admitted that they are concerned about the risks associated with medicines. Over half (193; 59.4%) of the respondents reported that they do have time to report suspected ADRs. A high proportion (231; 71.1%) of respondents admitted that it may be difficult to accurately detect whether an adverse drug reaction has occurred. Most of the respondents (269; 82.8%) thought that awareness regarding pharmacovigilance in their professional environment is inadequate.

Table 4-7: Attitudes-related questions and scores

#	Question	Yes n (%)	No n (%)	Unfamiliar n (%)
1	Do you think reporting of adverse drug reactions is necessary?	**320 (98.5%)**	1 (0.3%)	4 (1.2%)
2	Do you have any concern about the risk(s) associated with medicines you prescribe?	**287 (88.3%)**	31 (9.5%)	7 (2.2%)
3	Do you think you have time to report suspected ADRs?	**193 (59.4%)**	106 (32.6%)	25 (7.7%)
4	Do you think it may be difficult to accurately detect whether an adverse drug reaction has occurred?	**230 (71%)**	82 (25.2%)	12 (3.7%)
5	Do you think there's adequate awareness regarding pharmacovigilance in your professional environment?	51 (15.7%)	**269 (82.8%)**	7 (2.2%)

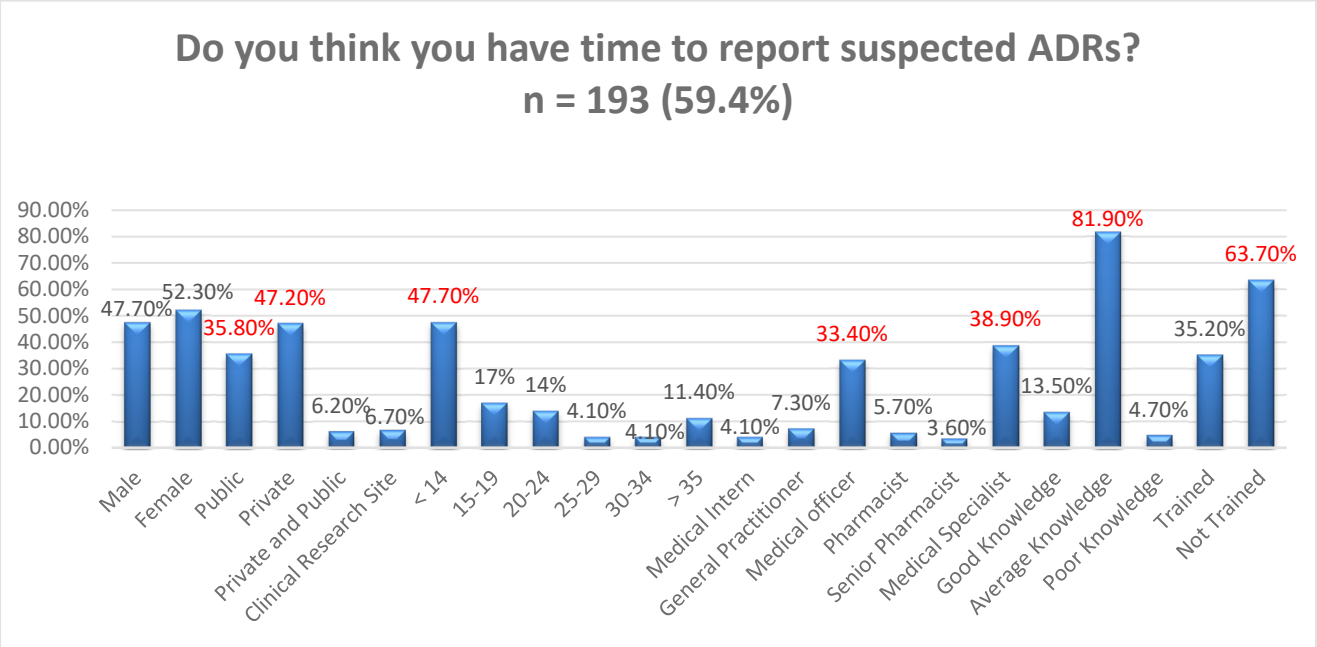


Figure 4-1: Background characteristics of those who have time for ADR reporting

From the (193; 59.4%) respondents who reported that they have enough time for ADR reporting, a slightly higher proportion were females (101; 52.3%). Of the 193 respondents, most are working at private healthcare facilities (91; 47.2%), closely followed by those working at public healthcare facilities (69; 35.8%). Those who consult less than 14 patients a day, made up (92; 47.7%) of the respondents. Of the respondents who admitted to having

time for ADR reporting, (75; 38.9%) were medical specialists, and (76; 33.4%) were medical officers, (123; 63.7%) had never received training on ADR reporting and (158; 81.9%) of them had an average level of knowledge on PV.

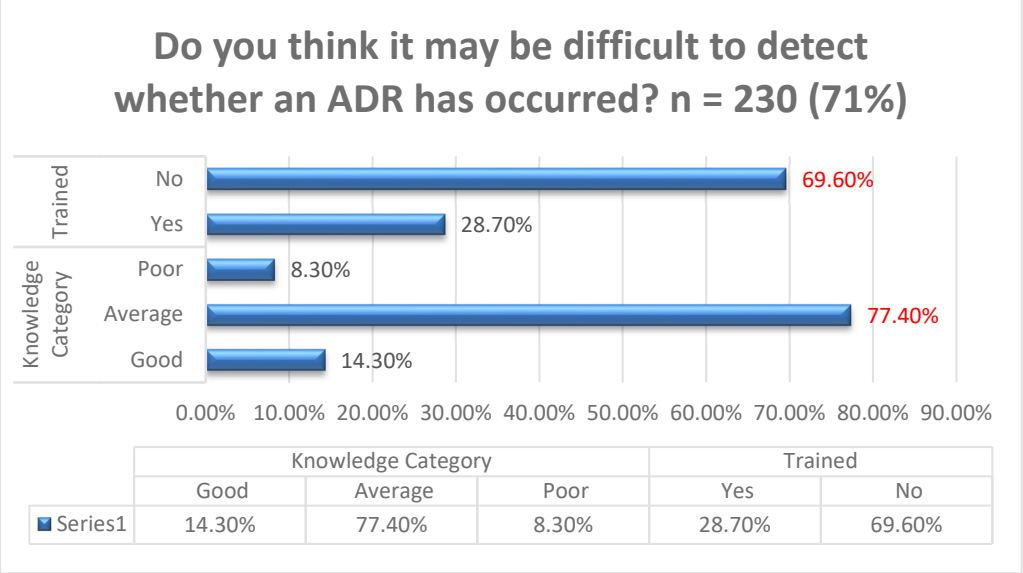


Figure 4-2: Knowledge and training breakdown of those who noted that it was difficult to identify ADRs

From the (230; 71%) respondents who agreed that it is difficult to detect whether an adverse drug reaction has occurred, the majority (160; 69.6%) had never received ADR reporting training, yet a high proportion of them (178; 77.4%) were found to have an average knowledge level.

4.6 Practices

Most of the respondents (266; 81.8%) have previously encountered an ADR in a patient. More than sixty percent (206; 63.4%) have seen an ADR reporting form before and (172; 52.9%) have previously reported an ADR. Of the (152; 46.8%) who have not previously reported an ADR, (65; 20.0%) responded that they were not aware of the reporting procedure, (31; 9.5%) mentioned that the ADR reporting form was not available in the facilities of their employment, (26; 8.0%) have never been able to identify an ADR and (25; 7.7%) did not know that they were supposed to report ADRs. An extremely low (91; 28%) had been trained on ADR reporting previously and (229; 70.5%) had not been trained on ADR reporting previously. Five (5; 1.5%) of the respondents did not provide a response to this question.

Table 4-8: Practices-related questions and scores

#	Questions	Yes n (%)	No n (%)	Not Sure n (%)	Other n (%)
1.	Have you ever encountered an adverse drug reaction in your patient in professional practice?	266 (81.8%)	39 (12%)	20 (6.2%)	0
2.	Have you ever seen an ADR reporting form?	206 (63.4%)	119 (36.6%)	0	0
3.	Have you ever reported a suspected adverse drug reaction?	172 (52.9%)	152 (46.8%)	0	0
4a	If your answer to the above question was "no", select the most appropriate reason(s) below: *The reporting form was not available*	0	0	0	31 (9.5%)
4b	If your answer to the above question was "no", select the most appropriate reason(s) below: *I have never been able to identify an adverse drug reaction*	0	0	0	26 (8.0%)
4c	If your answer to the above question was "no", select the most appropriate reason(s) below: *I am/was unaware of the reporting procedure*	0	0	0	65 (20.0%)
4d	If your answer to the above question was "no", select the most appropriate reason(s) below: *I did not know I was supposed to report*	0	0	0	25 (7.7%)
5.	Have you ever been trained on how to report suspected adverse drug reactions?	91 (28%)	229 (70.5%)	0	0

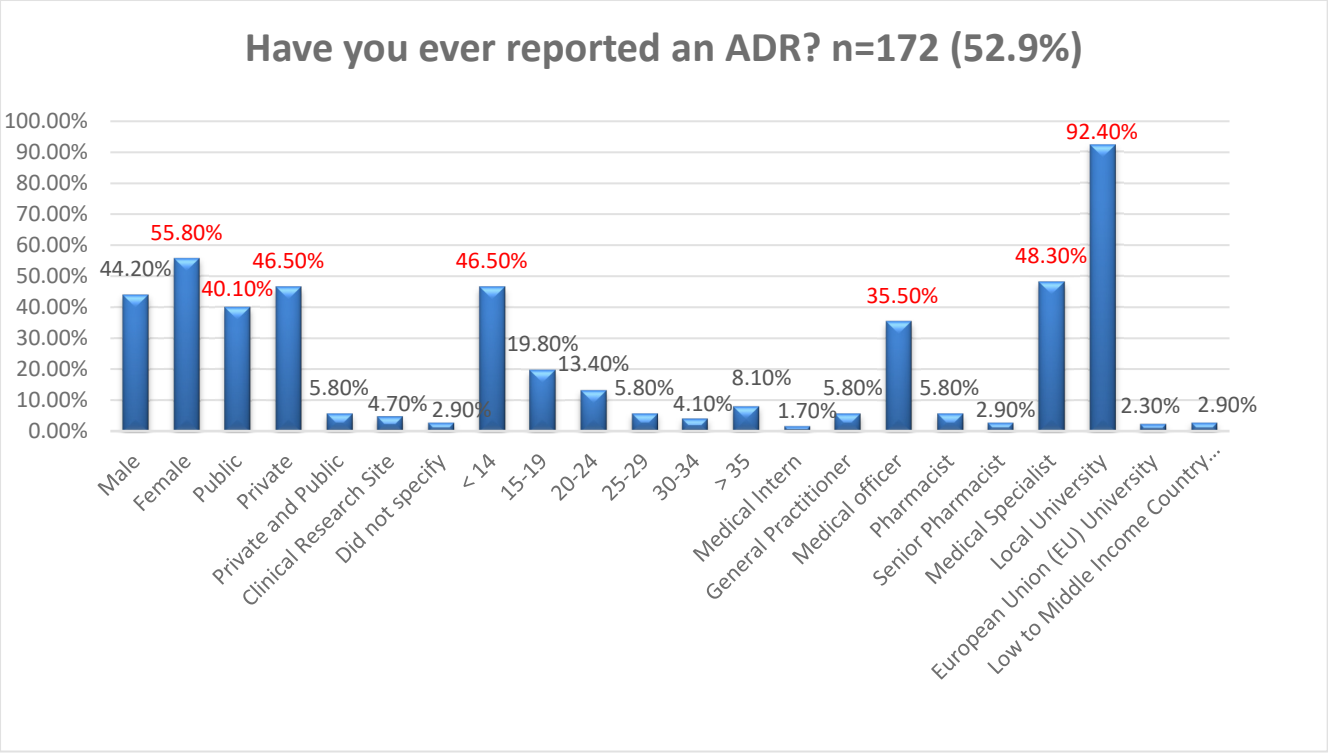


Figure 4-3: Background characteristics of respondents participating in ADR reporting

Of those respondents contributing to ADR reporting (172; 52.9%), a slightly higher proportion were females (96; 55.8%), work at private healthcare facilities (80; 46.5%) and consult less than 14 patients a day (80; 46.5%) respectively. Most (83; 48.3%) were medical specialists, followed by medical officers (61; 35.5%) and the majority (159; 92.4%) achieved their undergraduate qualifications at local South African universities.

Table 4-9: Factors associated with ADR Reporting – Multivariate binomial regression.

Baseline Characteristics	Univariate Binomial Regression Model			**Multivariate Binomial Regression Model**		
	Unadjusted Risk Ratio (RR)	p-value	95% Confidence Interval (95% CI)	**Adjusted Risk Ratio (RR)**	**p-value**	**95% Confidence Interval (95% CI)**
Gender, n (%)						
Male	1 (Ref)			**1 (Ref)**		
Female	1.29	0.02	1.05 1.59	**1.26**	**0.001**	**1.10 1.44**
Professional level, n (%)						
Medical Intern	1 (Ref)			**1 (Ref)**		
General Practitioner	1.48	0.48	.49 4.43	**1.91**	**0.22**	**.68 5.35**
Medical officer	1.94	0.19	.71 5.25	**2.29**	**0.09**	**.88 5.95**
Pharmacist	3.08	0.03	1.10 8.57	**2.84**	**0.03**	**1.10 7.29**
Senior Pharmacist	1.82	0.32	.56 5.88	**1.50**	**0.49**	**.47 4.81**
Medical Specialist	2.52	0.07	935 6.76	**3.16**	**0.02**	**1.23 8.13**
Training, n (%)						
No	1 (Ref)			**1 (Ref)**		
Yes	1.78	<0.001	1.48 2.14	**1.84**	**<0.001**	**1.57 2.15**
Knowledge Category, n (%)						
Poor	1 (Ref)			**1 (Ref)**		
Average	1.34	0.22	.97 2.70	**1.08**	**<0.001**	**1.08 1.08**
Good	1.62	0.07	.83 2.16	**1.04**	**<0.001**	**1.04 1.04**

The prevalence of ADR reporting amongst the respondent was found to be common at 52.9%. The appropriate regression approach to estimate the risk ratio of ADR reporting was a binomial regression model. A univariate binomial regression was initially performed to confirm which individual characteristics could be included in the multivariate binomial regression model. A significant probability of $p = 0.1$ was used as a cut-off point to select variables to be included in the multivariate regression model. This is a standard cut-off point commonly used in descriptive statistics, and it is used to remail conservative, thus avoiding exclusion of variables which could become significant when included into the multivariate regression model. Variables which are known, through literature, to have a possible association with ADR reporting were included with $p > 0.1$ to ensure that they were included in case are significant when included in the multivariate binomial model, when adjusting for confounding. The variables selected were gender, professional level, ADR training, and level of knowledge. Facility type and number of patients consulted with per day were excluded

from the multivariate regression model due to p-values which were far greater than the cut off pint of p = 0.1. In the multivariate binomial regression, a p-value of p < 0.05 was considered statistically significant.

The multivariate regression results showed that females were 26% (RR = 1.26) more likely to report ADRs than males (p < 0.001). Medical specialists were more than three times (RR = 3.16) more likely to report ADRs than their colleagues from other professional levels (p < 0.017). Across the different professions, the likelihood of pharmacists to report ADRs was more than double (RR = 2.84) compared to medical interns (p < 0.030). Those who received training on ADR reporting were almost more than twice likely (RR = 1.84) to participate in ADR reporting than those who did not receive any training (p < 0.001). Respondents with average knowledge on PV were 8% more likely (RR = 1.08), and those with good knowledge were 4% more likely (R = 1.04) to report ADRs than those with poor knowledge (p < 0 .001).

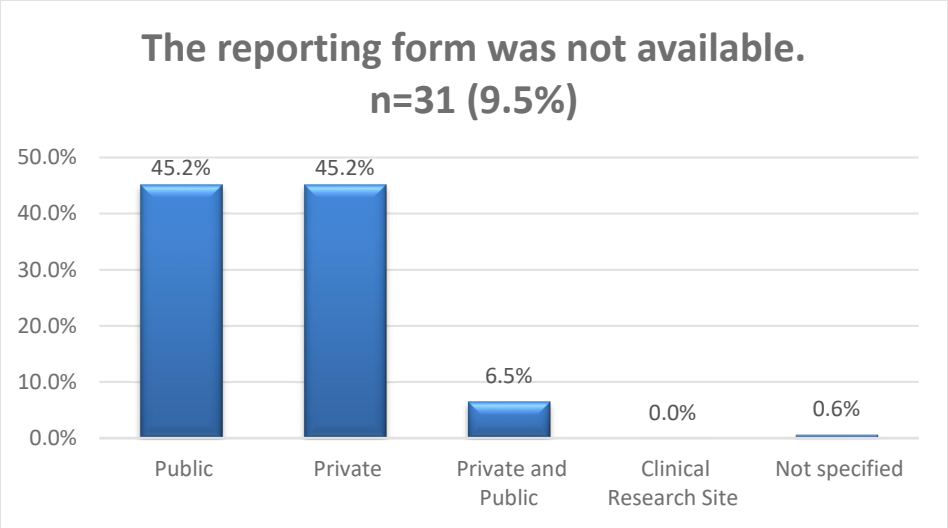


Figure 4-4: Type of facility breakdown of those who noted that the reporting form was not available

Respondents who noted that ADR reporting forms are not available in their workplace were equally distributed between private-public healthcare facilities (14; 45.2%). None (0; 0%) of the respondents working at clinical research sites and a small portion (2; 6.5%) of those working at private-public healthcare facilities noted that the ADR reporting form was not available in their workplace.

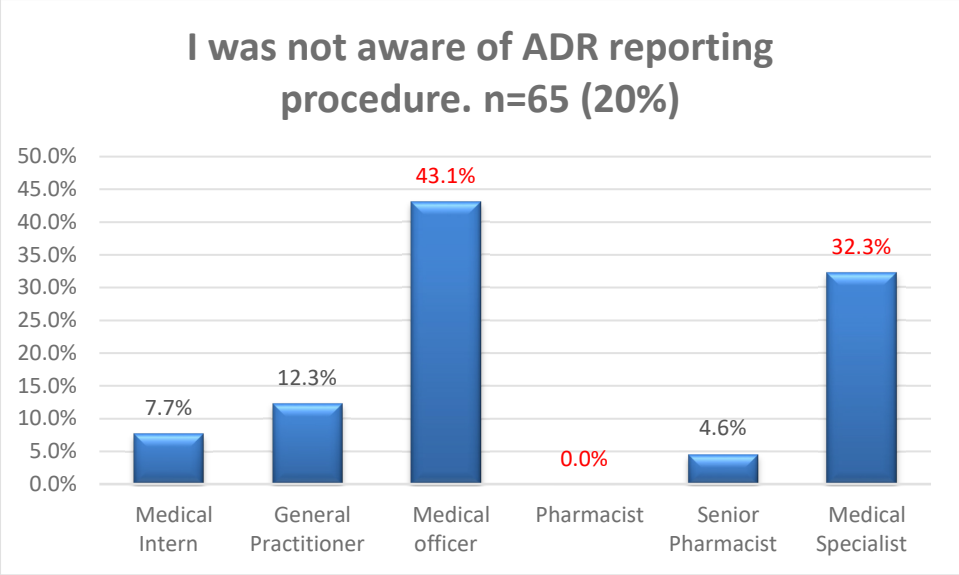


Figure 4-5: Professional level characteristics of those who answered that they were not aware of the reporting procedure

Of the (65; 20%) who responded that they were not aware of the ADR reporting procedure, (28; 43.1%) were medical officers and (21; 32.3%) were medical specialists. None (0; %) of the pharmacists reported that they were not aware of the ADR reporting procedure.

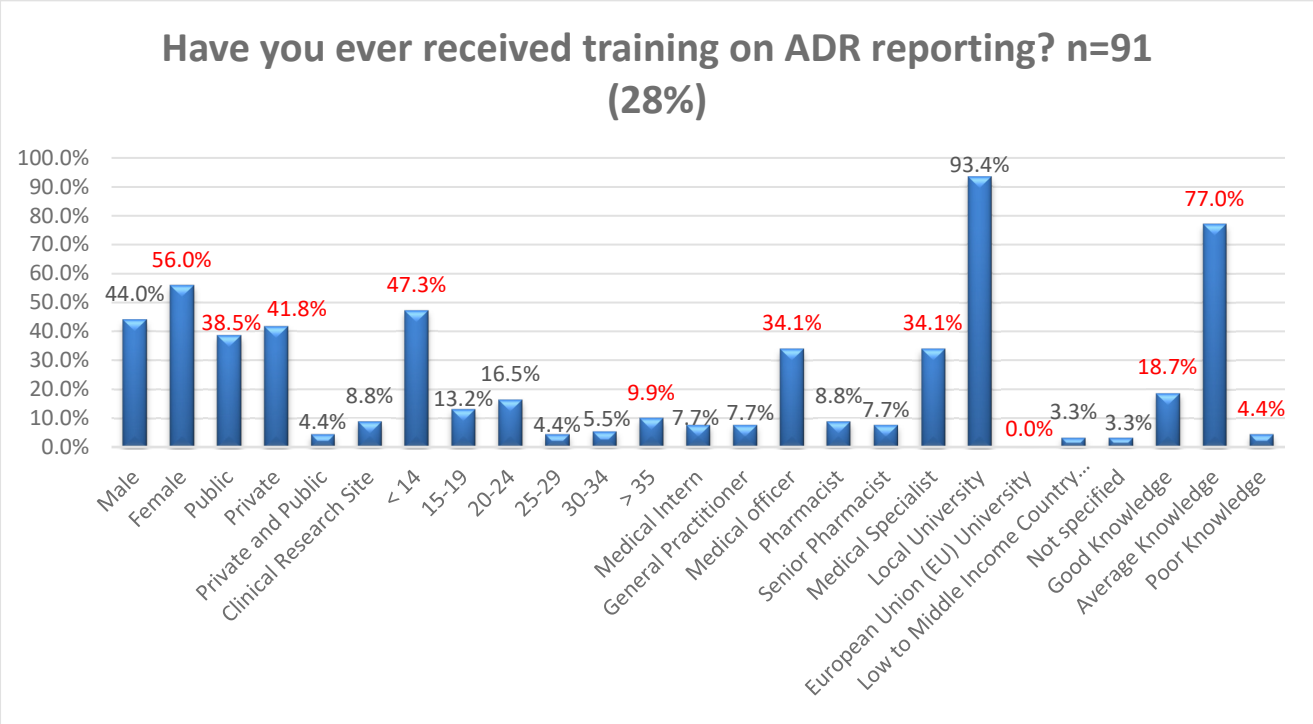


Figure 4-6: Background characteristics of those who have received training on ADR reporting.

A slightly higher proportion of females (51; 56%) than males (40; 44%) had previously received training on ADR reporting. A small difference was noted between those working in private (38; 41.8%) and public (35; 38.5%) healthcare facilities. Most consulted less than 14 patients a day (43; 47.3%). Those who consulted more than 35 patients (9; 9.9%) were a

higher proportion than those who serve between 25 to 34 patients a day (ranging from 4.4 – 5.5%). There was an equal distribution (31; 34.1%) of medical officers and specialists who had previously received training on ADR reporting. None (0; 0%) of the respondents who qualified at European universities had received ADR reporting training previously. Of the respondents who were previously trained on ADR reporting, (4; 4.4%) had poor knowledge, (17;18.3%) had good knowledge (70; 77%) had average knowledge.

4.7 Suggestions

The method that could potentially improve ADR reporting in South Africa selected by most of the respondents (266; 81.8%), was the inclusion of PV training to the undergraduate curricula at universities. More than seventy percent (235; 72.3%) of respondents agreed that implementation of on-line or telephonic ADR reporting could potentially increase reporting rates. Other suggestions included continuous and refresher training (226; 69.5%), and frequent communication and feedback from national PV centres (220; 67.7%). Only (45; 13.8%) of the respondents suggested remuneration for ADR reporting.

Table 4-10: Suggestions from study participants on promoting PV

#	**Suggestions**	**N (%)**
1	Include Pharmacovigilance training to the undergraduate curricula at Universities.	**266 (81.8%)**
2	Provide continuous & refresher training.	**226 (69.5%)**
3	Increase awareness on ADR reporting of patients, prescribers, and dispensers by the relevant Authorities at a National level.	171 (52.6%)
4	Implement a pharmacovigilance centre within each hospital.	159 (48.9%)
5	Provide frequent communication & feedback from pharmacovigilance centres with updates on the benefit-risk profiles of drugs resulting from ADR reporting efforts.	**220 (67.7%)**
6	Have an ADR specialist in each hospital department?	50 (15.4%)
7	Implement on-line or telephonic reporting.	**235 (72.3%)**
8	Collaboration among all healthcare professionals (Doctors, Pharmacists, Nurses, etc.) is required in the reporting process, i.e., completing the reporting forms.	194 (59.7%)
9	Implement departmental meetings to discuss potential ADRs.	111 (34.2%)
10	Implement remuneration for each reported ADR case.	**45 (13.8%)**

4.8 Additional explorative associations

1. An analysis of the following additional explorative associations, as stipulated in the study protocol (Methods Section 5.4.2, page 18 and 19) was performed; however, none of them were significant (data not shown).

2. If professional level has an influence on whether the participants think it may be difficult to detect an ADR.

3. Comparing the type of facility where the participants work and whether they have ever reported a suspected adverse drug reaction.

4. Comparing the number of patients served on an average day and whether the participants have encountered an adverse drug reaction in their patient in professional practice.

5. Comparing the universities where the participants achieved their undergraduate degree and the total knowledge score/percentage of participants per university.

6. Comparing those who agreed that pharmacovigilance is their professional obligation with whether they have ever reported a suspected ADR.

CHAPTER 5
Discussion

5.1 Introduction

This chapter discusses the results obtained in the research study. A comparison was made with results obtained in similar peer reviewed studies to highlight similarities and notable differences. The significance and possible implications of the study results will be discussed. Limitations of the study which came to light upon analysing the study results will be outlined.

5.2 Demographics

A total of 325 completed responses were received from members the South African Medical Association (SAMA) and the South African Clinical Research Association (SACRA), equating to 85% of the target sample size. This is a higher response rate than was achieved in similar studies conducted in South Africa (68.9%) amongst community and hospital pharmacists in the North West Province (Joubert M, 2016), (78.5%) amongst nurses and pharmacists working in a private hospital (Bogolubova, 2018) and lower but similar to those achieved in other similar studies in South Africa (87.7%) amongst doctors, nurses and pharmacist working in a tertiary hospital in Johannesburg (Gordhon Y, 2020), (91.7%) in healthcare practitioners (HCPs) working in primary healthcare facilities (Haines, 2020).

A little over half (164; 50.5%,) of the respondents were male, (298; 91.7%) were medical doctors, across several professional levels, ranging from medical interns to medical specialists; (24; 7.4%) were pharmacists. Amongst the medical doctors, most of them were medical specialists (133; 40.9%). Just above forty percent (137; 42.2%,) of all respondents consult < 14 patients per day. Most of the respondents (298; 91.7%,) obtained their undergraduate qualifications at local South African universities and inclusively, (308; 94.8%) at universities in low to middle income countries.

5.3 Knowledge

The primary objective of this study was to determine the knowledge on pharmacovigilance, among medical doctors and pharmacists in South Africa. The results indicate that there is an average level of knowledge on pharmacovigilance among medical doctors and pharmacists in South Africa. The knowledge scores achieved by participants in this study ranged between 2-9, with a mean of 6.25 and a range of 7. Knowledge scores were categorized into *good*, *average,* and *poor*. The *good* category was allocated to a score of 8-10; an *average* category was allocated to a score of 5-7 and a *poor* category to a score of ≤ 4. Most of the study participants (252;77.5%) achieved an average score for knowledge, followed by a good knowledge score at (45; 13.8%) and a poor knowledge score at (28; 8.6%).

Medical specialists comprised the largest proportion of those having average knowledge (102; 40.5%) followed by medical officers (96; 38.1%); whereas in other similar studies, with the same objectives, pharmacists had a higher knowledge on ADR reporting compared to medical doctors. This is likely due to the higher number of doctors on current study (298; 91.7%) compared to pharmacists (24; 7.4%) participating in this current study. A 2020 study

conducted in South Africa by Haines *et al.* (Haines, 2020), reported higher mean knowledge scores for pharmacists (91.4%; $p = 0.003$) compared to nurses (84%; $p < 0.0001$) and medical doctors (82.8%; $p = 0.017$). Another South African study conducted by Gordhon and Padayachee in 2020 (Gordhon Y, 2020), reported that 83% of pharmacists, compared to 54% of doctors and 54% of nurses stated that they knew how to report ADRs.

In similar studies from other parts of Africa, a study conducted in Nigeria by Ezeuko *et al.* (Ezeuko, 2015), with the representation of pharmacists at 22 participants, compared to 24 in this current study, it was reported that pharmacists were more aware of ADR reporting at 81.8% of the participants and the difference in awareness among the respondents was statistically significant ($p < 0.001$). In another Nigerian study by Emeka and Badger-Emeka [149] (Emeka, 2017), in which the sample population included pharmacists only, three quarters (75%) of the respondents were knowledgeable ($p = 0.046$) and most of them (85%) were familiar with the signs and symptoms that could be exhibited by a patient suffering from an ADR ($p = 0.006$). These findings are further supported by Ezeuko *et al.* (Ezeuko, 2015) in their reporting on more pharmacists (90.9%) compared to nurses (85.3%) and doctors (83.5%), believing that ADR reporting is their professional responsibility. If pharmacists believe that it is their professional responsibility to report ADRs, they probably take it upon themselves to remain informed on how to identify and report ADRs.

In terms of individual knowledge related questions, only (90; 27.7%) of the respondents selected the correct definition for pharmacovigilance, compared to 45% in a similar study conducted by Joubert & Naidoo in South Africa in 2016 (Joubert M, 2016). It should be noted that the ability to select the correct definition for pharmacovigilance may not necessarily be the best way to measure a respondent's knowledge on the subject, because as new developments in the field of pharmacovigilance transpired, the definition and scope of pharmacovigilance have also evolved. It is therefore appreciated that while healthcare professionals may be familiar with the concept of pharmacovigilance, they may not know the correct definition thereof. This is evidenced by the (278; 85.5%) respondents who knew that the purpose of pharmacovigilance is to enhance patient care and patient safety in relation to the use of medicines. This also explains why (310; 95.4%) agreed that it is their professional obligation to report ADRs and consistent with the 89% reported by Haines *et al.* (Haines, 2020), who also reported that 92.5% of respondents in his study were aware that ADRs must be reported.

Studies from other LMICs outside of South Africa also supported this notion. In the 2015 study by Ezeuko and colleagues (Ezeuko, 2015) conducted across a combination of public and private healthcare facilities in Nigeria (Ezeuko, 2015), 85.8% of the respondents, including doctors, pharmacists, and nurses, agreed that ADR reporting is their professional responsibility. A 2017 study in India by Srinivasan *et al.* (Srinivasan, 2017), reported that nearly 83.9% of the respondents felt that reporting is necessary. A 2014 study in Ghana by Sabblah *et al.* (Sabblah, 2014) found that 96.4% of medical doctors participating in the study, agreed that it is not only their responsibility, but that of other HCPs as well.

Over seventy percent of respondents (232; 71.4%) knew what NADEMC stands for. This score is higher than those reported in a similar 2016 study by Joubert & Naidoo (Joubert M, 2016), where about half (49%) of the participants answered this question correctly. Considering the time difference between the current study and the 2016 study, it is possible that with more studies being conducted covering the topic of pharmacovigilance, awareness has increased amongst HCPs.

5.4 Attitudes

Most respondents (320; 98.5%,) agreed that reporting of adverse drug reactions is necessary. A similar 2018 study by Bogolubova *et al.* (Bogolubova, 2018), conducted at private hospitals and clinics in the Gauteng Province, reported that three-quarters of the participants (76%) thought that reporting ADRs was particularly important. Bogolubova *et al.* (Bogolubova, 2018) also reported that in the opinion of over 80% of respondents "it is important to report ADRs to help establish the safety of new drugs" and "to identify new ADRs". When asked if they have any concern about the risk(s) associated with medicines, almost ninety percent (287; 88.3%) of the respondents agreed they are concerned. This is encouraging as it indicates that the importance of ADR reporting is well understood by HCPs in South Africa.

Almost 60% (193; 59.4%) of the respondents reported that they do have time to report suspected ADRs. From this group, a slightly higher proportion (101; 52.3%) were female. An almost equal number of 47.2% and 47.7% were working at private health facilities and consulted <14 patients a day, respectively. Medical officers and specialists were the highest number of HCPs who admitted to having time to report ADRs, ranging between 33.4 – 38.9%. The majority (158; 81.9%) of HCPs within this group had average knowledge on ADR reporting. Medical officers and specialists were also equally distributed (31; 34.1%) as the highest proportion of respondents who had received training.

Over seventy percent (231; 71.1%) of respondents admitted that it may be difficult to detect an ADR. Srinivasan *et al.* (Srinivasan, 2017), reported that a low number (35.2%) of their study respondents admitted that it was difficult to detect whether ADR has occurred or not. Emeka *et al.* (Emeka, 2017) reported that 45% cited this as a barrier for ADR reporting. The same concern was raised by 47.5% of medical doctors in a Nigerian study by Oshikoya and Awobusuyi (Oshikoya, 2009).

Most of the respondents (269; 82.8%) in the current study thought that awareness regarding pharmacovigilance in their professional environment is inadequate. In the 2017 study by Srinivasan *et al.* (Srinivasan, 2017), 91.3% of the participants agreed that pharmacovigilance should be taught in detail to healthcare professionals.

5.5 Practices

Of all 325 respondents, (229; 70.5%) have never received PV training and only (91; 28%) had received training. From this sub-group, an equal number (34.1%) of medical officers and medical specialists had received training. None of the 12 study participants who completed their undergraduate qualifications in European universities had received training previously. This is contrary to the assumption that PV training is incorporated into European university curricula, unlike at LMIC universities. The majority (70; 77%) of the respondents who have been trained had average knowledge and only (17;18.7%) had good knowledge. Despite having received training, (4; 4.4%) had poor knowledge. The low rate of training is consistent with findings from similar studies across South Africa as reported on by Gordhon and Padayachee (Gordhon Y, 2020), Bogolubova *et al.* (Bogolubova, 2018) and Joubert and Naidoo (Joubert M, 2016). Similar findings were reported in Ghana, where Sabblah *et al.* (Sabblah, 2014) reported that only 27.4% of the medical doctors, participating in the study, had received training. In the study by Srinivasan *et al.* (Srinivasan, 2017), 64.3% of the respondents had received training, in comparison to a mere 28% in the present study. Although a higher number of HCPs in the Srinivasan study had received training, a lower number (36.5%) had participated in ADR reporting, despite 89.5% of them having expressed their willingness to report. These factors

raise questions about the type of training received and whether comprehension was assessed during training.

In this current study, training, gender, professional level, and level of knowledge were found to be associated with the likelihood of participating in ADR reporting and all observations reached statistical significance. This is consistent with the Sabblah *et al.* study (Sabblah, 2014), where training was found to significantly improve ADR reporting ($p < 0.001$) and medical officers and medical specialists were more likely to report ($p = 0.035$). Bogolubova *et al.* (Bogolubova, 2018) also concurred that those who had received training were more likely to understand ADR reporting procedures ($p < 0.001$).

Most of the respondents (266; 81.8%,) have previously encountered an ADR in a patient. This finding is and improvement from other studies. In a 2020 study conducted in South Africa by Gordhon and Padayachee (Gordhon Y, 2020), 59% respondents reported that they had encountered ADRs; however, a much lower (17%) proportion had participated in ADR reporting. An Indian study by Srinivasan *et al.* (Srinivasan, 2017), and a Ghanaian study by Sabblah *et a*l. (Sabblah, 2014), both reported that 59.5% of the respondents in their studies, previously encountered an ADR in a patient.

In this current study, a surprisingly high number of respondents (36.6%) had never seen an ADR reporting form before. This is slightly higher than the 24.8% in the study by Srinivasan *et al.* (Srinivasan, 2017). Approximately half (172; 52.9%;) of the study participants have previously reported an ADR. A similar, but slightly lower 44.1% was reported by Joubert and Naidoo (Joubert M, 2016) in 2016. This is higher than the 18% in the 2018 study published by Bogolubova *et al.* (Bogolubova, 2018), 36.5% in the 2017 study by Srinivasan *et al.* (Srinivasan, 2017) and 20% in the 2014 study by Sabblah *et al*. (Sabblah, 2014).

Of the (152; 46.8%) who have not previously reported an ADR, the highest reason cited was a lack of knowledge of the reporting procedure (65; 20.0%). This is consistent with the finding of 28.5% of respondents by Sabblah *et al.* (Sabblah, 2014). Almost 10% (31; 9.5%) cited that their reason for under reporting ADRs is the unavailability of the ADR reporting form in their place of work. This is an improvement to the reports of Sabblah *et al.* (Sabblah, 2014) that shows that 43.1% of respondents in their study cited the reason for non-reporting as being the unavailability of the ADR reporting form. Other barriers to reporting as reported by other researchers, included non-remuneration for reporting (13.9%), lack of time to report ADR (33.4%), a single unreported case may not affect ADR database (17.3%) (Srinivasan, 2017). In the study by Emeka *et al.* (Emeka, 2017), it was reported that factors discouraging ADR reporting include non-availability of forms and unavailability of a professional environment to encourage discussion about ADRs. Other factors included the fact that the reactions were not deemed serious and therefore did not appear to meet reporting requirements and a lack of understanding of the need to report. These are consistent with findings from other local studies as reported by Gordhon and Padayachee (Gordhon Y, 2020), Bogolubova *et al*. (Bogolubova, 2018) and Joubert and Naidoo (Joubert M, 2016).

5.6 Suggestions to improve ADR reporting

The top suggestion selected by the respondents in the current study to improve ADR reporting in South Africa was the inclusion of PV training in the undergraduate curricula at universities (266; 81.8%,). More than seventy percent (235; 72.3%,) of respondents agreed that implementation of on-line or telephonic reporting could potentially increase reporting

rates. Other suggestions included continuous and refresher training (226; 69.5%,) and frequent communication and feedback from national PV centres (220; 67.7%,). These suggestions are consistent with those reported by Srinivasan *et al.* (Srinivasan, 2017), Sabblah *et al.* (Sabblah, 2014), Ezeuko *et al*. (Ezeuko, 2015) and Olsson *et al.* (Olsson, 2015)).

To address the urgent need for PV training among HCPs, a PV training initiative was piloted by Jusot *et al.* (Jusot, 2020) between 2016 and 2018 in Malawi. As a result, an exponential increase in ADR reports was reported (228 in total). From these, 84.6% were reported from districts where training had been conducted and 98.2% contained all the minimum mandatory information, whereas previous reports had been found to be missing some key information. As suggested by Joubert and Naidoo (Joubert M, 2016), and Bogolubova *et al*. (Bogolubova, 2018), there is a willingness to participate in PV activities among HCPs and they are willing to receive appropriate training on an ongoing basis. Most (89.5%) of the respondents on the study by Srinivasan *et al*. (Srinivasan, 2017) agreed with this notion.

5.7 Significance of the study

This current study builds on previous studies conducted across LMICs and within South Africa with the objectives of assessing the knowledge, attitudes, and practices of pharmacovigilance among healthcare professionals. The results of this study, in line with those of previous studies, contribute to the body of evidence aimed at creating an awareness about PV among HCPs and inevitably, increasing ADR reporting. The results show that although the attitude towards PV appears to be positive and HCPs show a good understanding on the importance of PV, it does not necessarily translate into acceptable levels of ADR reporting. The findings of the current study show that HCPs who have received formal training are more likely to participate in ADR reporting, which suggests that adequate training indeed has a significant impact on the level and quality of ADR reporting.

5.8 Limitations

The major limitation of this study is that it does not include nurses and only includes the low number of responses received from pharmacists. Nurses play a pivotal role in the care of patients, even more so in primary healthcare facilities. It is imperative to include nurses in similar studies to this one and to all efforts made to promote ADR reporting. This was mainly due to the unequal proportions of medical doctors and pharmacists being members of the two professional societies, viz the South African Medical Association (SAMA) and the South African Clinical Research Association (SACRA), respectively. SAMA has a higher number of medical doctor memberships than the total number of SACRA memberships, which include pharmacists and doctors. Another limitation relates to the selection of questions to assess knowledge. When questions include definitions and acronyms, it may not be an accurate measure of knowledge due to the possibility that an individual may be familiar with a certain concept in a general sense, without knowing the exact textbook definitions. It would be advisable for researchers to in future, consider the use of questions which may be a better measure of knowledge. In this study, a balance of questions was created by including questions which pertain to the ADR reporting procedure; these are deemed more valuable in assessing knowledge on ADR reporting.

CHAPTER 6
Conclusions and contributions

6.1 Introduction

This chapter provides recommendations based on the findings of this study, while aligning with recommendations from other researchers. It concludes the thesis by providing a summary of the study results in relation to the objectives.

6.2 Summary of results

In summary, the majority (252; 77.5%) of HCPs who participated in this study demonstrated an average level of knowledge o ADR reporting, despite low levels (91; 28%) of training. Although the majority (310; 95.4%) of respondents agreed that ADR reporting is their professional obligation, (119; 36.6%) had never seen a reporting form and only (172; 52.9%) had ever participated in ADR reporting.

The overall aim of study was to promote ADR reporting in South Africa. To facilitate this, the study investigated the factors that inhibit ADR reporting. This was done by assessing the knowledge, attitudes and practices of medical doctors and pharmacists in SA. The results of this study support findings from other studies which suggest that providing PV training which includes how to detect potential ADRs, with practical instructions on how to report, together with implementation of online ADR reporting platforms, will indeed impact ADR reporting.

Respondents in this study also suggested that communication of signals and general feedback to HCPs from national PV centres on reported ADRs will create a better awareness of pharmacovigilance and improve future PV activities and the general knowledge, attitudes and practices of HCPs with regards to pharmacovigilance.

6.3 Recommendations

Reports received by the WHO from other parts of the world, have also shown that in addition to adverse events, there are also increasing incidents of medication errors as well as a surge in counterfeit medication. It is alarming therefore, that so few ADR reports (0.88% from 1992 to 2015) (Ampadu, 2016) and a mere 0,93% by 2018 (Watson, 2019) are submitted to the WHO VigiBase® from African countries.

The study recommends the following actions to promote awareness, enhance reporting rates and increase communication among all stakeholders in South Africa:

6.3.1. Digitalize and diversify reporting platforms (e-forms, app, telephonic reporting)

To increase chances of reporting, reporting platforms must be made easily accessible and uncomplicated. To increase access, multiple options must be made available and, in some

situations, where one option is challenging to implement, alternatives must be made available.

As we enter a new age of technology, access to the internet and smart phones with apps if fast growing across South Africa. This is mostly still prominent in the urban areas, unfortunately, leaving those in remote rural areas and those in remote areas are the ones requiring online reporting platforms the most since they have limited access to care, due to long distances and on poor road infrastructure to get to the nearest healthcare facilities. In time for the South African national vaccine roll-out, SAHPRA on 22 April 2021 launched the MedSafety mobile reporting app (SAHPRA, 2021). suspected ADRs and AEFIs by both the public and healthcare providers. The App also allows the public and healthcare providers to learn about medicine safety news from SAHPRA, thereby creating an awareness of medicines, their potential adverse effects and pharmacovigilance (SAHPRA, 2021).

The limitation is that the app does require a smart phone and has specific criteria that the phone software must meet (system version is at the minimum, version 3.0 for Android OS and version 8 for iOS). Although, it should be noted that the app does allow for offline data entry. This is a step in the right direction; however, since the reality is that not everyone has access to a smartphone, a recommended strategy is making a digitalised format of the reporting form available to healthcare facilities; for downloading and for online completion on the SAHPRA website and implementing a tollfree telephonic reporting platform in parallel to that. This would allow reporters to call into the tollfree number to report an AEFI and an allocated PV healthcare worker at the facility would, in real time enter the data into the digitalised form; thereby also collecting any additional information required on the form.

As an ultimate back-up process, where the app and e-form cannot be accessed, paper ADR/AEFI forms (NDoH, 2021) must be distributed to all healthcare facilities across the country, especially in the rural areas. Albeit with paper forms comes the challenge that there is a delay between the time of reporting and the delivery of the report to SAHPRA PV unit and even so, there is a need to still transcribe the data onto an electronic format, which requires human resources.

6.3.2. Pharmacovigilance Awareness campaign

In settings such as South Africa, where stigma and suspicion exists towards the pharmaceutical industry, pharmacovigilance needs to be about much more than medicine safety. It is about building trust between local healthcare workers and the public which they serve, for the public to feel confident that the health structures are put in place for the protection of their rights and welfare. Education, at laymen level is paramount to this process. It is imperative that the messaging is kept simple, provides clear instructions, and brings out the altruistic motivation behind ADR/AEFI reporting. As suggested by Lopez-Gonzalez *et al.* (Lopez-Gonzalez, 2009) and Olsson *et al.* (Olsson, *et al.*, 2015) effective methods to promote and achieve increased ADR reporting, will have to involve all stakeholders, including healthcare professionals from public and private sectors, pharmaceutical companies, academic institutions as well as patients themselves. It is recommended that SAHPRA, in collaboration with relevant stakeholders such as academia, government, patient advocacy groups, pharmaceutical industry, etc. implements a national PV awareness campaign. The campaign should be tailored to promote an awareness among

patients, parents & teachers, children, HCPs and aim to reach all people across the country, including in remote areas. A diverse approach is required to build a safety culture within South Africa; however, there is a lot of groundwork that has already been covered by global stakeholders as such the WHO-UMC (refer to sec 2.9 global PV awareness). Tools provided by initiatives such as the Scope campaign (Jadeja, 2016) can be leveraged and adapted to suit the South African landscape. Like the WHO-UMC and Scope awareness activities already alluded to, social media platforms, comic books, print media (i.e., newspapers, where applicable), local radio stations, etc. should be used to widen the reach of the campaign.

6.3.3. Develop e-learning module on ADR reporting for HCPs

The current Covid-19 pandemic situation and vaccine roll-out programme, creates an urgent opportunity to educate HCPs on ADR reporting and even more so, AEFIs. The pandemic has also brought a challenge in terms of physical distancing regulations, thus limiting the amount of training sessions that can be attended physically. ADR reporting training of HCPs has been successfully implemented in Malawi (Jusot, 2020) and Nigeria (Tripathy, 2018) E-learning courses on ADR reporting, such as that developed by the Scope campaign (Jadeja, 2016), ISoP/ASoP (ISoP, 1992), WHO-UMC (UMC-eLearning, 2021), among others are available as a reference; however, courses must be tailored to local PV reporting processes and cultural nuances.

6.3.4. Introduce ADR reporting modules in undergraduate curriculums

To support WHO PIDM member countries, a WHO collaborating centre has been established in the Netherlands with the specific task of integrating pharmacovigilance within the curricula for health training institutions (Olsson, *et al.*, 2015). Such initiatives are good references for developing ADR reporting modules that are relevant to the South African requirements and processes.

6.3.5. ADR reported added to HCPs key performance indicators (KPIs)and reward reporting

To increase motivation of HCPs to attend ongoing CPD e-learning courses and to participate in ADR reporting, it is recommended that it should be included as part of their key performance indicators and the quantity and quality of reports submitted form part of performance appraisal processes.

6.3.6. Further studies

It is recommended that further studies are conducted to include a larger sample size, including patients, nurses, and any other healthcare workers who are suited to report ADRs. To better reflect a representation of healthcare workers across South Africa, it is recommended that future studies collect information on the geographical locations of the participants in terms of provinces and whether the locations is categorized as rural or urban.

The results of the study only reflect the knowledge, attitudes and practices of PV during the time period in which the study was conducted. Future studies are recommended to continuously assess the situation at different time periods.

6.4 Conclusion

In conclusion, this study supports the findings of other similar studies, which suggest that lack of knowledge on how to report ADRs is the main cause for under reporting and that training is the solution for this. The objectives of this study were to determine the knowledge on PV among medical doctors and pharmacists in South Africa. Most of the respondents (77.5%), were found to have average knowledge on pharmacovigilance. Another objective was to determine the attitude towards practicing PV among medical doctors and pharmacists in South Africa. It can be concluded that most respondents demonstrated a positive attitude towards ADR reporting. It was encouraging to note that over half (59.4%) of the respondents reported that they do have time to report suspected ADRs. The last objective was to determine the current practices of PV, among medical doctors and pharmacists in South Africa. Although most of the respondents (81.8%) had previously encountered an ADR in a patient, around half had previously reported an ADR. The most common reason for not reporting was lack of knowledge of the reporting procedure.

Training and awareness campaigns are the most pressing recommendations made by this study. Gaps in awareness and training are emphasized by factors such as the high proportion 71.1% of respondents agreeing that it may be difficult to accurately detect whether an adverse drug reaction has occurred and most of the respondents (70.5%) not having been trained on ADR reporting previously and 82.8% agreeing that awareness regarding pharmacovigilance in their professional environment is inadequate.

As a continuation to this study and
towards the achievement of the researcher's PhD studies,
an e-learning course is to be developed for the training of healthcare professionals (nurses, doctors, and pharmacists) at any level of their career,
across South Africa.

The e-learning course will focus on the principles of Drug Safety and pharmacovigilance as well the reporting processes for ADR and AEFIs.

The training will be aimed at creating an awareness of pharmacovigilance among healthcare professionals as well as provide practical instructions on ADR reporting procedures.

References

References

WHO, 2013. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach.* World Health Organization.

(UMC), U. M. C., 2020. *Who we are.*
Available at: https://www.who-umc.org/about-us/who-we-are/
[Accessed 28 May 2020].

American Academy of Allergy, 2013. *Drug Allergy.*
Available at: https://www.aaaai.org/Conditions-Treatments/Allergies/Drug-Allergy
[Accessed 04 August 2020].

Ampadu, H., 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 Safety,* Volume 39, p. 335–345.

Andrade, C., 2019. The P Value and Statistical Significance: Misunderstandings, Explanations, Challenges, and Alternatives. *Indian Journal of Psychological Medicine,* Volume 41, p. 210-215.

Angelis, D., 2016. Factors that condition the spontaneous reporting of adverse drug reactions among nurses: An integrative review. *Journal of Nursing Management,* Volume 24, p. 151–163.

Anon., 2012. *economist.com.*
Available at: www.economist.com/node/21564546.
[Accessed 26 February 2021].

Arlett, P., 2014. Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. *Nature Reviews Drug Discovery,* Volume 13, p. 255–257.

Aronson, J., 2009. Medication errors: what they are, how they happen and how to avoid them. *QJM: An International Journal of Medicine,* Volume 102, p. 513-521.

Arvas, A., 2014 . Vaccination in patients with immunosuppression. *Turkish Archives of Pediatrics,* Volume 49, p. 181–185.

Attaran, A., 2015. Stopping murder by medicine: introducing the model law on medicine crime. *The American Journal of Tropical Medicine and Hygiene,* Volume 92, p. 127–32.

Ballentine, C., 1981. *FDA Consumer magazine.*
Available at: https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf
[Accessed 23 May 2021].

Barry, A., 2020. Comparative Assessment of the National Pharmacovigilance Systems in East Africa: Ethiopia, Kenya, Rwanda and Tanzania. *Drug Safety,* Volume 43, p. 339–350 .

Bassi, P., 2013. Safety of Artemisinin-Based Combination Therapies in Nigeria: A Cohort Event Monitoring Study. *Drug Safety ,* Volume 36, pp. 747-56.

Bégaud, B., 1985. Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. *Therapies,* Volume 40, p. 111–8.

Berkrot, B., 2012. *Reuters.*
Available at: www.reuters.com/article/2012/03/12/us-avastin-drug-fake-idUSBRE82B0Y
[Accessed 26 February 2021].

Bharadwaj, V., 2016. A Survey to Assess the Awareness of Adverse Drug Reactions and Pharmacovigilance Practices among Healthcare Professionals. *International Journal of Medical Research Professionals,* 2(1), p. 134-37.

Binagwaho, A., 2013. Combatting Substandard and Falsified Medicines: A View from Rwanda. *PLoS Medicine,* 10(7), p. e1001476.

BMGF, 2013. *A Report to the Safety and Surveillance Working Group (SSWG),* Bill and Melinda Gates Foundation.

Bogolubova, S., 2018. Knowledge, attitudes and practices of nurses and pharmacists towards adverse drug reaction reporting in the South African private hospital sector, *Health SA Gesondheid,* 23(0), p. 1064.

Brightoncollaboration, 2021. *brightoncollaboration.*
Available at: https://brightoncollaboration.us/category/pubs-tools/templates/
[Accessed 27 February 2021].

Caster, O., 2017. *Benefit-harm Assessment_UMC Pharmacovigilance Training Course.* Uppsala: Uppsala Monitoring Centre.

Caster, O., 2020. Disproportionality Analysis for Pharmacovigilance Signal Detection in Small Databases or Subsets: Recommendations for Limiting False-Positive Associations. *Drug Safety,* Volume 43, p. 479–487.

CDC, 2019. *CDC.gov.*
Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mRNA.html.
[Accessed 27 February 2021].

CDER, 2005. *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Resear.*

Centre, U. M., 2018. *WHO-UMC.org.*
Available at: https://www.who-umc.org/global-pharmacovigilance/who-programme/
[Accessed 07 February 2021].

Chepkemboi, K., 2016. *The Vaccine Pharmacovigilance System of Kenya. Department of Pharmacology, School of Pharmacy, University of Nairobi. Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance Thesis,* Nairobi: University of Nairobi.

China FDA, 2013. *2012 Annual Report of National Adverse Drug Reaction Monitoring.* Beijing: China Food and Drug Administration.

CIOMS, 1999. *Guidelines for Preparing Core Clinical-Safety Information on Drugs – Report of CIOMS Working Groups III and V,* CIOMS Working Groups.

Clarke, A., 2006. ClarkeAn assessment of the publicly disseminated evidence of safety used in decisions to withdraw medicinal products from the UK and US markets. *Drug Safety,* Volume 29, p. 175–181.

Cohen, J., 2007. Tackling corruption in the pharmaceutical systems worldwide with courage and conviction. *Clinical Pharmacology and Therapeutics,* Volume 81, p. 445–9.

Dempster, A., 1971. An Overview of Multivariate Data Analysis. *Journal of Multivariate Analysis,* p. 316-346.

Dheda, M., 2013. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga success and moving forward. *Journal of AIDS and HIV Research,* 5(9), p. 370.

Directive, C., 1965. *Council Directive 65/65/EEC of 26 January 1965.*
Available at: https://www.echamp.eu/eu-legislation-and-regulation-documents/directive_65-65-eec-consolidated_version.pdf
[Accessed 23 May 2021].

Dodoo, A., 2014. Profile of Adverse Events in Patients Receiving Treatment for Malaria in Urban Ghana: A Cohort-Event Monitoring Study. *Drug Safety,* Volume 37, p. 433-48.

Doshi, P., 2018. Pandemrix vaccine: why was the public not told of early warning. *British Medical Journal,* p. 362-8.

EMA, 2017 . *European Medicines Agency. Legal framework London*, European Medicines Agency.

EMA, 2009. *EMA.europa.eu.*
Available at: https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-withdrawal-benfluorex-market-european-union
[Accessed 27 Feb 2021].

EMA, 2015. *History of EMA.*
Available at: https://www.ema.europa.eu/en/about-us/history-ema
[Accessed 23 May 2021].

EMA, 2019. *Explanatory note on pharmacovigilance fees payable to the European Medicines Agency EMA/131042/2019,* European Medicines Agency.

EMA, 2019. *Guidelines on good pharmacovigilance practices (GVP). EMA/659929/2019. 11 December 2019,* European Medicines Agency.

EMA, 2021. *European Medicines Agencies (EMA). List of medicines under additional monitoring,* European Medicines Agency.

Emeka, P., 2017. A Study on the Knowledge and Barriers Towards ADRs Reporting among Community Pharmacists in Enugu and Nsukka areas, South-Eastern Nigeria. *Pharmacology, Toxicology and Biomedical Reports,* 3(1), p. 1-6.

Erwin, B., 2014. The Health and Economic Effects of Counterfeit Drugs. *American Health and Drug Benefits ,* 7(4), p. 216-24.

EU, 2014. *Regulation (EU) no 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use,* European Parliament.

EU, 2001. *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use,* European Parliament .

EU, 2004. *Regulation (Eu) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance,* European Parliament.

EU, 2010. *Regulation (EU) no 1235/2010 of the European Parliament and of the council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorization,* European Parliament.

EU, 2012. *Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament,* European Parliament.

EU, 2012. *Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance.* Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:299:0001:0004:EN:PDF [Accessed 2020 June 28].

Evans, S., 2006 . Attitudes and barriers to incident reporting: a collaborative hospital study. *Quality and Safety in Health Care,* 15(1), p. 39-43.

Ezeuko, A., 2015. Adverse Drug Reaction Reporting by Different Categories of Healthcare Workers in Nnewi, Nigeria: Awareness, Knowledge and Attitudes. *British Journal of Medicine and Medical Research,* 7(11), p. 932-941.

FDA, 2012. *Kefauver-Harris Amendments Revolutionized Drug Development.*
Available at: https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development
[Accessed 23 May 2021].

FDA, 2018. *Part II: 1938, Food, Drug, Cosmetic Act.*
Available at: https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-ii-1938-food-drug-cosmetic-act#:~:text=FDR%20signed%20the%20Food%2C%20Drug,adequate%20directions%20for%20safe%20use.
[Accessed 23 May 2021].

FDA, 2019. *Part I: The 1906 Food and Drugs Act and Its Enforcement.*
Available at: https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-i-1906-food-and-drugs-act-and-its-enforcement
[Accessed 23 May 2021].

FDA, 2021. *Drug Developmemt Process: Step 3 Clinical Research.*
Available at: https://www.fda.gov/patients/drug-development-process/step-3-clinical-research
[Accessed 21 February 2021].

Ferner, R., 2006. Clarification of terminology in medication errors: definitions and classification. *Drug Safety,* Volume 29, p. 1011–22.

Fornasier, G., 2018. An historical overview over Pharmacovigilance. *International Journal of Clinical Pharmacy,* Volume 40, p. 744–747.

Frachon, I., 2011. "Benfluorex withdrawal in France: Still be hiding somewhere in the world?" *Journal of pharmacology & pharmacotherapeutics,* 2(4), p. 307-8.

Friedman, L., 1999. The risk of surgery in patients with liver disease. *Concise Review Hepatology,* 29(6), p. 1617-1623.

Garuba, H., 2009. Globalization and Health Transparency in Nigeria's public pharmaceutical sector: perceptions from policy makers. *Clinical Pharmacology and Therapeutics,* Volume 13, p. 1–13.

Gelfand, J., 2005. The UK general practice research database. *Strom BL (ed) Pharmacoepidemiology,* Volume 4.

Gordhon Y., 2020. Evaluating the knowledge, attitudes and practices of healthcare workers towards adverse drug reaction reporting at a public tertiary hospital in Johannesburg. *International Journal of Africa Nursing Sciences,* Volume 12. p. 100191

Govt, S., 2017. *Republic of South Africa. Medicines and Related Substances Act No. 101 of 1965.* Cape Town: South African Government.

Grissinger, 2018. Severe Harm and Death Associated with Errors and Drug Interactions Involving Low-Dose Methotrexate. *Pharmacy and Therapeutics,* 43(4), p. 191-248.

Haines, H, 2020. Knowledge, attitudes and practices of health care professionals towards adverse drug reaction reporting in public sector primary health care facilities in a South African district. *European Journal of Clinical Pharmacology,* 76(9), p. 991-1001.

Hamilton, W., 2016. Public health interventions to protect against falsified medicines: a systematic review of international, national and local policies. *Health Policy and Planning,* 31(10), p. 1448–1466.

Hanafi, S., 2013. An educational intervention to improve nurses' knowledge, attitude, and practice toward reporting of adverse drug reactions. *Iranian Journal of Nursing and Midwifery Research, 19(1)*, p. 101–1.

Hauben, M., 2009. Defining 'signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Safety,* 32(2), p. 99-110.

Hazell , L., 2006. Under-reporting of adverse drug reactions: a systematic review. *Drug Safety,* Volume 29, p. 385–396.

Health, 2007. *Drug and Therapeutics Committee Training Course.* Arlington: Management Sciences for Health and World Health Organization.

HHS, 2017. *HHS acting secretary declares public health emergency to address national opioid crisis,* https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-p: HHS.

ISoP, 1992. *ISoP.*
Available at: https://isoponline.org
[Accessed 27 Feb 2021].

Jadeja, M., 2016. *Evaluation of the first EU-wide social media ADR awareness.*
Available at: https://isoponline.org/wp-content/uploads/2017/11/Winner-2nd-Poster-prize-ISoP-Social-media-campaign-SCOPE-poster-MITUL-JADEJA.pdf
[Accessed 24 May 2021].

Jones, J., 1982. Adverse drug reactions in the community health setting: Approaches to recognizing, counseling, and reporting. *Family Medicine and Community Health,* Volume 5, p. 58–67.

Jones, R., 2001. Comparative mortality in anaesthesia. *British Journal of Anaesthesia,* 87(6), p. 813-815.

Joubert, M., 2016. Knowledge, perceptions and practices of pharmacovigilance amongst community and hospital pharmacists in a selected district of North West Province, South Africa. *Health SA Gesondheid,* Volume 21, p. 238-244.

Renschler, J.P., 2015. . Estimated under-five deaths associated with poor-quality antimalarials in sub-saharan Africa. *The American Journal of Tropical Medicine and Hygiene,* Volume 92, p. 119–26.

Juhlin, K., 2015. Using VigiBase to Identify Substandard Medicines: Detection Capacity and Key Prerequisites. *Drug Safety,* Volume 38, p. 373–382.

Jusot, V., 2020 . Enhancing Pharmacovigilance in Sub-Saharan Africa Through Training and Mentoring: A GSK Pilot Initiative in Malawi.. *Drug Safety,* 43(6), p. 583-593.

Kasliwal, R., 2012. Spontaneous Reporting in Pharmacovigilance: Strengths, Weaknesses and Recent Methods of Analysis. *Journal of Clinical and Preventive Cardiology,* Volume 1, p. 20-23.

Kim, J.H., 2011. Thalidomide: the tragedy of birth defects and the effective treatment of disease. *Toxicological Sciences,* 122(1), p. 1-6.

Kongkaew, C., 2008. Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies. *The Annals of Pharmacotherapy,* Volume 42, p. 1017-25.

Kovacs, S., 2017. Donor support for quality assurance and pharmacovigilance of anti-malarials in malaria-endemic countries. *Malaria Journal,* Volume 16, p. 282.

Kramer, M., 1979. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *Journal of the American Medical Association,* Volume 242, p. 623–32.

Kumari, S., 2015. Evaluation of Knowledge, Awareness and Attitude Practice among Nurses in Pharmacovigilance at Tertiary Care Hospital in Delhi. *Journal Of Harmonized Research in Pharmacy,* 4(1), p. 76-86.

Lancet, T., 1893. Report of the lancet commission appointed to investigate the subject of the administration of chloroform and other anesthetics from a clinical standpoint.. *The Lancet,* 141(3629), p. 629-638.

Laxton, D., 2004. Chapter 2 Research design and methodology. Dans: C. a. F. Herbst., éd. *Business Research.* New York: Juta Academic.

Lessa, N., 2016. *Pharmacovigilance: New Challenges for WHO. Safety and Vigilance: Medicines*, World Health Organization.

Leufkens, H., 2005. Automated pharmacy record linkage in the Netherlands. *Strom BL (ed) Pharmacoepidemiology,* Chapter 20.

Lopez-Gonzalez, E., 2009. Determinants of Under-Reporting of Adverse Drug Reactions A Systematic Review. *Drug Safety ,* 32(1), p. 19-31.

Mackey, K., 2015. After counterfeit Avastin®-what have we learned and what can be done? *Nature Reviews Clinical Oncology,* Volume 5, p. 302-8.

Maigetter, K., 2015. Pharmacovigilance in India, Uganda and South Africa with reference to WHO's minimum requirements. . *International Journal of Health Policy and Management,* 4(5), p. 295.

Mancl, L., 2013. *Advanced Regression Methods.* Washington, University of Washington.

Marques, J., 2013. A survey of spontaneous reporting of adverse drug reactions in 10 years of activity in a pharmacovigilance center in Portugal. *International Journal of Pharmacy Practices,* Volume 22, p. 275-282.

McBride, W., 1961. Thalidomide and Congenital Abnormalities. Letter to the Editor. *The Lancet,* Issue 1358, p.291-2

Mehta, U., 2014. Strengthening pharmacovigilance in South Africa. *South African Medical Journal,* 104(2), p. 104–6.

MHRA, 2021. *Yellow Card.*
Available at: https://yellowcard.mhra.gov.uk/monitoringsafety/
[Accessed 23 May 2021].

MHRAgovuk, 2016. *SCOPE ADR Campaign Animation.*
Available at: https://www.youtube.com/watch?v=3et5LdYLc8M
[Accessed 24 May 2021].

Mouton, J.P., 2014. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *British Journal of Clinical Pharmacology,* 80(4), p. 818–26.

Naranjo, C., 1981. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics,* 30(2), p. 239-245.

Nayyar, G. e. a., 2015. The global pandemic of falsified medicines: laboratory and field innovations and policy perspectives.. *The American Journal of Tropical Medicine and Hygiene ,* Volume 92, pp. 2-7.

Ndagije, H., 2015. Ndagije H, Nambasa V,Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda. *Drug Safety,* Volume 38, pp. 395-408.

Ndagije, H., 2015. Targeted spontaneous reporting of suspected renal toxicity in patients undergoing highly active anti-retroviral therapy in two public health facilities in Uganda. *Drug Safety,* 38(4), p. 395-408.

NDoH, 2021. *Case Report Form_AEFI_All vaccines incl COVID-19.*
Available at: https://www.sahpra.org.za/wp-content/uploads/2021/03/Case-Report-Form_AEFI_All-vaccines-incl-COVID-19_20210128.pdf
[Accessed 24 April 2021].

NDoH, S., 2021. *SA Corona Virus.*
Available at: https://sacoronavirus.co.za.
[Accessed 28 Feb 2021].

Newton, P., 2014. Falsified medicines in Africa: all talk, no action. *The Lancet. Global Health,* Volume 2, p. 509–10.

Ofir, L., 2017. *FDA Post-Marketing Drug Safety Surveillance,* Division of Phamacovigilance.

Olsson S, 2015. Pharmacovigilance in resource-limited countries. *Expert Review of Clinical Pharmacology,* Volume 8, p. 449-460.

Onakpoya, I., 2016. Correction to: Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Medicine,* Volume 10, p. 1294-9.

Oshikoya, K., 2009. Perceptions of doctors to adverse drug reaction reporting in a teaching hospital in Lagos, Nigeria. *BMC Clinical Pharmacology,* Volume 9, p. 1-8.

Ouma, C., 2012. *Africa Pharmacovigilance Meeting 2012: Technical Report. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services Program,* Management Sciences for Health.

Pal, S., 2015. The monitoring medicines project: a multinational pharmacovigilance and public health project. *Drug Safety,* Volume 38, p. 319–28.

Parchment, R., 1998. Predicting hematological toxicity (myelosuppression) of cytotoxic drug therapy from in vitro tests. *Annals of Oncology,* Volume 9, p. 357-364.

Pardi, N., 2018. mRNA vaccines - a new era in vaccinology. *Nature Reviews Drug Discovery,* Volume 17, p. 261-279.

Paul, R., 2002. An Unexplained Death Hannah Greener and Chroroform. *Anesthesiology,* Volume 96, p. 1250–3.

PIDM, 2020. *WHO Programme for International Drug Monitoring.*
Available at: https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/
[Accessed 28 May 2020].

Pirmohamed, M., 1998. Adverse drug reactions. *British Medical Journal (Clinical Research Edition),* Volume 316, p. 1295-1298.

Poland, G., 2009. Adversomics: The emerging field of vaccine adverse event immunogenetics. *Pediatric Infectious Disease Journal,* Volume 28, p. 431-432.

Porter, E., 2006. Neonatal nephrocalcinosis: long term follow up. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* Volume 91, p. F333-6.

PREVENT, 2016. *PREVENT initiative.*
Available at: http://preventfaking.com/
[Accessed 26 February 2021].

Raujeau, T., 1995. Medication use and the risk of Stevens Johnson Syndrome or Toxic Epidermal Necrolysis. *New England Journal of Medicine,* Volume 333, p. 1600-7.

Rayner, J., 1989. *Smooth Tests of Goodness of Fit.* New York: Oxford University Press.

Reason, J., 2000. Human error: models and management. *British Medical Journal Clinical Research,* Volume 320, p. 768-770.

Reddy, V., 2014. Assessment of Knowledge, Attitude and Perception of Pharmacovigilance and Adverse Drug Reaction (ADR) Reporting among the Pharmacy Students in South India. *IOSR Journal of Pharmacy and Biological Sciences,* Volume 9, p. 34-43.

Reif, D., 2008. Genetic basis for adverse events after smallpox vaccination. *Journal of Infectious Diseases,* Volume 198, p. 16-22.

Renschler, J., 2015. Estimated under-five deaths associated with poor-quality antimalarials in sub-saharan Africa. *The American Journal of Tropical Medicine and Hygiene,* Volume 92, p. 119–26.

Rentz, E., 2008. Outbreak of acute renal failure in Panama in 2006: a case-control study. *Bulletin of the World Health Organization,* Volume 86, p. 749-56.

Heale, R., 2015. Validity and reliability in quantitative studies. *British Medical Journal,* Volume 18, p. 66-67.

Robyn, M., 2005. *Association or Causation: Evaluating links between "environment and disease".* Geneva: WHO.

Routledge, P., 1998. 150 years of pharmacovigilance. *The Lancet,* Volume 51, p. 1200-1201.

SA Govt, 2006. *South Africa. Children's Act No. 38 of 2005,* South African Government.

SA NDoH, 2015. *The UBOMI Report: Understanding birth outcomes from mothers and infants: Report on the pilot phase of the national pregnancy exposure registry and birth defect surveillance (PER/BDS) system: A review of the initial 12 months of data and experiences,* South African National Department of Health.

Sabblah, G., 2014. Adverse drug reaction reporting by doctors in a developing country: a case study from Ghana. *Ghana Medical Journal,* Volume 48, p.189-193

SAHPRA, 2018. *South African Health Products Regulatory Authority (SAHPRA): Strategic plan for the fiscal years 2018/19–2022/23,* SAHPRA.

SAHPRA, 2019. *South African Health Products Regulatory Authority (SAHPRA) Safety reporting_during clinical trials.* SAHPRA.

SAHPRA, 2020. *South African Health Products Regulatory Authority (SAHPRA) Post-marketing reporting of adverse drug reactions to human medicines in South Africa,* SAHPRA.

SAHPRA, 2020. *South African Health Products Regulatory Authority (SAHPRA) Adverse Drug Reaction (ADR) reporting_post_marketing,* SAHPRA.

SAHPRA, 2021. *The Med Safety App.*
Available at: https://medsafety.sahpra.org.za/
[Accessed 24 May 2021].

SAMRC, 2021. *Sisonke Study Website.*
Available at: http://sisonkestudy.samrc.ac.za/
[Accessed 28 Feb 2021].

Sentinelinitiative, 2016. *sentinelinitiative.org.*
Available at: https://www.sentinelinitiative.org/
[Accessed 27 February 2021].

Sisonke PSRT, 2021. *Sisonke AEFI.*
Available at: Sisonke AEFI. https://urldefense.proofpoint.com/v2/url?u=https-3A__is.gd_sisonke-5Fae&d=DwMF-g&c=eRAMFD45gAfqt84VtBcfhQ&r=sAl5hu3jHWWJLrFr3xHuwSiltKxFVgvaxDdygoPOIIg&m=1zoaD-9hPUiDcV0CiOPMGraSl0QG_1TsExGUIyEUlTU&s=jCuhect2rexThbb_ylOfyeN2-bY-51xqqe96gCHM9
[Accessed 2021 Feb 2021].

Smith, M., 2018. *Statistical Analysis Handbook*. Edinburgh: The Winchelsea Press.

Sobolev, O., 2016. Adjuvanted influenza-H1N1 vaccination reveals lymphoid signatures of age-dependent early responses and of clinical adverse events. *Nature Immunology,* Volume 17, p. 204–213.

SPS Program, 2009. *Strengthening Pharmaceutical Systems (SPS) Program S. Indicator-based pharmacovigilance assessment tool: manual for conducting assessments in developing countries,* Arlington: Management Sciences for Health.

Srinivasan, V., 2017. Knowledge, Attitude, and Practice of Pharmacovigilance Among the Healthcare Professionals in A Tertiary Care Hospital – A Questionnaire Study. *Biomedical and Pharmacology Journal,* Volume 10, p. 1441-1447.

Suku, C., 2015. Experiences and Lessons From Implementing Cohort Event Monitoring Programmes for Antimalarials in Four African Countries: Results of a Questionnaire-Based Survey. *Drug Safety,* Volume 38, p. 1115–1126.

Sultana, J., 2013. Clinical and economic burden of adverse drug reactions. *Journal of Pharmacology and Pharmacotherapeutics,* Voume 4, p. 73-77.

Svanström, H., 2014 . Common variants associated with general and MMR vaccine-related febrile seizures. *Nature Genetics,* Volume 46, p. 1274-82.

Taber, S., 2008. The epidemiology of drug-induced disorders: the kidney. *Expert Opinion on Drug Safety,* Volume 7, p. 679-690.

Taherdoost, H., 2016. Validity and Reliability of the Research Instrument; How to Test the Validation of a Questionnaire/Survey. *International Journal of Academic Research in Management,* Volume 5, p. 28-36.

Taylor, D., 2014. . RFID in the pharmaceutical industry: addressing counterfeits with technology. *Journal of Medical Systems,* Volume 38, p. 141.

Terblanche, A., 2017. Knowledge, attitudes and perspective on adverse drug reaction reporting in a public sector hospital in South Africa: baseline analysis. *Hospital Practice,* Volume 45, p. 238-245.

Tripathy, J., 2018. Does the Structured Operational Research and Training Initiative (SORT IT) continue to influence. *Global Health Action,* Volume 11, p. 1-10

UMC, 2020. *Medicines safety on air.*
Available at: https://www.who-umc.org/global-pharmacovigilance/pharmacovigilance-communications/drug-safety-matters-podcast/
[Accessed 24 May 2021].

UMC, 2021. *Communicating benefits and risks of medicines.*
Available at: https://www.who-umc.org/global-pharmacovigilance/pharmacovigilance-communications/
[Accessed 24 May 2021].

UMC, 2021. *Uppsala Reports.*
Available at: https://www.uppsalareports.org/
[Accessed 24 May 2021].

UMC-eLearning, 2021. *Pharmacovigilance training at arm's reach.*
Available at: https://www.who-umc.org/education-training/online-learning/e-learning-in-

pharmacovigilance/
[Accessed 28 May 2021].

Union, E., 2010. *Directive 2010/84/EU.*
Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
[Accessed 24 May 2021].

Uppsala Report 61, 2013. *Country distribution in the WHO global ICSR database in 22 March 2013,* WHO-UMC.

US, FDA, 2021. *BeSafeRx: know your online pharmacy.*
Available at: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/BuyingMedicinesOvertheInternet/BeSafeRxKnowYourOnlinePharmacy/index.htm
[Accessed 26 February 2021].

User manual for the revised WHO classification, 2018. *Causality assessment of an adverse event following immunization (AEFI),* 2nd edition éd. WHO.

Wang, Y., 2013. Wang The Expected Number of Background Disease Events during Mass Immunization in China. *PLoS ONE,* Volume 8, p. e71818

Watson, S., 2019. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. *E-Clinical Medicine,* Volume 17, p. 2589-5370.

WHO, 2016. *WHO Global Patient Safety Challenge on Medication Safety.* WHO-HQ Geneva, Working Groups Meeting.

WHO Collaborating Centre Ghana, 2012. *PV Toolkit,* WHO-UMC.

WHO, 1999. *Guidelines for the development of measures to combat counterfeit medicines,* Geneva: World Health Organization.

WHO, 2006. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool,* Geneva: World Health Organization.

WHO, 2007. *A practical Handbook on the Pharmacovigilance of Antimalarial medicines,* World Health Organization .

WHO, 2008. *Progress in global measles control and mortality reduction, 2000–2007,* Geneva: WHO Weekly Epidemiological Record.

WHO, 2012. *A practical Handbook on the Pharmacovigilance of medicines used in the treatment of Tuberculosis,* World Health Organization.

WHO, 2012. *WHO Definition and Application of Terms for Vaccine Pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance,* World Health Organization.

WHO, 2013. *A practical Handbook on the Pharmacovigilance of Antiretroviral medicines,* World Health Organization .

WHO, 2014. *Reporting and learning systems for medication errors: the role of pharmacovigilance centers,* World Health Organization .

WHO, 2015. *World Health Organization. 2015c. WHO List of Prequalified Quality Control Laboratories.*
Available at: http://apps.who.int/prequal/,
[Accessed 26 February 2021].

WHO, 2016. *World Health Organization. 2016. International Medical Products Anti-Counterfeiting Taskforce-IMPACT.*
Available at: http://apps.who.int/impact/en/
[Accessed 26 February 2021].

WHO, 2017. *WHO member state mechanism on substandard/spurious/falsely labelled/falsified/counterfeit (ssffc) medical products working definitions,* Seventieth World Health Assembly update, 29 May 2017.

WHO, 2017. *WHO. Falsifi ed batches of Coartem recently circulating in Cameroon..*
Available at: http://www.who.int/ medicines/publications/drugalerts/ drugalertindex/en/
[Accessed 26 February 2021].

WHO, 2020. *Covid-19 vaccines: safety surveillance manual. World Health Organization.* Available at: https://covid19.who.int.
[Accessed 27 Feb 2021].

WHO, 2020. *WHO Vaccine Safety Basics e-Training Course.* Available at: https://vaccine-safety-training.org/Importance-of-immunization-programmes.html.
[Accessed 26 February 2021].

WHO, s.d. *World Health Organization (WHO) Aide-mémoire on AEFI Investigation.* Available at: https://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_Aide_Memoire.pdf
[Accessed 25 January 2021].

WHO-UMC, 2015. *WHO Pharmacovigilance indicators: A practical manual for the assessment of pharmacovigilance systems,* World Health Organization .

WHO-UMC, 2020. *Joining the WHO Programme for International Drug Monitoring.* Available at: https://www.who-umc.org/media/1436/joining.pdf
[Accessed 28 May 2020].

WHO-UMC, 2021. *who-umc.org.* Available at: https://www.who-umc.org/research-scientific-development/signal-detection/what-is-a-signal/
[Accessed 26 Feb 2021].

WHO-UMC, s.d. *The use of the WHO-UMC system for standardised case causality assessment.,* Geneva: WHO-UMC.

Wolf, K., 1998. Epidemic of Pediatric Deaths from Acute Renal Failure caused by Diethylene Glycol Poisoning. *Journal Of The American Medical Association,* Volume 279, p. 1175-80

Wood, N., 2012. Influenza Vaccine Safety in Children Less Than 5 Years Old: The 2010 and 2011 Experience in Australia. *The Pediatric Infectious Disease Journal,* Volume 31, p. 199-202.

Xueref, S., 2013. The Global Fund and pharmacovigilance systems in resource limited settings. *The Lancet,* Volume 381, p. 1360.

Appendices

Appendix A – Informed Consent Form_V3.0_09 Sep 2019

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM

Study Title: A cross-sectional study to investigate the knowledge, attitudes and current practices of pharmacovigilance, among Medical Doctors & Pharmacists in South Africa.
Researcher: Ms Nyeleti Rikhotso [portia.rikhotso@gmail.com; 072 253 9109]
Supervisor: Dr Carine Page, Senior Lecturer, Division of Clinical Pharmacology [carinepage@sun.ac.za; 082 871 5127]
Co-Supervisor: Prof Helmuth Reuter, Head of Division of Clinical Pharmacology [hr@sun.ac.za; 021 938 9860]

Introduction
You are being invited to participate in a research study to investigate the knowledge, attitudes, and current practices of pharmacovigilance, among Medical Doctors& Pharmacists in South Africa. The study is conducted by Ms Nyeleti Rikhotso, in fulfilment of the Master of Science Degree at the University of Stellenbosch, Division of Clinical Pharmacology. You were selected as a possible participant in this study because you are a Medical Doctor or Pharmacist in South Africa.

The aim of this study is to investigate the factors influencing the low ADR reporting levels in South Africa, as reported by the WHO on submission of Individual Case Safety Reports (ICSRs) to the Vigibase database. The investigation will be conducted by investigating the knowledge, attitudes, and current practices of pharmacovigilance, among Medical Doctors & Pharmacists in South Africa.

How big is this study?
384 Medical Doctors & Pharmacists combined are required for the conduct of this study.

What are the benefits of participating in the study?
The information gathered through this study will contribute towards science in general and more so towards the endeavor to promote post marketing drug surveillance. You will not be reimbursed to participate in this study, and you will not bear any costs for participating.

What are the risks associated with this study?
There are no risks to participating in this study. The questionnaire will take 10-15 minutes to complete.

Can I change my mind about being in the study?
Your participation in this study is entirely voluntary and you will face no consequences should you choose not to participate. You have the right to withdraw participation from the study at any point without providing a reason.

How will my information be used?
The results of this study will be used to make recommendations on how to promote post-marketing pharmacovigilance in South Africa. After conduct of the study, efforts will be

made for opportunities to present the study results to relevant people within Academia, National Health & Tertiary Education Departments, the pharmaceutical industry, SADC, and BRICS member countries. The study results will also be shared with the participants of the study in the same manner that the questionnaire is presented to you now.

What precautions will be taken to protect my privacy?
To protect your privacy as a study participant, you will not be requested to provide your name or any information which may identify you as an individual. Your participation will remain strictly confidential.

Who do I call if I have questions?
Should you have any questions or wish to discuss any matter related to the study, you may contact the researcher or supervisors:
Researcher: Ms Nyeleti Rikhotso [portia.rikhotso@gmail.com; 072 253 9109]
Supervisor: Dr Carine Page, Senior Lecturer, Division of Clinical Pharmacology [carinepage@sun.ac.za; 082 871 5127]
Co-Supervisor: Prof Helmuth Reuter, Head of Division of Clinical Pharmacology [hr@sun.ac.za; 021 938 9860]

Declaration by Participant:

Please TICK appropriate box ***(All information is strictly confidential)***

I agree to participate in the Pharmacovigilance study.

Yes	No

Appendix B – Questionnaire Form_V2.0_09 Sep 2019

A cross-sectional study to investigate the knowledge, attitudes, and current practices of pharmacovigilance, among Medical Doctors & Pharmacists in South Africa.

Section A: Demographics

Please TICK appropriate box *(where applicable)*

What type of health institution do you work in? (i.e. private practice, public/private hospital, hospital pharmacy, retail pharmacy, etc.)

_____

Gender

Male	Female

Age (Years)

_____

Average patients seen per day

≤ 14	15 - 19	20 - 24	25 - 29	30 - 34	≥ 35

Professional level

Medical Intern	Medical Officer	Medical Specialist	Senior Pharmacist	Pharmacy Manager	Other (specify)

At which University did you achieve your undergraduate Medical/Pharmacy degree?

_____

Section B: Knowledge

1. Select a definition of Pharmacovigilance below by ticking the box next to the correct alphabet letter:

	A	The science and activities relating to the detection, assessment, understanding and prevention (mitigating) of adverse events/effects or any other drug related problems
	B	The science and activities relating to the detection, assessment, understanding, monitoring and prevention of adverse events/effects
	C	The science relating to detection, assessment, monitoring and preventing of adverse events and other drug related problems
	D	The science and activities relating to the detection, assessment, understanding, monitoring and prevention of adverse drug reactions

2. The most important purpose of pharmacovigilance is:

	A	To enhance patient care and patient safety in relation to the use of medicines
	B	To identify adverse drug reactions (ADRs)
	C	To calculate the incidence of ADRs
	D	To assess the benefit-risk ratio of a marketed medicine

3. Is it your professional obligation to report Adverse Drug Reactions (ADRs)?

Yes	**No**
x	

4. Where is the Pharmacovigilance unit situated in South Africa?

	A	Clinical Evaluation and Trials Directorate of the MRA
	B	Medicines Regulatory Affairs Cluster (MRA) of the Department of Health
	C	South African Health Products Regulatory Agency (SAHPRA) Cluster of the Department of Health
	D	Clinical Cluster of the Department of Health

5. What does NADEMC stand for?

	A	National Adverse Drug Effect Monitoring Center
	B	National Adverse Drug Event Monitoring Center
	C	National Adverse Drug Effect Manufacturing Center
	D	National Adverse Drug Event Manufacturing Center

6. What is the name of the International Centre for ADR monitoring?

	A	Uppsala Monitoring Centre
	B	NADEMC
	C	Pharmacovigilance Reporting Centre
	D	Pharmacovigilance Risk Assessment Committee (PRAC)

7. What document is used when for ADR reporting in South Africa?

	A	Case Report Form (CRF)
	B	Individual Case Safety Report (ICSR)
	C	Yellow Form
	D	Vigilance Adverse Reaction Reporting Form

8. Tick all the applicable minimum information required when reporting an ADR. More than **one option may apply.**

	A	An identifiable source (reporter) of the information
	B	An identifiable patient
	C	Suspected medicine(s)
	D	Patient home address

Section C: Attitude

Tick appropriate option for each question below:

#	Question	Yes	No	Unfamiliar
1	Do you think reporting of adverse drug reactions is necessary?			
2	Do you have any concern about the risk(s) associated with medicines you prescribe?			
3	Do you think you have time to report suspected ADRs?			
4	Do you think it may be difficult to decide whether an adverse drug reaction has occurred?			
5	Do you think there's adequate awareness regarding pharmacovigilance in your professional environment?			

Section D: Practice

1. Have you ever experienced an adverse drug reaction in your patient in professional practice?

Yes	No	Not sure

2. Have you ever seen an ADR reporting form?

Yes	No

3. Have you ever reported a suspected adverse drug reaction?

Yes	No

4. If your answer to the above question was "no", select the most appropriate reason(s) below; **more than one may apply:**

	A	The reporting form was not available
	B	I have never been able to identify an adverse drug reaction
	C	I am/was unaware of the reporting procedure
	D	I did not know I was supposed to report
	E	Other (specify)

5. Have you ever been trained on how to report suspected adverse drug reactions?

Yes	No

Section E: Suggestions

Tick next to all the methods below that you believe may improve ADR reporting in South Africa.
More than one may apply:

	#	Methods
	1	Inclusion of Pharmacovigilance to undergraduate curriculums at Universities
	2	Continuous & refresher training
	3	Increased awareness on ADR reporting to patients, prescribers and dispensers by the relevant Authorities at a national level
	4	Implementing a pharmacovigilance centre within each hospital
	5	Frequent communication & feedback from pharmacovigilance centres with updates on the benefit-risk profiles of drugs resulting from ADR reporting efforts
	6	Having an ADR specialist in each hospital department
	7	Implementing on-line or telephonic reporting
	8	Collaborating among all healthcare professionals (Doctors, Pharmacists, Nurses, etc.) in the reporting process, i.e. completing the reporting forms
	9	Implementing department meetings to discuss potential ADRs
	10	Remuneration for each reported ADR case

Thank you for your participation!