Pharmacists' perception towards pharmacovigilance and the reporting of adverse drug reactions in South Africa.

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Dissertation submitted in fulfilment of the requirements for the degree *Master of Pharmacy* in Pharmacy Practice at the North-West University

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PREFACE

The dissertation was written in article format as specified by the requirements of the North-West University. The dissertation is divided into four chapters. Chapter 1 provides the background to the study, the problem statement, research objectives and research method. Chapter 2 executes the objectives for the literature review. Chapter 3 contains the manuscripts related to the objectives of the empirical study. This chapter contains two manuscripts, presenting the results of the study. The two manuscripts were prepared for submission to the journals *Journal of Research in Pharmacy Practice* and *International Journal of Pharmacy Practice*. The manuscripts were prepared in accordance with the author guidelines specified by each journal (see Annexure F and Annexure G).

Finally, Chapter 4 includes the conclusions, recommendations and limitations of the study. The annexures and reference list conclude the dissertation.

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ABSTRACT

Pharmacists' perception towards pharmacovigilance and the reporting of adverse drug reactions in South Africa.

Key terms: adverse drug event, adverse drug reaction, adverse drug reaction reporting, medication errors, pharmacist perspective, pharmacovigilance, South Africa

Pharmacovigilance in South Africa is not being utilised in a desired manner. This study highlights pharmacists' expectations and limitations towards adverse drug reaction reporting in their pharmaceutical sector. Current and previous experience and education of pharmacists towards adverse drug reaction reporting is also questioned. Pharmacists and regulatory bodies in South Africa should consider the value of pharmacovigilance, especially adverse drug reaction reporting in their daily activities and responsibility towards quality pharmaceutical care.

The study was undertaken with two main objectives:

A comprehensive literature review included the history and development of pharmacovigilance in South Africa, roles of the pharmacist in adverse drug reaction monitoring and reporting, the challenges regarding reporting locally and internationally and the impact of education on adverse drug reaction reporting.

The empirical study consisted of a cross-sectional study that used a structured questionnaire, completed by participants, to obtain data. The study population consisted of 11 732 pharmacists from various pharmaceutical sectors across South Africa. The response rate was 5.6% (n=656).

The inclusion criteria for participants were as follow:

- Participants had to be under 65 years of age,
- Pharmacists still had to be practicing as a pharmacist, and
- Be registered with the South African Pharmacy Council (SAPC).

The respondents consisted of 70.7% (n = 464) female pharmacists. Most respondents were aged between 37 – 43 years (n = 143, 21.8%). Additional training in ADR reporting was received by 64.4% (n = 421) of the respondents, mostly being in-service training (n = 191, 29.1%). Training in pharmacovigilance was also recieved by 191 (29.1%) pharmacists. Most pharmacists were practicing in the private healthcare sector (n = 350, 58.0%). The highest qualification was a Baccaleurs in Pharmacy degree (BPharm/BSc) (n = 477, 72.7%). The highest average years of experience as a practicing pharmacist (N = 603) was more than twenty years (n = 198, 32.8%).

The results of the study relating to pharmacists' perception toward adverse drug reaction reporting in their current pharmaceutical sector indicated that although pharmacists are willing to report ADRs, they feel the need for training in this specific field in pharmacovigilance should be a priority. Pearson's chi-square (x^2) indicated a statistically significant association between respondents who received additional training and the reporting of well-known ADRs $x^2(1, N = 488) = 22.6$, $p<0.001$, (Cramér's $V=0.216$), ADRs caused by OTC medication $x^2(1, N = 488) = 9.9$, $p=0.002$, (Cramér's $V=0.143$) and ADRs caused by herbal- and traditional medication $x^2(1, N = 488) = 15.1$, $p<0.001$, (Cramér's $V=0.176$).

Most respondents (N = 412, n= 383, 92.9%, $p<0.000$, $\delta½=0.859$) reacted positively toward believing that they have the ability to report ADRs, as indicated by the Binomial test. More than half (n = 421, 64.4%) of the pharmacists had not received any additional training in ADR reporting. There were pharmacists who received training in pharmacovigilance (n = 191, 29.1%) and drug-related problems (n = 165, 25.1%), but still half of the pharmacists (n = 296, 52.7%) have never reported an ADR in their careers and 29.0% (n = 163) have reported between one and five ADRs, while working in either the public- (n = 106, 42.5%) or private- (n = 92, 36.9%) healthcare sector or a pharmaceutical company (n = 51, 20.4%) at the time of reporting. Pearson's chi-square indicated a statistically significant association between practice sector and the reporting of well-known ADRs $x^2(1, N = 488) = 29.9$, $p<0.001$ (Cramér's $V=0.248$) and ADRs caused by over-the-counter (OTC) medication $x^2(1, N = 488) = 7.6$, $p=0.022$ (Cramér's $V = 0.125$). Pharmacists working in the public healthcare sector (n = 107, 78.7%) are more likely to report well-known ADRs and pharmacists in the private healthcare sector (n = 255, 88.5%) are more likely to report ADRs caused by OTC medication.

Although, pharmacists are willing to report ADRs, certain barriers still refrain them from reporting these ADRs in their pharmaceutical sector, keeping the reporting statistics in South Africa low. Pharmacists reported that ADR reporting is too time-consuming (57.0%) and that they have a lack of clinical knowledge to detect ADRs (50.0%). Pharmacists are well aware of the term pharmacovigilance, but only 11.9% were able to define the term. Pearson's chi-square indictaed a statistically significant association between knowledge toward the term pharmacovigilance and whether the pharmacist received additional ADR training ($p= 0.000$, Cramér's $V= 0.409$).

The study reflects on the shortcomings in the pharmacovigilance system in South Africa. Pharmacists in South Africa need on-going training in the field of pharmacovigilance and specifically toward ADR reporting. Pharmacists, as the go-to healthcare professionals, do have the willingness and ability to report these reactions.

AUTHORS' CONTRIBUTION TO MANUSCRIPT 1

AUTHORS' CONTRIBUTION TO MANUSCRIPT 1

The contributions of each of the authors of manuscript 1, "Pharmacists' perception toward the past and future of adverse drug reaction reporting in South Africa", were as follows:

Author	Contribution to the study
Ms PH Jordaan	Planning and design of the study Conducting the literature review Interpreting of results Conclusion Write the manuscript
Prof MS Lubbe	Supervisor: Study concept and design Guidance for result interpretation Revision of the manuscript
Ms I Kotze	Co-supervisor: Study concept and design Guidance for result interpretation Revision of the manuscript
Dr D M Rakumakoe	Assistant supervisor: Study concept and design

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the abovementioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give consent that it may be published as part of the MPharm study of PH Jordaan.

Prof MS Lubbe

Ms I Kotze

Dr D M Rakumakoe

AUTHORS' CONTRIBUTION TO MANUSCRIPT 2

AUTHORS' CONTRIBUTION TO MANUSCRIPT 2

The contributions of each of the authors of manuscript 2, "Pharmacists' pharmacovigilance and adverse drug reaction reporting perception and barriers affecting the reporting rates: A South African online survey", were as follows:

Author	Contribution to the study
Ms PH Jordaan	Planning and design of the study Conducting the literature review Interpreting of results Conclusion Write the manuscript
Prof MS Lubbe	Supervisor: Study concept and design Guidance for result interpretation Revision of the manuscript
Ms I Kotze	Co-supervisor: Study concept and design Guidance for result interpretation Revision of the manuscript
Dr D M Rakumakoe	Assistant supervisor: Study concept and design

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the abovementioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give consent that it may be published as part of the MPharm study of PH Jordaan.

Prof MS Lubbe

Ms I Kotze

Dr D M Rakumakoe

LIST OF DEFINITIONS

Adverse drug event (ADE): Any unmanageable medical manifestation that may occur during treatment with a medicine, but which does not necessarily have any relation to this treatment (MCC, 2012:4).

Adverse drug reaction (ADR): The Medicine and Related Substances Control Act (101 of 1965) defines an adverse drug reaction (ADR) as a response that occurs in a human or animal to a medicine which is unsafe and unexpected and which results at any dosage and can appear from lack of potency of a medicine, off-label use of medicine, overdose, misuse or abuse of a medicine.

Adverse drug reaction report: It is a report, detailed with suitable data associated with the use of a medicine in a subject or patient (SAHPRA, 2019:6).

Allergic reaction: This is an immunologically mediated drug hypersensitivity reaction, which is unpredictable and could be either immunoglobulin E (IgE)-mediated (immediate) or non-IgE-mediated (delayed) hypersensitivity reactions (WAO, 2014).

Causality: The relating of causes to the effect medicine produces; the pathogenesis of disease and epidemiology are largely concerned with causality (Medical Dictionary for the Health Professions and Nursing, 2012).

Conative: A mental process or behaviour towards actions or changes, including striving, volition and desire (American heritage dictionary of the English language, 2016).

Drug-related problem: An experience or episode relating to drug therapy that literally or probably restricts desired health results (van Mil, 2006:2).

Healthcare professional: Any person who is experienced and qualified to give healthcare to an individual and this includes: doctors, nurses, dentists, pharmacists and midwives (Lindquist, 2007:827).

Health practitioner: Any person, including a student, registered with the relevant council in a profession registrable in terms of the Health Professions Amendment Act (29 of 2007).

Idiosyncratic reaction: An uncommon, unpredictable ADR that appears rarely and does not involve the therapeutic outcome of the medicine, but is often life-threatening, targeting the skin, liver and blood cells (Uetrecht & Naisbitt, 2013:779).

Medicines Control Council: The Medicines Control Council (MCC) [now South African Healthcare Products Regulatory Authority (SAHPRA)] implements standards laid down by the Medicines and Related

Substances Control Act (101 of 1965) which administers the manufacture, distribution, sale and marketing of medicines in South Africa (MCC, 2017).

Medicine: The Medicines and Related Substances Control Act (101 of 1965) defines medicine as "any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine".

Narrow therapeutic drug index: The difference between the least toxic concentration of medicine and the least effective concentration of medicine in the blood (McGraw-Hill Concise Dictionary of Modern Medicine, 2002).

Perception: The Medical Dictionary for the Health Professions and Nursing (2012) defines perception as a mental development of becoming aware of or observing an object or idea; primarily cognitive rather than affective or conative.

Pharmacovigilance: The science and activities relating to the observation, judgment, comprehension and avoidance of adverse effects of medicines and any other drug-related complication (WHO, 2002:5).

Pharmacist: A pharmacist, according to the Pharmacy Act (53 of 1974), is "a person registered as such under the Pharmacy Act, 1974".

Re-challenge: The re-administration of a medicine or other substance which is suspected of causing a prior ADR to be able to determine a definitive link by observing the patient's reaction (Merriam Webster Dictionary, 2019).

Register of pharmacists: When *register* is used as a noun, it means a register kept in consensus with the provisions of the Pharmacy Act (53 of 1974), the term "registered", "registrable", "registration" and all other terms formed with or derived from the term "register" having a comparable meaning.

Side-effect: Any unforeseen result of a drug developing at doses usually used in man and which is associated with the pharmacological characteristics of the medicine (WHO, 2000:20).

South African Health Products Regulatory Authority (SAHPRA): SAHPRA is a section 3A public entity formed by the South African government to oversee the regulation of health products (medicines, medical devices, in-vitro diagnostic tests and devices, radiation-emitting products and devices used in healthcare and industry). SAHPRA replaces the Medicines Control Council (MCC) as well as the Directorate of Radiation Control (DRC) (SAHPRA, 2019).

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
ADE	adverse drug event
ADR	adverse drug reaction
ADRAC	Adverse Drug Reaction Advisory Committee
AEFI	adverse events following immunisation
AEMS	Adverse Event Management System
AIDS	Acquired Immunodeficiency Syndrome
ARV	antiretroviral drug
ART	antiretroviral therapy
COPD	chronic obstructive pulmonary disease
DAIDS	Division of Allergy and Infectious Disease
ESRC	Economic and Social Research Council
EEA	European Economic Area
EMA	European Medicines Agency
EML	Essential Medicines List
EU	European Union
FAERS	FDA Adverse Events Reporting System
FDA	Food and Drug Administration
HCP	healthcare professional
HIV	Human Immunodeficiency Virus
HREC	Health Research Ethics Committee

HSE	Health, Safety and Environment
ICSR	Individual Case Safety Report
IRIS	Incident Reporting and Investigation Scheme
MCC	Medicines Control Council
MEDUNSA	Medical University of South Africa (Sefako Makgatho Health Sciences University)
MHRA	Medicines and Healthcare Product Regulatory Agency
MIC	Medicine Information Centre
MRA	Medicines Regulatory Authority
MUSA	Medicine Usage in South Africa
NADEMC	National Adverse Drug Event Monitoring Centre
NAFDAC	National Agency for Food Drug Administration and Control
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NDoH	National Department of Health
NMP	National Medicine Policy
NMRA	National Medicine Regulatory Authority
NPAC	National Pharmacovigilance Advisory Committee
NORGEP	Norwegian General Practice
NPC	National Pharmacovigilance Centre
NSAID	nonsteroidal anti-inflammatory drugs
NWU	North-West University
ODPHP	Office of Disease Prevention and Health Promotion
OTC	over the counter
PHARMGKP	Pharmacovigilance Knowledge Base

PHP	Public Health Programme
PIASA	Pharmaceutical Industry Association of South Africa
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
SA	South Africa
SAE	serious adverse event
SAHPRA	South African Healthcare Products Regulatory Authority (former MCC)
SAMRC	South African Medical Research Council
SAPC	South African Pharmacy Council
SASQC	South African Society for Quality Control
SAVIC	South African Vaccination and Immunisation Centre
SMU	Sefako Mokgatho University
SOP	standard operating procedure
SSA	sub-Saharan Africa
STGs	Standard Treatment Guidelines
TB	tuberculosis
TFDA	Tanzania Food and Drugs Authority
TGA	Therapeutic Goods Administration
UFS	University of the Free State
USA	United States of America
USAID	US Agency for International Development
USD	US Dollar
WAO	World Allergy Organization

WHO	World Health Organization
WHO-UMC	World Health Organization Uppsala Monitoring Centre
YCS	Yellow Card System

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CHAPTER 1

INTRODUCTION AND RESEARCH METHODOLOGY

1.1 Introduction

Adverse drug reactions (ADRs) are a notable cause of grief and fatality in patients, which lead to excessive healthcare costs (Blockman, 2015:248) and have become a major burden in healthcare systems (Lagnaoui *et al*., 2002:181).

This study focuses on the perceptions and attitudes of pharmacists towards the reporting of ADRs and their understanding of the South African pharmacovigilance system. The World Health Organization's (WHO) International Drug Monitoring Programme co-ordinates international pharmacovigilance activities and South Africa (SA) was the initial country in Africa to become a member of this organisation in 1992 (Metha *et al*., 2013:104).

In chapter 1, the background, problem statement, research questions, research aim and objectives, research methodology, ethical considerations, study limitations, budget and timelines are discussed.

1.2 Background

Healthcare professionals and the public have begun to realise that morbidity and mortality related to medicine are among the leading healthcare problems (Blockman, 2015:248). In the United States of America (USA), ADRs are under the top ten notable causes of death (Montanari-Vergallo, 2013:2). The Medicines Control Council (MCC) (2012:4) defines ADRs as a "*response to a medicine in humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine*".

Adverse drug reactions can be classified into three different categories (Wakaskar, 2017:1):

- Idiosyncratic reactions that occur in fewer patients, where the reaction is not dose-related or an allergy.
- Allergic reactions are normally not dose-related and the patient should have had previous exposure to the drug.
- Dose-related reaction is a common way of an ADR occurring from a drug with a narrow therapeutic drug index.

According to Smith-Marsh (2016:2), ADRs can also be classified according to their severity into four different categories:

- Mild ADRs do not require treatment or antidote, as hospitalisation is not prolonged.
- Moderate ADRs require a change in medication or discontinuation of the medicine.
- Severe ADRs are probably life-threatening and discontinuation of the medicine and treatment for the specific ADR is required.
- Lethal ADRs which lead directly or indirectly to the death of the patient.

The European Commission's (2008:52) data indicated that 5% of all hospital admissions were because of ADRs; 5% of all hospital patients experienced an ADR; and on average, ADRs caused at least 1.91 extra days of hospitalisation. A study in European hospitals, done over a 120-day period, revealed that 4% of urgent hospitalisations were caused by ADRs (Pedros *et al.*, 2014:361). The overall in-hospital stays over the 120-day period for patients admitted with ADRs were 1 785 days. In 90% of those cases, ADRs were dose-related and predictable. Pedros *et al.* (2014:361) further found risk factors for those ADRs, which included advanced age and polypharmacy. In Germany, a study done by Hoogervorst-Schilp *et al.* (2015:531) revealed that hospital patients with an adverse drug event (ADE) stayed in hospital for 5.11 days longer. According to this study, patients with ADEs cost €2 600 per patient (R33 702 in April 2015) more, compared to patients not suffering from an ADE.

A study done on 2 400 paediatric patients in Nigeria revealed that 12% of patients were admitted to hospitals because of ADRs and 23% of patients admitted to hospital developed ADRs (Oshikoya *et al.*, 2011:153). The most suspected drugs were antibiotics (50%). Approximately 1.83 million Naira ($15 466; R109 960 in June 2011) were spent per hospital stay (± 7 days) to manage all admissions due to ADRs (Oshikoya *et al.,* 2011:153). Hospital-attained ADRs place a large economic implication on healthcare systems in Europe, with the overall cost for a hospitalised patient with an ADR reported to be $2 401 per patient (R24 883 per patient in December 2013), which is equal to a 19.86% growth in the total cost of care and an addition in the average length of hospital stays by 8.25% (Khan, 2013a:96).

A recent study conducted at the Groote Schuur Hospital, Edendale Hospital, Cecilia Makiwane Hospital and Frere Hospital in South Africa revealed that ADRs contributed to 2.9% of hospital admissions, where 16% of deaths were ADR-related (Mouton *et al*., 2014:818). Approximately one in 12 hospital admissions were because of an ADR, of which 43% were considered preventable. Antiretroviral (ARV) drugs, anti-tuberculosis (TB) drugs and co-trimoxazole were the most frequently implicated drugs in ADR-related deaths (Mouton *et al*., 2014:824). A study conducted by Mehta *et al*. (2008:399), found that cardiovascular medicines, ARVs, oral hypoglycaemic agents and non-steroidal anti-inflammatory drugs (NSAID) were the most regularly implicated medication in community-acquired ADRs.

Voluntary reporting of ADRs is the foundation of pharmacovigilance (Mehta *et al*., 2013:104). According to the WHO (2012a:5), spontaneous (or voluntary) reporting can be explained as "*no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns*". Reporting is based totally on the capability and rationale of potential reporters. According to the WHO (2012a:1), pharmacovigilance can be defined as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems*".

The specific aims of pharmacovigilance are to:

- develop patient protection and welfare in correlation to the use of medication and all medical and paramedical involvement;
- progress public health and welfare in correlation to the use of medication;
- play a role in the evaluation of benefit, harm, efficacy and risk of medication, motivating their safe, logical and more constructive (including cost-effective) use; and
- encourage understanding, guidance and clinical education in pharmacovigilance and developing effective communication to the public (WHO, 2002:8).

Pharmacovigilance rests on three pillars (Yadav, 2008:2):

- Collecting new data from scientific resources, healthcare professionals, journals and literature that is reliable.
- Analysing and classifying the above data received.
- Circulating information and data received to all health sectors.

The following figure illustrates the three pillars d the ADR monitoring system (adapted from Yadav, 2008:2):

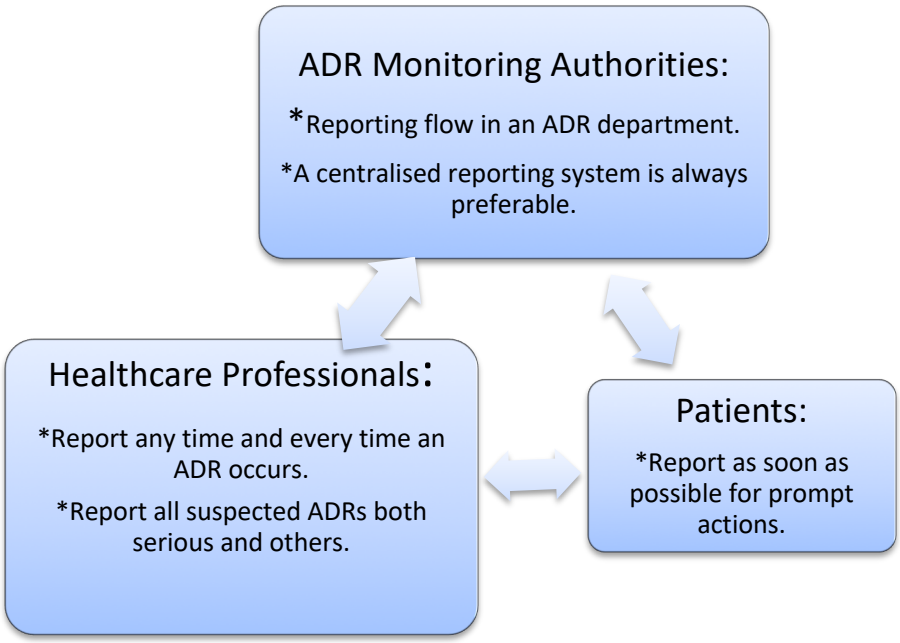

Figure 1-1 Adverse drug reaction (ADR) monitoring system

Drug safety monitoring is an important factor to ensure the safe and suitable use of medicine to improve quality medical care. It can improve determination and faith among patients and healthcare professionals in the healthcare system (Satku, 2006:5).

Legislation accountable for carrying out these activities in South Africa is Regulation 40 issued in terms of the Medicines and Related Substances Control Act 101 (Act 101 of 1965) as amended. The system used in South Africa by the South African Health Products Regulatory Authority (SAHPRA) [previously MCC] for voluntary reporting of suspected ADRs, is mainly through the National Adverse Drug Event Monitoring Centre (NADEMC), Medical University of South Africa (MEDUNSA) [currently the Sefako Makgatho Health Science University (SMU)] and the Bloemfontein Pharmacovigilance Centre at the University of the Free State (SAHPRA, 2019:13; Dheda, 2016:215). SAHPRA emphasises that reports regarding safety information associated with registered human medicines should be sent to either SAHPRA or NADEMC (SAHPRA, 2019).

SMU [previously MEDUNSA] and the Bloemfontein Pharmacovigilance Centre are mainly responsible for providing data to the Medicine Regulatory Authority (MRA) and the MCC on antiretroviral therapy (ART) safety (Dheda, 2016:215). Figure 1-2 indicates the pharmacovigilance system in South Africa, which includes the Medicines Control Council (MCC [SAHPRA since 2019]), Sefako Makgatho Health Science University's (SMU) Medicine Information Centre (MIC), Medicines Regulatory Authority (MRA) and the National Adverse Drug Event Monitoring Centre (NADEMC) (adapted from Dheda, 2016: 215).

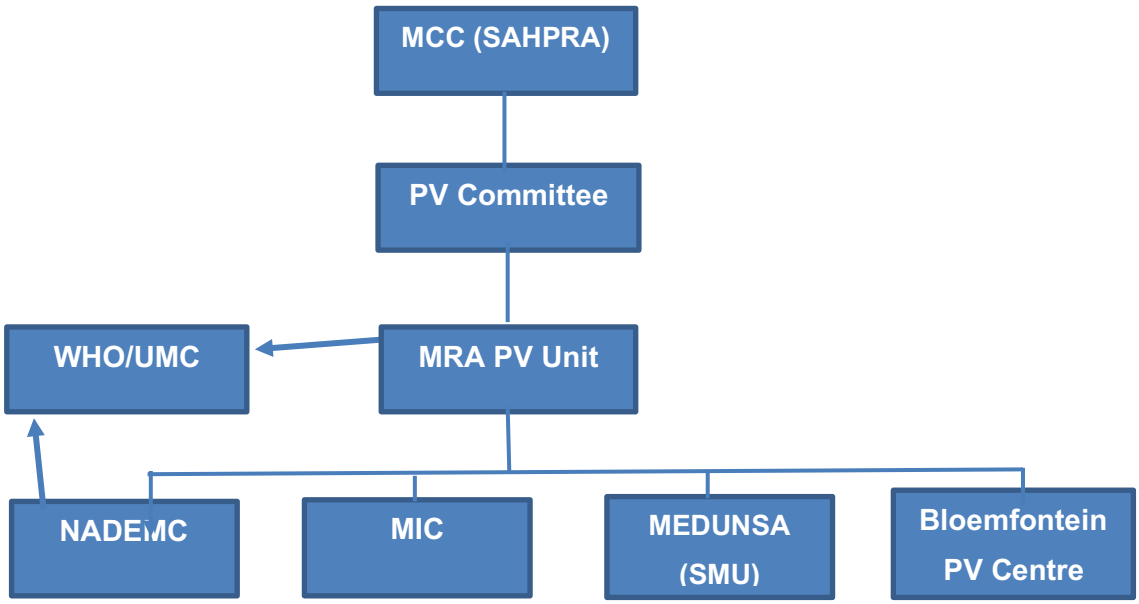

Figure 1-2: Collaboration centres of the national pharmacovigilance programme.

Adapted from Dheda, M. 2016. Perspectives on the emergence of pharmacovigilance in public health programmes in South Africa. *Pharmaceutical Medicine*, 30:213–219.

When NADEMC receives a filled ADR report form, they review and analyse the form to determine the causal relationship between the drug and the reported reaction before sending it to the WHO-UMC using VigiBase (UMC, 2019). The person or healthcare provider reporting the ADR will also be able to use E2B, an online reporting system, reporting directly to UMC. This reporting method assists the reporter to import the report and generates an identification code immediately (UMC, 2019).

A study done by the Medunsa National ARV Pharmacovigilance Surveillance System revealed that 590 HIV/AIDS patients were registered on the programme, starting on regimen: stavudine, lamivudine and efavirenz. Of the 590 HIV/AIDS patients, 37% had encountered at least one ADR and 67% were initiated on ART between 2009 and 2011 (Masenyetse *et al.,* 2015:12).

In a media report from the WHO, they called for more research to be done in this area, focusing on developing countries, as research estimated that 7%-10% of patients in acute care experience an ADE of which some 28-56% are avoidable (WHO, 2007). A study conducted by Almandil (2016:1359) in Saudi Arabia on the perception and understanding of ADRs and pharmacovigilance revealed that 62.2% of healthcare providers were aware of the pharmacovigilance centre in their country. This revealed that healthcare providers should be made aware of their pharmacovigilance units to be able to report ADRs.

Pharmacists in South Africa can and should assist in reporting ADRs to improve the value of health for patients in the healthcare system. Patients should also be entitled to report ADRs more often when

experiencing them, seeing that there is an increase in the use and access of over-the-counter (OTC) medication (Cox, 2009:1; Staniszewska *et al*., 2017:48). A report done by Cox (2009) in the *Pharmaceutical Journal* stated that up to 5.2% of patients reported a higher number of life-threatening ADRs compared to healthcare professionals only reporting 2.7% of those ADRs in Birmingham, England.

According to a report done by the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) for 2011 to 2018, there has been an increase in the reporting of ADRs by pharmacists and physicians (FAERS, 2019). In 2017, healthcare professionals reported 962 760 ADRs, which increased to 1 163 920 in 2018. However, by March 2019, the FAERS has only received 294 919 reports as yet. This data describes information about the reporter. Physicians and pharmacists are the healthcare professionals who submit reports to the FDA most frequently. Reports have also been received by consumers. In 2018, 978 057 reports were filed by consumers (FAERS, 2019).

It is critical to create awareness and an optimistic attitude among pharmacists to report ADRs (Shamim *et al.,* 2016:4). Pharmacovigilance and the reporting of ADRs should become a routine responsibility among pharmacists (Mohamed & Basel, 2015:158).

Underreporting is a common problem in all countries, as, according to a study done in Saudi Arabia, only 30% of pharmacists were willing to report ADRs (Khan, 2013b:47). These pharmacists also believed that it was not necessary to report ADRs occurring from OTC medication (Khan, 2013b:48). A study done by Joubert and Naidoo (2016:241) in South Africa stated that 55.9% of pharmacists felt that the pharmacovigilance unit NADEMC was remote. The major barrier to reporting ADRs was a lack of understanding about the reporting process (Elkalmi *et al.,* 2011b:71). The overall care of a patient should be just as important as the commitment to reporting ADRs (Mohamed & Basel, 2015:159).

According to the South African National Department of Health's (NDoH) health report for 2016-2017, 189 611 patients started on ARV treatment and a significant increase in ADR reports from 2012 (55 reports) up to 2016 (261 reports) were revealed. A recent study in South Africa at the (NDoH) Pharmacovigilance Centre for public health programmes, showed that ART and TB drugs had a total of 251 ADR reports for the period 1 October 2016 to 31 December 2016 (NPC, 2016:2).

Adverse drug reactions were vastly underreported. Pharmacists failed to recognise ADRs, and believed that the physicians were responsible for the reporting process. Unfamiliar reactions in patients caused by medication were being treated with drug therapy after drug therapy (Oberg, 1999:199). According to Varallo *et al.* (2014:743), the main cause for underreporting of ADRs included ignorance and insecurity. The study identified that ongoing education for healthcare professionals will be effective in improving attitudes towards noticing ADRs. Another cause of underreporting identified by Varallo *et al.* (2014:744) included the lack of interest in completing the ADR form and shortage of time. A study done by Khan (2013b:49) in the Eastern region, Alahsa, Saudi Arabia on the barriers towards ADR reporting among

community pharmacists, revealed that 70% of pharmacists felt that ADR reporting forms were unavailable and 40% did not know how to report ADRs. Furthermore, 14% felt that the forms were too complicated, while 32% felt ADR reporting was time-consuming. 48% of the pharmacists also agreed that no professional environment was available to report ADRs (Khan, 2013b:49).

Pharmacists have the need to be educated about the reporting of ADRs (Suleman, 2010:57). A study conducted in South Africa on barriers to ADR reporting indicated that health professionals, including pharmacists, could not comprehend what should be reported, and that there was a shortage of skills and understanding to classify or identify ADRs (Ruud *et al*., 2010:5). An important aspect of pharmacovigilance is the importance of ongoing under- and post-graduate training of healthcare professionals (WHO, 2000:16). The WHO (2000:18) emphasised that education will improve the understanding and perception of ADRs, which will lead to reporting. Pharmaceutical companies, national pharmacovigilance centres and academia could all contribute to the education and training of pharmacovigilance and the ADR reporting skills of healthcare professionals.

Definitions used in the field of pharmacovigilance need to be understood by pharmacists. Pharmacists should be able to explain the specific ADRs to establish reliability and extensive comprehension of data obtained through the ADR reporting systems. An important aspect of the WHO report was to encourage recognition of drug safety problems and the importance of appropriate use of drugs among health professionals and the public.

1.3 Problem statement

Adverse drug reactions (ADRs) have become one of the biggest problems in the healthcare system (Tumwikirize *et al*., 2011:72). In 2018, FAERS reported 1 108 880 serious ADRs (hospitalisation, life-threatening situations, disability, congenital anomaly, required intervention or serious outcome) and 196 926 ADRs that resulted in the death of a patient (FAERS, 2019). ADRs may lead to hospitalisation, patient agony and economic distress (Almandil, 2016:1359; Mehta *et al*., 2013; Nagaraju *et al*., 2015:72). A study done by Green *et al.* (2001:84) revealed that pharmacists were not aware that they had a responsibility towards reporting ADRs, as pharmacists believed it is the physicians' responsibility to do so. Another study done by Goosen (2015:93) at the Dr Kenneth Kaunda District in South Africa, revealed that pharmacists believed that medical practitioners and pharmacists are responsible to report ADRs. This is why it is important to make pharmacists aware and motivate them to understand their role in the understanding and reporting of ADRs.

Pharmacists do not possess the necessary knowledge and training to report ADRs, which results in them not reporting the reactions (Suleman, 2010:58). Pharmacists need to be made aware that they could and should report ADRs. If they suspect any reactions caused by the medicine the patient is taking, they have

a responsibility as a healthcare professional to act in the best interest of the patient and potential future patients who may have the same reactions.

Problems occurring with pharmacovigilance and ADR reporting led to the following questions that were investigated in the study among pharmacists of all different sectors in South Africa:

- Why are pharmacists not reporting ADRs?
- Do pharmacists have the necessary understanding of the pharmacovigilance process to report ADRs?
- According to pharmacists' perception, will they be able to recognise ADRs?
- Do pharmacists need additional training or education in ADR reporting?
- Are pharmacists willing to report ADRs, and do they feel it will make a difference in the healthcare system?

The implication of ADRs on public health remains, even though advancement has been made in the field of pharmacovigilance. It is clear that pharmacists should play a more important role in the future advancement of pharmacovigilance (Suleman, 2010:58). Pharmacists are experts in the effect and use of medication and should therefore consider the reporting of ADRs as an important responsibility.

The result of this research study will assist the current healthcare system to determine those aspects that hinder the documentation of ADRs by pharmacists in the healthcare system.

1.4 Research aims

The aim of the study was to evaluate the pharmacovigilance system of South Africa from the perspective of pharmacists from different pharmaceutical sectors.

1.5 Specific research objectives

The research project consisted of a literature review and an empirical investigation in order to achieve the research aim of the study. The specific research objectives of the literature review and empirical investigation are presented in sections 1.5.1 and 1.5.2.

1.5.1 Literature review

Previous research had reported extensively on various aspects of pharmacovigilance, including the role of the various healthcare professionals in pharmacovigilance, their understanding and perceptions, the reasons for underreporting, the barriers healthcare professionals faced regarding the documentation of

ADRs and the facilitators that improved ADR reporting (Blockman, 2015:248; Bogolubova *et al*., 2018; Nagaraju *et al*., 2015:2; Shamim *et al*., 2016:1778).

The specific research objectives of the literature review were to:

- describe the relationship between inappropriate drug use, medication errors, ADEs and ADRs by means of an extensive literature review;
- identify the current prevalence of ADRs and drug-related problems globally and in South Africa;.
- compare and criticize the current national good pharmacovigilance practices with international guidelines;
- evaluate the current South African ADR report form in terms of international standards and its implementation in both the private and public health sector;and
- identify possible barriers/facilitators that influenced the successful implementation of pharmacovigilance in different health sectors in South Africa.

1.5.2 Empirical investigation

The specific research objectives of the empirical study were to:

- determine pharmacists' past experiences with the reporting of ADRs, stratified by pharmaceutical sector and demographical information;
- assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographical information;
- determine from the perceptions of pharmacists possible factors that influenced the successful implementation of pharmacovigilance in different pharmaceutical sectors in South Africa; and
- identify pharmacists' additional training needs regarding ADR reporting and pharmacovigilance.

Table 1-1: Objective article title

Objective	Article	Title
Determine pharmacists' past experience with the reporting of ADRs, stratified by pharmaceutical sector and demographical information.	Article 1	Pharmacists' perception toward the past and future of adverse drug reaction reporting in South Africa
Assess pharmacists' perceptions regarding their ability and willingness to report an ADR,		

stratified by pharmaceutical sector and demographical information.		
Determine from the perceptions of pharmacists possible factors that influenced the successful implementation of pharmacovigilance in different pharmaceutical sectors in South Africa.	Article 2	Pharmacists' pharmacovigilance and adverse drug reaction reporting perception and barriers affecting the reporting rates: A South African online survey.
Identify pharmacists' additional training needs regarding ADR reporting and pharmacovigilance.		

Those objectives were achieved by means of a structured questionnaire to collect data from pharmacists practising in South Africa.

1.6 Research methodology

The research study consisted of a literature review and an empirical study.

1.6.1 Literature review

Information was obtained from a comprehensive Internet search using applicable databases of the North-West University (NWU) such as Google Scholar®, PubMed®, EBSCOhost®, SA ePublications, Scopus®, the A to Z Journal list, Science Direct® and textbooks. The following keywords or combination of keywords were used, alone and in combination, in the search to identify literature related to the study:

- "Adverse drug reaction reporting."
- "Prevalence of adverse drug events in Africa."
- "Pharmacovigilance in SA."
- "Pharmacovigilance and WHO."
- "Adverse drug reaction forms."
- "Factors influencing underreporting of ADRs."
- "Factors influencing pharmacovigilance."

- “Adverse drug reactions in the South African healthcare system.”
- “Pharmacists perception towards ADR reporting.”
- “Adverse drug reaction reporting in SA.”
- “Costs of hospital admissions because of ADRs.”
- “Pharmacovigilance guidelines.”
- “The role of pharmacists in pharmacovigilance.”

The information obtained from the literature review was used to develop the data collection tool (questionnaire), formulate the introduction and background of the study, as well as Chapter 2 and the articles.

1.6.2 Empirical investigation

1.6.2.1 Study design

A quantitative, descriptive, cross-sectional survey research study design was used to conduct the study. Quantitative research is a mechanism that is organised and open-minded, using numerical data from only a certain subgroup of a universe to understand the findings to the universe that are being studied (Maree & Pietersen, 2013:145). Quantitative research can be divided into experimental and non-experimental designs. For the purposes of this study, a non-experimental, quantitative approach was followed to ensure that participants were not influenced by the researcher (Maree, 2013:144).

According to the National EMSC Data Analysis Resource Centre (NEDARC) (2010), a descriptive, cross-sectional study is a study in which the disease or condition and other related factors are measured at a specific point in time in a specific population. Cross-sectional studies are concurrent in nature and are done at a specific point in time. No exact study will be done in a certain period of time, as all the information on the specific topic is collected at the same time from the same participants (Brink *et al*., 2012:101).

1.6.2.2 Target population

The target population included all registered pharmacists on the Register of Pharmacists on 31 October 2018, which was obtained from the South African Pharmacy Council (SAPC).

The Register of Pharmacists includes all pharmacists in South Africa regardless of the pharmaceutical sector where they are currently working. This is the only complete list of all registered pharmacists in South Africa. In terms of the requirements of the Pharmacy Act (53 of 1974), the SAPC is in charge of the

registration of persons and organisations (pharmacies and providers of pharmaceutical education and training), as well as keeping the registers of such persons and organisations. To safeguard the public, registrations with the SAPC is a pre-requisite to practice the pharmacy profession. The public can access the Register of Pharmacists online for free or buy an electronic version: (http://www.pharmcouncil.co.za/B_Regs_Search.asp.)

1.6.2.3 Study population

No sampling was necessary because all pharmacists on the Register of Pharmacists of the SAPC who comply with the inclusion criteria were included in the study.

The following inclusion and exclusion criteria were applied to select the study population:

1.6.2.3.1 Inclusion criteria

The following criterion applied:

- All pharmacists on the Register of Pharmacists on 31 October 2018 were invited to participate in the study.

1.6.2.3.2 Exclusion criteria

The following criterion applied:

- Pharmacists who did not have an email address on the Register of Pharmacists of the SAPC or whose email address was incorrect or inactive were not able to participate in the study, the reason being that the questionnaire was distributed via their email addresses as indicated on the Register of Pharmacists of the SAPC.
- Pharmacists who acted as supervisors of the project or reviewers of the research protocol or questionnaires could also not participate.
- Pharmacists older than 65 years of age, or pharmacists who were not practising any longer were excluded from the study as well.

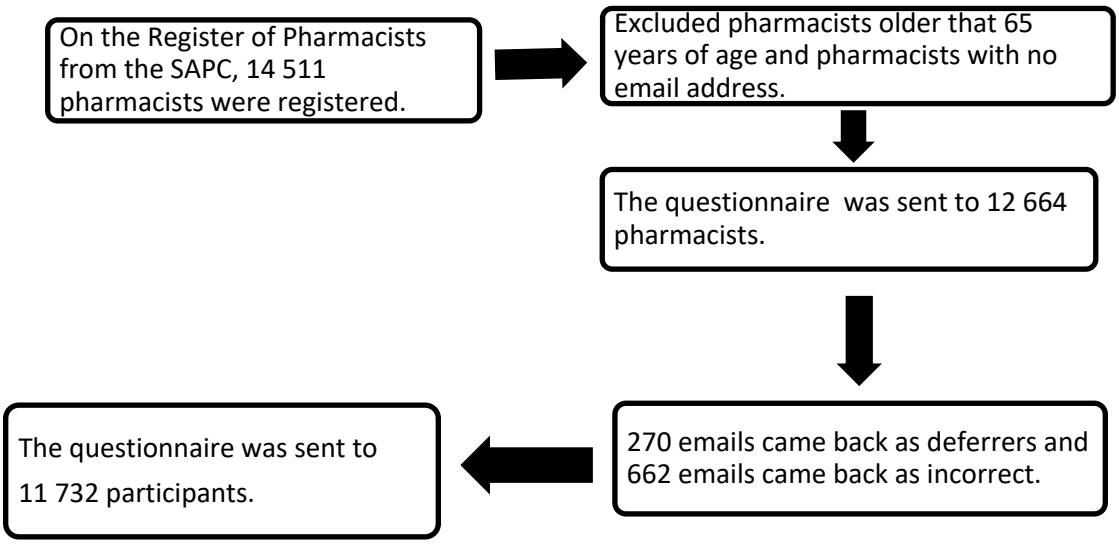

Figure 1-3: Population outcome of the study

1.6.3 Research instrument

In this study a structured questionnaire, with open and closed-ended questions, dichotomous, ranking and biographical questions was used as data-collection tool to collect data from participants. Fink (2009:1) defines a questionnaire as an approach of information gathering that is used to portray, compare and explain individual or societal perception, recognition, values, attitude and preferences. The objective of a questionnaire is to gather facts and opinions about a circumstance from people who are informed on the particular matter. Structured questionnaires typically include a set of standardised questions that investigate a specific topic and collect information about demographics, opinions, attitudes or behaviours. Table 1-2 presents the advantages and disadvantages of structured questionnaires (Bresee, 2014:3; Brink *et al.,* 2012:153;).

Table 1-2: Advantages and disadvantages of structured questionnaires

Advantages	Disadvantages
Questionnaires are a quick way to retrieve data from a vast group of people.	Response rate may be low.
Questionnaires take less time and cost less.	Respondents might present socially respectable answers.
Testing for reliability and validity is easier.	Respondents might not be able to answer some of the questions.
Participants are more likely to provide honest answers, because they feel that their identities are anonymous.	Participants must be educated to be able to read and understand the questions.

Advantages	Disadvantages
The format is the same for all participants and does not depend on the mood of the interviewer.	Questions cannot be clarified when the participant does not understand a question.

1.6.3.1 Development and construction of the research instrument

In order to develop the questionnaire, a series of search phrases (refer to section 1.6.1) were used to collect information from databases such as Google Scholar®, PubMed®, EBSCOhost®, SA ePublications, Scopus®, the A to Z Journal list, Science Direct® and textbooks. All these databases can be accessed from the library services on the North-West University (NWU) website. The following articles were specifically used to construct the questionnaire:

Table 1-3: Literature used to develop the questionnaire

Article	Date published	Journal/textbook
Community pharmacists' knowledge and perceptions about adverse drug reactions and barriers towards their reporting in the Eastern region, Alahsa, Saudi Arabia.	2013	Khan, T.M. 2013. *Therapeutic advances in drug safety*, 4(2):45-51.
Recognition and reporting of suspected ADRs by surveyed healthcare professionals in Uganda: key determinants	2014	Kiguba, R., Karamagi, C., Waako, P., Ndagije, H.B. & Bird, S.M. *British medical journal*, 4:1-11, Jul.
Adverse drug events – why we care	2015	Blockman, M. *Current allergy & clinical immunology*, 28(4):248-250, Dec.
Evaluation of the pharmacovigilance system in the Dr Kenneth Kaunda District in the North-West Province.	2015	Goosen, L. Potchefstroom: NWU (Dissertation – MPharm)
A study on creating awareness of ADRs in community pharmacists in Bangalore	2015	Nagaraju, K., Satheesh, V.K., Shankar, U. & Banu, R. 2015. *Indian journal of pharmacy practice*, 8(2):72-77.
Factors affecting ADR reporting of healthcare professionals and their knowledge, attitude and practice toward ADR reporting in West Ethiopia	2016	Gurmesa, L.T. & Dedefo, M.G. *Biomed research international*, 1-6, Oct.
How to promote ADR reports using information systems – a systematic review and meta-analysis	2016	Ribeiro-Vaz, I., Costa Santos, C. & Cruz-Correia, R. *BioMed central medical informatics and decision making*, 16:27, Mar.

1.6.3.2 General aspects that were considered

The following aspects were carefully considered during the development of the structured questionnaire:

1.6.3.2.1 Instructions

The instructions on completing the questionnaire successfully were simple, clear and concise. The instructions helped the participants to complete the questionnaire without any obstacles.

1.6.3.2.2 Completion time of questionnaire

The participants were able to complete the questionnaire electronically in their own time at the office or at home. The questionnaire would not take longer than 30 minutes to complete.

1.6.3.2.3 Question sequence

The questions were ordered in such a manner as not to confuse the participant. The questionnaire starts with a few demographic information questions. Subject-specific questions follow in logical order.

1.6.3.2.4 Question-wording

The questionnaire was in both English and Afrikaans. No leading or double questions were asked to avoid guiding the respondent in a certain direction. Questions were formulated in the first person.

1.6.3.2.5 Types of questions

The following aspects were avoided during the development of the questionnaire (Neuman, 2014:321-325):

- Asking questions beyond the respondents' capabilities.
- Doubt, vagueness and distraction.
- False promises.
- The use of ambiguous language.
- The use of emotional language and prestige bias.
- The use of overlapping or unequal response categories.
- Using double negatives in English.
- Using jargon, abbreviations and slang.

- Using leading questions.

A combination of question types was used to get a clear view of the pharmacist's knowledge and perceptions regarding the reporting of ADRs, namely:

- **Open questions:** An open question is a question where space is provided for a word, phrase or a comment (Maree & Pietersen, 2013:161). With open questions in the questionnaire, respondents are able to give honest answers and details.

- **Closed-ended questions:** Close ended questions can be a simple 'yes' or 'no' question, multiple-choice questions, checklist-type questions, 'true' of 'false' questions and matching questions (Brink *et al*., 2012:154). These questions are more easily analysed and better suited for computer analysis.

- **Dichotomous questions**: This type of question is one of which there are only two possible answers, for example, "yes" or "no" (Brink *et al*., 2012:155).

- **Ranking questions:** These questions may be used to analyse how respondents rank certain issues in terms of their relevance or preference. Instructions must be formulated carefully (Maree & Pietersen, 2013:162). Ranking questions help to determine the respondent's attitude towards something.

- **Biographical questions:** Important information is retrieved from the participant by asking a number of biographical questions, for example, the respondent's gender, age and qualification are important to determine the profile of the sample (Maree & Pietersen, 2013:164).

1.6.3.3 Sections in the questionnaire

The arrangement of questions in a questionnaire is critical. The questions in this study were arranged in such a way that they were logical and relevant to the participant. The following sections were included in the questionnaire:

1.6.3.3.1 Cover letter

A cover letter with background information that explained the purpose of the study was added at the beginning of the questionnaire. The cover letter included the following (Brink *et al*., 2012:39):

- The introduction to the study.

- The title of the research project.

- The rationale for conducting the study.

- The value and usefulness of the study.

- The target population that would be asked to take part in the study.
- Ethical issues of the study.
- A warning of any risks that participation in the study might have, and how these risks would be handled.
- Confirmation of confidentiality and anonymity.
- Guidance on how to complete the questionnaire.
- Contact information of the researcher.

1.6.3.3.2 Structure of the questionnaire

The questionnaire consisted of four sections. The first section was the demographic information that comprised 11 questions. The other three sections of the questionnaire contained 37 questions that focused on the following topics: the reporting of ADRs, pharmacists' perceptions on reporting ADRs and the barriers attached thereto and their knowledge of pharmacovigilance in South Africa.

In order to conclude the empirical research objectives, certain questions needed to be asked in the structured questionnaire. The following questions in the questionnaire obtained the necessary information to achieve the empirical research objectives:

Table 1-4: Questions to achieve empirical research objectives

Empirical research objectives	Questionnaire sections to obtain research objectives
Objective 1: **Determine pharmacists' past experience with the reporting of ADRs, stratified by pharmaceutical sector and demographic information.**	Section A: Demographic information
	Section B: Experience with reporting of ADRs • Have you observed any ADRs during the previous months? • When did you observe the above ADRs? • Have you ever heard of ADR reporting? • Do you know where to obtain the ADR forms?

	• Have you reported an ADR in your professional career? • Give a brief description of the reported ADR(s) and the process you followed to report the ADRs: • Estimate the number of ADRs you have reported in your professional career. • Which ADRs do you think should be reported? • Which product stability problems do you think should be reported? • Have you received completed ADR forms from a patient / physician? • Which healthcare professionals do you think should report ADRs? • To whom do you think should patients report ADRs? • Indicate the minimum information required to report an ADR on the official ADR form.
Objective 2: **Assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographic information.**	Section A: Demographic information
	Section C: Perceptions on reporting ADRs and the barriers thereof
Objective 3:	Section C: Perceptions on reporting ADRs and the barriers thereto

Determine from the perceptions of pharmacists possible factors that influence the successful implementation of pharmacovigilance in different pharmaceutical sectors in SA.	Section D: Knowledge of pharmacovigilance in South Africa • Are you familiar with the term pharmacovigilance? • Please define pharmacovigilance in your own words. • Who acts as South-Africa's pharmacovigilance unit? • Does pharmacovigilance in South Africa and the identification of ADRs influence national regulatory decision-making? • Is drug monitoring in South Africa of value as a tool for detecting ADRs? • Is the effectiveness of a national post marketing surveillance programme directly dependent on the active participation of health professionals? • Does pharmacovigilance improve patient care and safety regarding the use of medicine? • Is pharmacovigilance improving public health and safety towards the use of medicine? • Pharmacovigilance promotes education in the reporting of ADRs. • The current ADR reporting system in South Africa is sufficient. • More educational training is needed in this field during and after the completion of the BPharm degree. • More training in pharmacovigilance regarding specific products is needed by pharmaceutical companies.

	• More training in pharmacovigilance is needed by pharmacy schools in the under-graduate programmes. • More continuing education programmes in pharmacovigilance are needed by pharmacy schools and other training institutions. • Do you think if more pharmacists reported ADRs, it would make a difference in the current healthcare system of South Africa? • In your opinion, do you believe that reporting of ADRs is included in your task performance in your current work environment?
Objective 4: **Identify pharmacists' additional training needs regarding ADR reporting and pharmacovigilance.**	Section A: Demographic information
	Section D: Knowledge of pharmacovigilance in South Africa

1.6.3.4 Validity of data collection tool

The validity of a questionnaire or instrument indicates the extent to which it assesses what it is supposed to measure (Maree & Pietersen, 2013:216). The validity of the questionnaire can be threatened by the following factors (Maree & Pietersen, 2013:218):

- The reliability of the instrument -- In this study unreliability was avoided through methods discussed in 1.6.3.5.
- Respondents may tend to answer "yes" to all the questions. -- In this study, formulating some questions positively and some negatively prevented this.
- Item bias – Some groups systematically score items higher/lower than others due to external factors.

For this data collection tool, face and content validity are evaluated by specialists in the field to ensure that the questionnaire is acceptable, objective and reliable (Maree & Pietersen, 2013:216).

- Face validity

Face validity indicates the degree to which the questionnaire "looks" valid and that it appears to evaluate what it is supposed to evaluate (Maree & Pietersen, 2013:217). It is based on the intuition made by a specialist in the field of questionnaire development and data analysis (Brink *et al*., 2012:166). The face validity of this study's questionnaire was evaluated by a statistician of the North-West University (NWU).

- Content validity

Content validity indicates the degree to which the questionnaire or instrument covers the complete content of the specific construct that it is set out to evaluate (Maree & Pietersen, 2013:217). It is an assessment of how well the questionnaire represents all the components of the variables to be evaluated (Brink *et al*., 2012:166).

The content validity of this study's questionnaire was confirmed by subject specialists, as well as registered pharmacists. The instrument was given to the supervisors and personnel of the subject areas Pharmacy Practice and Clinical Pharmacy at the NWU to evaluate the content in terms of clarity of questions and terms and whether it measured the essential elements of pharmacovigilance. Participants partaking in the evaluation of the questionnaire were not permitted to participate in the study as participants (refer to the exclusion criteria, section 1.6.2.3.2).

1.6.3.5 Reliability of data collection tool

Reliability is when an identical instrument is used at distinct times or given to different subjects from the same population, the findings should be the identical (Maree & Pietersen, 2013:215).

1.6.4 Recruitment and data collection process

1.6.4.1 Permission

Approval from the following sectors was obtained before the questionnaire was distributed to participants:

- Ethics approval from the Health Research Ethics Committee (HREC) of the NWU Potchefstroom (Annexure E).
- The study mediator signed a confidentiality agreement.

1.6.4.2 Identification of possible participants

The research entity, Medicine Usage in South Africa (MUSA), bought the Register of Pharmacists from the SAPC (Annexure D). The public can access the Register of Pharmacists online for free. A printable or

electronic version of the Register of Pharmacists is available at a cost from the office of the registrar of the SAPC. Table 1-5 presents the number of registered pharmacists as on 18 March 2018 (SAPC, 2018).

Table 1-5: Number of registered pharmacists on Pharmacist Register of the SAPC

Province	Pharmacist	Specialist pharmacist
Eastern Cape	1 786	0
Free State	496	0
Gauteng	5 053	5
KwaZulu-Natal	2 078	0
Limpopo	634	0
Mpumalanga	621	0
North West	653	1
Northern Cape	193	1
Unknown	499	3
Western Cape	2 397	2

SAPC (South African Pharmacy Council). 2018. Statistics for registered persons and organisations. http://www.pharmcouncil.co.za/B_StatsRolesByProv.asp Date of access: 18 Mar. 2018.

1.6.4.3 Recruitment

Pharmacists with email addresses on the register of pharmacists received an email inviting them to participate in the study with a link attached to the questionnaire. Email addresses were obtained from the Register of Pharmacists and were used according to the Protection of Personal Information (POPI) Act (4 of 2013). The study mediator sent the invitation, including the informed consent with the attached questionnaire to all possible participants. Participants had the choice to participate or not. No participant (pharmacist) was excluded after he or she indicated that they wanted to participate.

1.6.4.4 Role of the study mediator

The study mediator, Mrs Celeste Rossouw, was appointed by MUSA to recruit the participants. The study mediator was furthermore responsible for distributing the questionnaires via email and also received the completed electronic questionnaires. Once the completed questionnaires were received by the study mediator, the results were exported to a Microsoft Excel® spreadsheet and sent to the supervisor, researcher and/or statistician.

The study mediator obtained the email addresses from the Register of Pharmacists which was bought from the SAPC by MUSA. The structured questionnaire was distributed by using the SurveyMonkey® software. SurveyMonkey® provides customisable surveys, as well as back-end programmes that can analyse data, select samples, eliminate bias and data representation tools.

The study mediator also assisted in the preliminary statistical analysis of the responses and gave feedback in the form of an article to participants via email.

1.6.4.5 Process of obtaining informed consent

All pharmacists on the Register of Pharmacists of the SAPC with email addresses received an email from the study mediator. The sample size consisted of 11 732 pharmacists. The email included a short description of the study and an informed consent document. When the participant agreed to participate in the study, he/she gave consent by clicking the "agree" button. When consent was given, the link led to the questionnaire. The detailed consent document (Annexure A) included information about the purpose of the study, as well as the procedures that were to be followed during the study.

1.7 Statistical analysis

The IBM SPSS® Statistics Version 26 was used to analyse the data received, with the involvement of a statistician of the NWU.

Both descriptive and inferential statistics were used. Variables were expressed using descriptive statistics which include, *inter alia,* frequencies (n), and percentages (%). Inferential statistics include the chi-square test (x^2). All statistical significance was considered with a two-sided probability of $p < 0.05$.

The chi-square test (x^2) was used to determine whether an association exists between proportions of two or more categorical variables. The Cramér's *V* statistic was used to test the practical significance of this association (with Cramér's $V \geq 0.5$ defined as practically significant) (SPSS, 2019).

The Binomial test was used to compare two proportions and to determine whether the difference between the two proportions was of statistical significance. The results were seen as statistically significant when the *p*-value was $p \leq 0.05$.

The following equation was used to calculate the effect size (Steyn, 2000):

$$\delta_{\frac{1}{2}} = 2\left(\frac{x}{n}\right) - 1$$

where x = number of people who responded positively and n = sample size. The effect was calculated as small (non-significant) when $\delta_{\frac{1}{2}}$ = 0.1, medium (observable) when $\delta_{\frac{1}{2}}$ = 0.3, and large (statistically significant) when $\delta_{\frac{1}{2}}$ = 0.5. The following data-analysis plan was followed:

Table 1-6: Data-analysis plan

Empirical research objective	Measurement	Variables		Statistics		
		Independent	**Dependent**	**Descriptive**	**Inferential**	**Practical Significance**
Objective 1: **Determine pharmacists' past experience with the reporting of ADRs, stratified by pharmaceutical sector and demographic information.**	Past experience with the reporting of ADRs, stratified by pharmaceutical sector and demographic information.	• Age group • Gender • Highest pharmacy qualification obtained • Years of experience • Current and former work environment (pharmaceutical sector)	**Section A:** Additional training	Frequency (%)	Chi-square	$p < 0.05$. Cramér's *V* Binomial test
			Questions in Section B: • Have you noticed any ADRs during the last months? • How long ago did you notice the above ADRs? • Have you ever heard about ADRs reporting? • Have you reported an ADR in your professional career? • Estimate the number of ADRs you have reported in your professional career. • Have you observed any ADRs that caused the following? what? • Have you received completed ADR forms from a patient / physician? • Which healthcare professionals do you think should report ADRs? • If you are going to report an ADR, to whom would you report it?	Frequency (%)	Chi-square	$p < 0.05$. Cramér's *V* Binomial test

Objective 2: **Assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographical information.**	Assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographical information.	• Age group • Gender • Highest pharmacy qualification obtained • Years of experience • Current and former work environment (pharmaceutical sector)	**Questions in Section C:** • Are you as a pharmacist willing to report ADRs? • Do you think you have the ability to report ADRs? • The following factors may encourage you to report an ADR? • The following factors may discourage you from reporting and ADR?	Frequency (%)	Chi-square	$p < 0.05$. Cramér's *V* Binomial test
Objective 3: **Determine from the perceptions of pharmacists, possible factors that influence the successful implementation of pharmacovigilance in different pharmaceutical sectors in South Africa.**	Determine possible factors that influence the successful implementation of pharmacovigi-lance in different pharmaceutical sectors in South Africa.	• Age group • Gender • Highest pharmacy qualification obtained • Years of experience • Current and former work environment (pharmaceutical sector)	**Questions in Section C:** • The following factors may encourage you to report an ADR? • The following factors may discourage you from reporting and ADR?	Frequency (%) *If normal distributed:* Mean ± SD, *If skew distributed*: Median, IQR	Chi-square	$p < 0.05$. Cramér's *V* $p < 0.05$.

Objective 4: **Identify pharmacists' additional training needs about ADR reporting and pharmacovigilance.**	Identify pharmacists' additional training needs about ADR reporting and pharmacovigi-lance.	• Age group • Gender • Highest pharmacy qualification obtained • Years of experience • Current and former work environment (pharmaceutical sector)	**Questions in Section D:** • Do you understand the process of reporting an ADR? • Are you willing to undergo additional training regarding the reporting of ADRs? • Do you think it would be financially beneficial for hospitals (community and public) if more healthcare professionals reported ADRs? • Do you think if more pharmacists report ADRs, it would make a difference in the current healthcare system of South Africa? • In your opinion, do you believe that reporting ADRs forms part of the Scope of Practice of the pharmacist?	Frequency (%)	Chi-square	$p < 0.05$. Cramér's *V*

Abbreviations: ADR: Adverse drug reaction, ANOVA: Analysis of variance; Cl: Clearance; IQR: Interquartile range; SD: Standard deviation.

1.8 Ethical considerations

The following ethical principles were considered when conducting the research project:

1.8.1 Ethical approval, permission and informed consent

Before the commencement of the study, ethical approval for the study was obtained from HREC of the NWU (NWU-00137-17-S1) (Annexure E).

Informed consent (Annexure A) was obtained from each participant before answering the questionnaire. This included providing them with the necessary information regarding the study, giving them the opportunity to raise any concerns they might have had regarding the research project. They were also aware that they may at any time choose to withdraw from the study without any consequences to themselves. The participants were informed that their identities would remain anonymous and that all data would be handled with confidentiality.

1.8.2 Anonymity

During the study and analysis of the results, the members of the research team were not able to see the participants' responses, thus no link could be made between a specific respondent and a specific questionnaire. The study mediator signed a confidentiality agreement. When completed questionnaires were received, the study mediator sent only the participants' responses to the study leader or statistician for the data to be analysed. No link could then be made between the responses and the participants' email addresses. Therefore, the anonymity of the participant was ensured. The process of obtaining the respondents' email addresses was thoroughly discussed in point 1.6.4.3.

1.8.3 Confidentiality

The participants' right to privacy was respected by the researcher and mediator. The researcher and mediator were not able to identify the participants from the responses received, as the email addresses were not linked to their data. Each participant has the right to determine the extent to which his/her private information is shared with others (Brink *et al*., 2012:37). This includes the participant's attitudes, beliefs, behaviour and opinions. During analysis of the data, the statistician was not able to identify the participants. Results would be published as an article, where no information about the participants would be revealed. When participants agreed to participate in the study, their information would remain anonymous and confidential.

1.8.4 Justification of the study

Pharmacists can be utilised to supervise the safe and effective use of available medication, which includes the management of ADRs. Pharmacists are valuable in gathering and delivering pharmacovigilance information. Not many studies have been done on exploring the knowledge and perceptions of pharmacists in South Africa towards the practise of pharmacovigilance and the reporting process of ADRs (Joubert & Naidoo, 2016; Khan, 2013b). In this study, the researcher also wants to differentiate between different sectors.

1.8.5 Respect for required participants

Participants have the right to autonomy, which implies that they had the right to decide whether or not they wanted to partake in the research, without the prospect of penalty. Withdrawal from the study is also in the rights of the participant, after being allowed to ask for clarification about the purpose of the study (Brink *et al*., 2012:35). The researcher protected the participants from any harm during the study – be it physical, psychological, emotional, spiritual, economic, social or legal. During the study, all participants' identities were protected. Before participating in the study, participants were asked whether they wanted to partake in the study. If the participant decided to participate in the study, a statement was attached to the questionnaire explaining that they could withdraw from the study at any time, without penalty. If they felt that any harm was being done to them, they could also withdraw from the study.

During the study, all participants were treated as autonomous agents, i.e. he/she had to be capable of self-determination as prescribedby the NWU Research Ethics Policy, 2016. The Merriam-Webster Dictionary (2017) defines self-determination as "the unrestricted choice of one's own acts or states without external coercion". If during the study the participant was incapable of such self-determination, the research would be conducted in such a way as to safeguard the participant against distress, taking into account the principles of beneficence and justice as discussed in 1.8.4.

Respect for participants during the study also required having due regard for their health, beliefs, judgment, customs and cultural heritage, both individual and collective, of those involved in the research. Any specific agreements made with the participants were fulfilled.

1.8.6 Benefit-risk ratio analysis

1.8.6.1 Anticipated benefits

1.8.6.1.1 Direct benefits

- The participants will gain knowledge of the reporting processes of ADRs.

- There will be development in the participants' understanding of the importance of ADR reporting and the processes that should be followed.

1.8.6.1.2 Indirect benefits

- The healthcare delivery to the public will improve through the understanding of pharmacists regarding the distinguishing and reporting of ADRs.
- There will be an increase in the understanding of preventative health measures.
- Pharmacists will be able to assist in the identification of ADRs, report these reactions and change the patients' treatment regimes to improve the efficacy of their medication.

1.8.6.2 Anticipated risks and precautions

Table 1-7 Anticipated risks and precautions for consideration prior to the study

Risks and precautions of the study, i.e. ethical considerations		
	Precautions	**Risks**
Right to self-determination	All participants will be competent to complete the questionnaire. No participants that are mentally/terminally ill will need to participate in the study.	The risks of not being able to identify whether or not the participant will be able to complete the questionnaire can be a small risk.
Right to anonymity and confidentiality	Codes will be used to ensure the participants' details are kept private.	There is a small risk of identification involved.
Right to fair treatment	All pharmacists with the correct and active email addresses on the Register of Pharmacists will be requested to partake in the study. No pharmacists will be excluded after they have indicated that they want to participate.	The small risk involved is that some pharmacists may be excluded. Participants are not unfairly selected. Participation in the study is not compulsory.

Right to protection from discomfort and harm	Participation in this study is optional and no discomfort will come to the respondent if he/she chooses not to partake in the study.	No risk is involved.
Right to privacy	To protect the respondents' information, only the researcher, project leader and study mediator will have access to the possible participant's email address, which will only be used by the study mediator. The researcher and supervisors will not know who, from the list of pharmacists, participated in the study.	The respondents' email addresses will not be used in the analysis of the data of the study. The returned data from the study mediator will be saved on the supervisor's and researcher's computers, which are password protected and in a locked room at all times. There will be no risks associated with privacy.
Risks involved for the participant and the researcher		
Risk	**Risk for participant**	**Risk for researcher**
Informed consent not given by participant	No harm or risk involved.	The participant can decide not to agree to participate in the study, which will make the study population smaller.
Information misunderstood by participants	Participants might feel illiterate.	Incomplete questionnaires could lead to insufficient data.
Time for completing the questionnaire	Participants might feel that it is a loss of time to complete the questionnaire.	Incomplete questionnaires could be returned. Questionnaires might be completed hastily, leading to insufficient data.

1.8.6.3 Level of ethical risk

If anonymity and confidentiality are maintained, the benefits of conducting this study will **outweigh** the associated **risks**.

The anticipated risks level associated with this study was medium.

1.9 Chapter summary

Chapter 1 explained the aim and purpose of this research. The need for the study is explained in the background section as well as within the problem statement. A relevant data collection tool was used to reach the objectives of the study by following an appropriate research method. The data analysis plan was created to explain how data would be retrieved to ensure validity and reliability. Ethical permission was compulsory through ethical guidelines to prevent risk and harm to any participants and researchers.

CHAPTER 2

ADVERSE DRUG REACTIONS AND PHARMACOVIGILANCE

2.1 Introduction

In this chapter the terms adverse drug reaction (ADR), adverse drug event (ADE), inappropriate drug use and medication error will be discussed in detail as well as the relationship between the terms. Adverse drug reactions will be defined and discussed according to their different categories and severity. The burden of ADRs will be discussed globally and in South Africa.

2.1.1 Background

Adverse drug reactions cause a lot of agony and casualty in patients that lead to an increase in healthcare costs (Blockman, 2015:248) and have become a large implication in healthcare systems (Lagnaoui *et al.*, 2002:181).

Adverse drug reactions are amongst the top ten major causes of death in the United States of America (USA) (Montanari-Vergallo, 2013:2). A study in Nigeria disclosed that 23% of patients admitted to hospitals developed ADRs during their stay and 12% of patients admitted to hospitals were as a result of of ADRs. In South Africa, ADRs contributed to 2.9% of hospital admissions where 16% of the deaths were the result of ADRs (Mouton *et al*., 2014:818). This study also indicated that approximately one in 12 hospital admissions was due to ADRs, of which 43% were preventable (Mouton *et al*., 2014:818). In a regional hospital in Uganda, ADRs have become one of the major burdens in their healthcare system (Tumwikirize *et al*., 2011:72). These reactions may lead to hospitalisation, patient suffering and economic agony (Almandil, 2016:1359; Mehta *et al*., 2013; Nagaraju *et al*., 2015:72).

The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) reported that there has been an increasing number of reports of ADRs by pharmacists and physicians in the United States from 2011 to 2018 (FAERS, 2019). Underreporting by pharmacists is a communal problem in various countries (Ali *et al.,* 2018; Bogolubova *et al*., 2018; Joubert & Naidoo, 2016; Shamim *et al*., 2016). A study done in Damman, Saudi Arabia indicated that only 34% of healthcare providers, which included 25 doctors, 65 nurses, 50 pharmacists and 25 other healthcare providers, had ever reported an ADR (Ali *et al*., 2018:21). Pharmacists are not aware that they have a responsibility for reporting ADRs. Pharmacists believe it is the physicians' responsibility to do so (Green *et al*., 2001). Joubert and Naidoo (2016:241) identified that 55.9% of pharmacists in South Africa felt that the pharmacovigilance unit of the National Adverse Drug Event Monitoring Centre (NADEMC), is remote, which is discouraging them from reporting ADRs. The study done by Bogolubova *et al*. (2018) in the South African private hospital sector stated that

13.7% of healthcare professionals do not receive any feedback once the reporting form has been sent. Healthcare professionals (54.5%) also revealed that they do not have the knowledge to report ADRs as 76.2% of the participants have not received any pharmacovigilance training (Bogolubova, 2018:1). In Saudi-Arabia a study revealed that 16 out of 25 pharmacists in hospitals were not aware of the national pharmacovigilance system (Mohamed & Basel, 2015:157).

2.2 Adverse drug reactions, adverse drug events, inappropriate drug use and medication errors.

2.2.1 Adverse drug reactions

According to the WHO (2002), '*an adverse reaction to a drug is one that is noxious, is unintended and occurs at doses normally used in man.*' The South African Medicine and Related Substances Control Act (101 of 1965) defines an ADR as "*a response that occurs in a human or animal to a medicine which is unsafe and unexpected and which results at any dosage and can appear from lack of potency of a medicine, off-label use of medicine, overdose, misuse or abuse of a medicine"*. The South African Health Products Regulatory Authority (SAHPRA) defines an ADR as "*a response to a medicine in humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine"* (SAHPRA, 2019).

The definitions above therefore indicate that an ADR is a reaction to a drug that occurs in animals or humans, but is unintended and noxious and can occur as a result of an unsafe drug dose, overdose of the specific drug and incorrect use of the drug.

Adverse drug reactions can be classified into different categories according to how severe they are and their types. Table 2-1 illustrates the features and management of ADRs according to classification (Edwards & Aronson, 2000).

Table 2-1: Classification of adverse drug reactions

Type of reaction	Features	Examples of drugs	Reaction	Management
Type A: Dose-related (Augmented)	Common, according to pharmacological action of the drug. Forseeable. Low chance of death.	Tricyclic antidepressants. Opioids. Warfarin. SSRIs.	Dry mouth. Respiratory depression. Bleeding. Serotonin syndrome.	Reducing the dose or withholding the drug.

Type B: Non-dose related (Bizarre)	Not common. Not related to pharmacological action of the drug. Unforseen. High chance of death.	Penicillin. General anaesthetics.	Anaphylaxis. Malignant hyperthermia.	Withhold the drug and avoid future use of the drug.
Type C: Dose- & time related (Chronic)	Not common. Related to the cumulative dose.	Corticosteroids. Bisphosphonates.	Hypothalamic-pituitary-adrenal axis suppression. Osteonecrosis.	Decrease dose or withhold. Longer withdrawal period.
Type D: Time-related (Delayed)	Not common. Usually dose-related. It becomes visible some time after use of the drug.	Lomustine.	Leukopenia. Carcinogenesis. Teratogenesis.	Often intractable.
Type E: Withdrawal (End of use)	Not common. Effects occur soon after the withdrawal of the drug.	Opiates and benzodiazepines.	Insomnia, anxiety (withdrawal syndrome).	Reintroduce drug and withdraw slowly.
Type F: Unexpected failure of therapy (Failure)	Common. Dose-related. Mostly caused by drug interactions.	Antimicrobial agents.	Resistance.	Increase dose. Concomitant therapy should be considered.

SSRIs: Selective serotonin reuptake inhibitor

Adapted from Edwards, I.R. & Aronson, J.K. 2000. Adverse drug reaction: definitions, diagnosis and management. *The Lancet,* 356(9237):1255-9.

The WHO Uppsala Monitoring Centre (WHO-UMC) provides a practical method to assess case reports received. The system is used to detect unknown and unexpected ADRs. This assessment is based on the availability of the following criteria and the level of casualty is grouped into four categories, which are based on a number of the criteria below being met (WHO, 2000):

a) Correlation between the adverse reaction and the drug according to time.

b) The lack of appearance of other competing causes (medicine, disease).

c) Reaction to drug withdrawal or decreased dose.

d) Reaction to drug re-administration.

An ADR can be classified as 'certain' when all four (a, b, c, d) of the above criteria are met, 'probable' when criteria a, b and c are met, 'possible' if only criteria a is met and 'unlikely' when criteria a and b are not met. The ADR can be classified as 'conditional' or 'unclassified' when more data is needed to determine the ADR, and as 'un-assessable' or 'unclassifiable' if the data of the ADR is insufficient or needs to be verified.

Table 2-2 describes a categorical system used by the World Health Organization Uppsala Monitoring Centre (WHO-UMC) to determine the causality of ADRs (WHO, 2014:1). According to the Medical Dictionary for the Health Professions and Nursing (2012), causality can be described as "*the relating of causes to the effect they produce; the pathogenesis of disease and epidemiology are largely concerned with causality*". This method is used to regulate the analysis of the likelihood that medicine is the causal agent of the ADR (Rodrigues *et al*., 2018). The causality assessment is described in Table 2-2.

Table 2-2: WHO-UMC causality categories

Causality assessment	Description
Certain	When an irregularity exists with the clinical or laboratory results, which occurs in a certain time in relation to the drug administration. It cannot be described by underlying simultaneous diseases or other medicines/chemicals. Response to the withdrawal of the drug is clinically possible. The event is definitive as pharmacological or phenomenological. Re-challenge is acceptable, if needed.
Probable/Likely	When an irregularity exists with the clinical or laboratory results, which occurs in a certain time in relation to the drug administration. Not likely to be attributed to underlying simultaneous disease or other medication/chemicals. Response to the withdrawal of the drug is clinically possible. Re-challenge is not necessary.
Possible	When an irregularity exists with the clinical or laboratory results, which occurs in a certain time in relation to the drug administration. Could be explained by underlying simultaneous disease or other medication/chemicals. Particulars on drug withdrawal may be absent or doubtful.

Unlikely	Clinical event or laboratory test irregularity with the time to drug administration that makes a relationship unlikely, but not impossible. Underlying simultaneous disease or other medication/chemicals provide possible explanations.
Conditional/Unclassified	Clinical event or laboratory test irregularity. Reported as an ADR. More data needed for decent assessment or additional data needs examination.
Un-assessable/ Unclassifiable	A report suggesting an adverse reaction/event. It cannot be determined because of inadequate or contradictory information. Data cannot be amplified or verified.

Adapted from: (WHO) World Health Organization. 2014. The use of the WHO-UMC system for standarised case causality assessment. Geneva.

Reporting suspected ADRs to the necessary authority could assist in identifying an informal relationship between the drug and the ADR (WHO, 2014). This will provide important information or warnings to other healthcare providers to prevent future ADRs in their patients. Several algorithms have been developing to assist with the determination of causality of ADRs (Gallagher, 2011; Naranjo, 1981; WHO, 2014). Among the WHO-UMC method (WHO, 2014), there are also the Naranjo probability scale and the Liverpool assessment tool (Gallagher, 2011; Naranjo, 1981) which are being used for their simplicity and time efficiency. These scales can be seen in Table 2-3 and Figure 2-1 respectively.

Table 2-3: Naranjo ADR Probability Scale

Question	Yes	No	Do not know	Score
"Are there previous conclusive reports on this reaction?"	+1	0	0	
"Did the adverse event appear after the suspected drug was administered?"	+2	-1	0	
"Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?"	+1	0	0	
"Did the adverse event appear when the drug was re-administered?"	+2	-1	0	
"Are there alternative causes that could have caused the reaction?"	-1	+2	0	
"Did the reaction reappear when a placebo was given?"	-1	+1	0	
"Was the drug detected in the blood in concentrations known to be toxic?"	+1	0	0	
"Was the reaction more severe when the dose was increased or less severe when the dose was decreased?"	+1	0	0	
"Did the patient have a similar reaction to the same or similar drugs in any previous exposure?"	+1	0	0	
"Was the adverse event confirmed by any objective evidence?"	+1	0	0	
ADR Probability Classification	**Total score**			
Highly Probable	9			
Probable	5-8			
Possible	1-4			
Doubtful	0			

Adapted from: Naranjo, C.A. 1981. A method for estimating the probability of adverse drug reactions. *Clinical pharmacological therapy,* 30:239-45.

The Gallagher flowchart, known as the Liverpool ADR causality tool (Figure 2-1) presents a series of questions with 'yes' or 'no' answers which lead to the reaction being definite, probable, possible or unlikely to help guide treatment and therapy options (Gallagher *et al*., 2011).

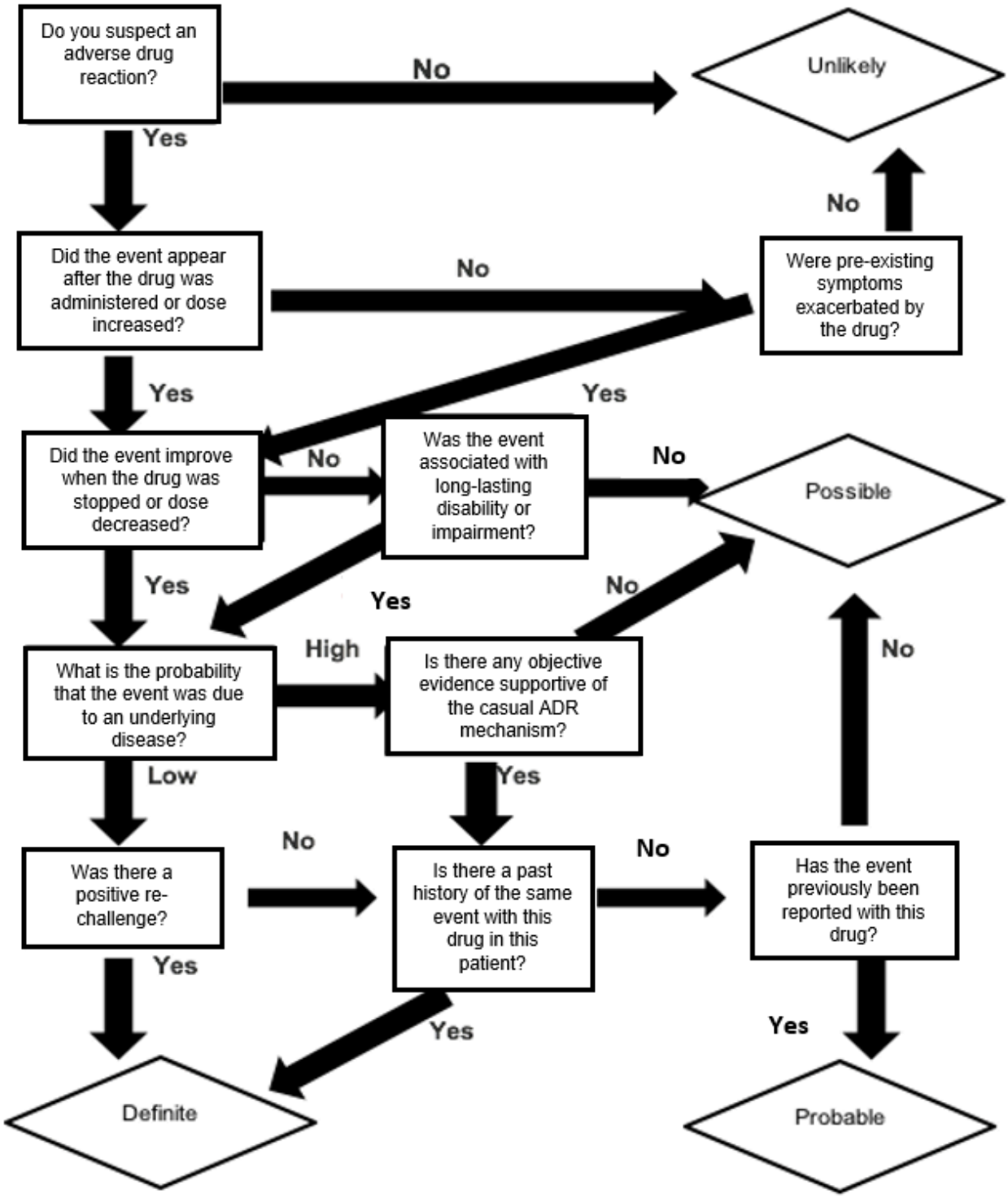

Figure 2-1: The Liverpool adverse drug reaction causality tool

Adapted from: Gallagher, R.M., Kirkham, J.J., Mason, J.R., Bird, K.A., Nunn, A.J., Turner, M.A., Smyth, R.L. & Pirmohamed, M. 2011. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. *Public library of science,* 6(12):e28096.

According to Smith-Marsch (2018), different types of ADRs and the severity of ADRs can be described in different ways by general practitioners. The types of ADRs are described in Table 2-4 and the severity of ADRs are described in Table 2-5 (Edwards & Aronson, 2000:1255; Smith-Marsh, 2018; WHO:2014:1).

Table 2-4: Types of adverse drug reactions

Reaction	Description	Example of reaction
Dose-related ADRs	This reaction is an amplification of the drug's therapeutic effects. Predictable, but sometimes unavoidable. The reaction occurs when the dose of the drug is too high (overdose reaction), if the person is uncommonly sensitive to the drug, or if another drug decreases the metabolism of the first drug and thus increases its level in the blood (drug interactions). Dose-related reactions are usually not serious, but are quite common.	Taking a drug to decrease high blood pressure might cause dizziness if the drug decreases the blood pressure too much. A patient with diabetes might develop weakness, sweating, nausea and palpitations if insulin or an oral antidiabetic drug decreases the blood sugar level too much.
Allergic drug reaction	Not dose-related, but requires previous exposure to a drug. After a person is sensitised, later exposures to the drug produce one of several different types of allergic reactions.	The body's immune system develops an inappropriate reaction to a drug, which leads to an allergic reaction.
Idiosyncratic ADRs	The results from mechanisms that are not clearly understood. Unpredictable. These reactions are more serious, but typically occur in a very small number of patients. Some ADRs are not related to the drug's therapeutic effect,but are often predictable because the mechanisms involved are highly understood.	Rashes, jaundice, anaemia, a reduction in the white blood cell count, kidney damage and nerve injury that may impair vision or hearing. Stomach irritation and bleeding often occur in patients who often use aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). These medicines decrease the production of prostaglandins, which help to protect the digestive tract from stomach acid.

Adapted from: Smith-Marsh (2018), World Health Organization (WHO) (2014), Edwards & Aronson (2000).

According to the Smith-Marsh (2018), there is no universal scale to describe or measure the severity of ADRs. Assessment is largely subjective. These ADRs are described as:

- Mild
- Moderate
- Severe
- Lethal (deadly)

Table 2-5: Severity of adverse drug reactions

Reactions	
Mild	Mild reactions usually include: • Trouble with the digestive system • Headaches • Tiredness • Vague muscle pain • A common feeling of illness or discomfort • Changes in sleep sequences The goal of treatment might not be achieved if patients tend to not take the medicine as instructed.
Moderate	Moderate ADRs include: • Rashes • Visual disruption • Muscle tremor • Difficulty with urinating • Any noticeable change in mood or mental function • Certain changes in blood components, such as a temporary, reversible reduction in the white blood cell count or in blood levels of some substances, such as glucose.
Severe	Severe reactions include those that may be life-threatening. • Liver failure, abnormal heart rhythms which result in on-going or remarkable disability or hospitalisation and which cause a birth defect. • Severe reactions are quite rare. People who develop a severe reaction should usually stop using the drug and must be treated.

	• Doctors must sometimes continue giving high-risk drugs (for example, chemotherapy to people with cancer or an immunosuppressant to people undergoing organ transplantation). • Doctors use every possible way to control severe ADRs.
Lethal	• Lethal reactions are those in which a drug reaction directly or indirectly caused death. • These reactions are quite severe reactions that were not noticed in time or did not respond to treatment. • Lethal reactions can be the reason why some drugs are withdrawn from the market.

Adapted from: Smith-Marsh (2018), WHO, 2014; Edwards & Aronson (2000).

Moderate ADRs from, for example, hormonal contraceptives and non-steroidal anti-inflammatory drugs that cause venous thrombosis and hypertension respectively, need a change in treatment, but not necessarily discontinuation of the medicine (Wakaskar, 2017). Hospitalisation may be prolonged with moderate ADRs (Wakaskar, 2017:1).

Adverse drug reactions classified as severe are life-threatening and discontinuation of the drug and treatment is required. Angiotensin-converting-enzyme inhibitors (ACEs) causing angioedema and phenothiazines causing abnormal heart rhythm are examples of these ADRs (Smith-Marsh, 2018:2).

An ADR that contributes directly or indirectly to the death of a patient is classified as severe. Severe ADRs occur as a result of, for example, acetaminophen overdose causing liver failure or from anticoagulants causing haemorrhage (Marsh, 2018:2).

Adverse drug reactions can be very difficult to pin down to one specific drug and may be the outcome of a group of drugs. Common drug reactions may include itching, rashes, difficulty in breathing, coughing and even hypotension. Anti-cholinergic drug reactions can affect numerous systems, causing a host of side-effects such as memory loss, confusion, hallucinations and delirium. These drugs are often prescribed to elderly patients, which causes more concern in the case of dementia and impaired cognition (Wakaskar, 2017).

Adverse drug reactions to antibiotics are frequent and often predictable with moderate severity (Stavreva *et al.,* 2008:7). A study conducted in Bulgaria revealed that out of 133 patients who received an antibiotic, 4.54% developed an ADR (Stavreva *et al.,* 2008:7). A study done by Trubiano *et al*. (2015) in Australia, revealed the prevalence of an antimicrobial allergy or ADRs to be 25% among 509 patients. In Uganda, a study on antibiotic-associated ADRs revealed that 19% of inpatients experienced an ADR while 117 patients had a serious ADR (Kiguba *et al*., 2017).

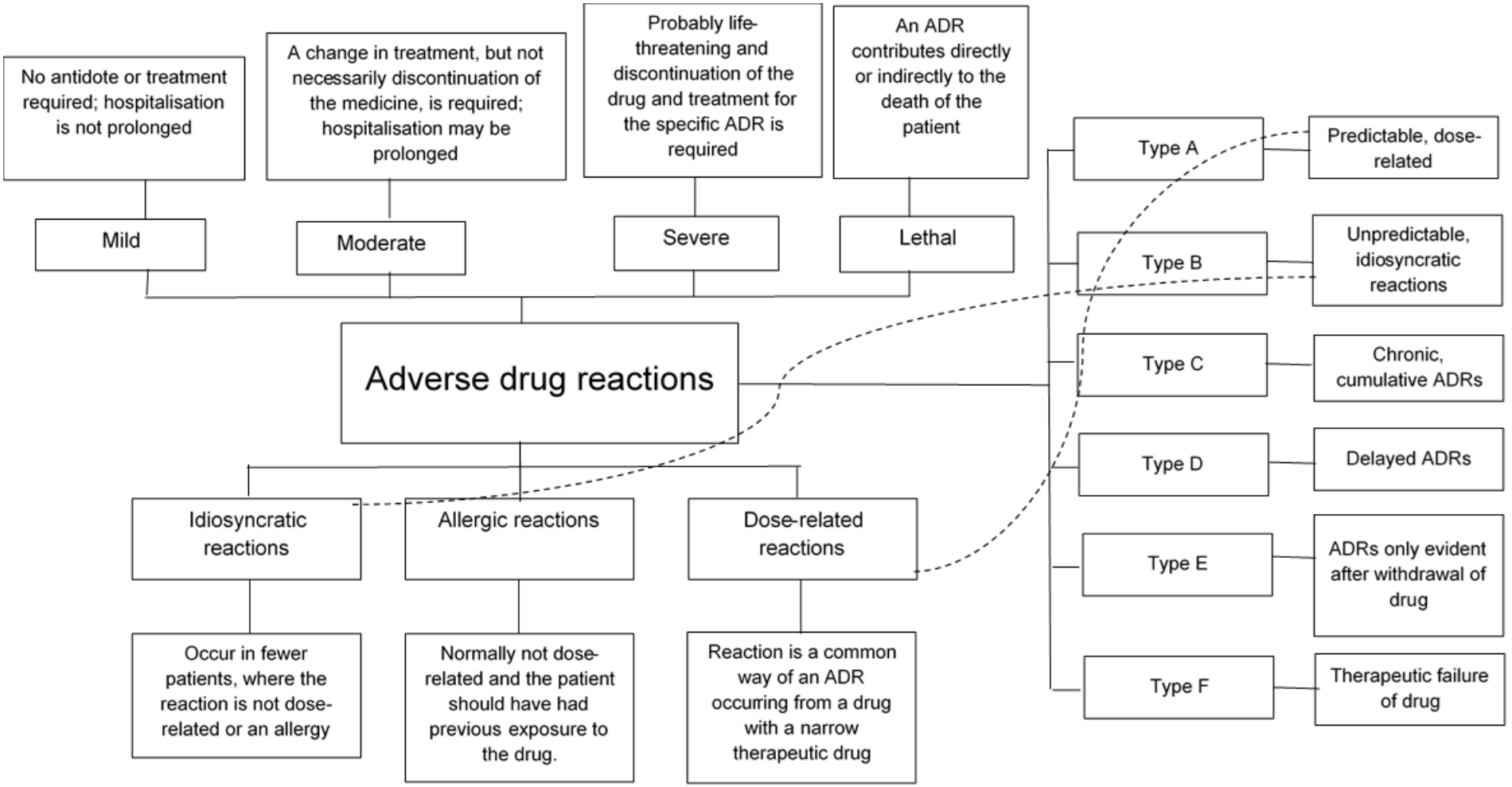

Figure 2-2: Classification of adverse drug reactions

Developed from: Marsh (2018), World Health Organization (WHO) (2014), Edwards & Aronson (2000).

2.2.2 Adverse drug events

An adverse drug event (ADE) is any unmanageable medical manifestation that may occur during treatment with a medicine, but which does not necessarily have any relation with this treatment (SAHPRA, 2019:4). Adverse drug events are both preventable and unpreventable. According to the WHO (2002), an ADE can be defined as a medical occurrence temporarily associated with the use of a medicinal product, but not necessarily causally related. The Office of Disease Prevention and Health Promotion (ODPHP, 2018) defines ADE as "*an injury resulting from medical intervention related to a drug, which includes medication errors, ADRs, allergic reactions and overdoses*".

ADEs can therefore be defined as a negative reaction to a drug caused by an ADR, medication error, allergic reaction or overdose, which can be both preventable and unpreventable. The relationship between ADRs, ADEs and medication errors are presented in figure 2-3. Figure 2-3 shows that most medication errors do not always cause harm to the patient, and the few medications that will cause harm, can be referred to as ADEs (Adapted from Office of Disease Prevention and Health Promotion) (ODPHP, 2018). Adverse drug events are not necessarily caused by medication errors, which shows that they can be prevented. Figure 2-3 explains the connection between the drug and the ADE can be defined as an ADR.

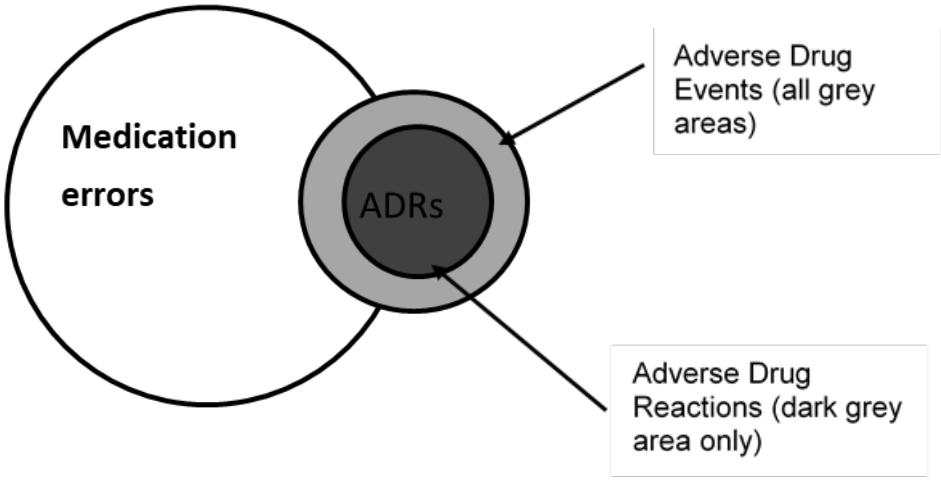

Figure 2-3: Relationship between ADRs, ADEs and medication errors

Adapted from: Office of Disease Prevention and Health Promotion (ODPHP). 2018. Preventing adverse drug reactions. https://health.gov/hcq/trainings/ade-diabetes-agents/Chapt1-NationalRatesADEs/slide02.aspx Date of access: 10 Jan. 2018.

2.2.2.1 Classification of adverse drug events

The U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS (DAIDS) (2017) table for grading adverse drug events (ADEs) consists of parameters to give guidance to the severity of ADEs in order to maintain precision and stability in the evaluation of adverse events. The extremity of a specific adverse drug event describes its potency, which is graded. The DAIDS (2017) grading table provides an adverse event severity grading scale ranging from grades 1 to 5 with descriptions for each adverse drug event based on the following common guidelines (refer to Table 2-6):

Table 2-6: The DAIDS grading table for the severity of ADEs

Parameter	Clinical ADE NOT identified elsewhere in the grading table
Grade 1 – Mild	Mild symptoms causing a minor interference with usual social and functional activities. Intervention is not indicated.
Grade 2 - Moderate	Moderate symptoms causing considerable interference with usual social and functional activities. Intervention is indicated.
Grade 3 - Severe	Severe symptoms causing incompetence to perform usual social and functional activities. Intervention or hospitalisation is indicated.
Grade 4 – Potentially life-threatening	Potentially life-threatening symptoms causing incompetence to perform basic self-care functions, permanent impairment or disability.
Grade 5 - Fatal	All deaths related to an ADE.

Adapted from: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. 2017 .Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events, https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdfpdf Date of access: 10 May 2019.

2.2.2.2 Preventability of adverse drug events

The Schumock criteria method is used to determine the preventability of ADEs. (Hakkarainen *et al*., 2012). The information obtained by this method is important for direction in educational programmes in order to facilitate a decrease in the number of ADEs that occur. The Schumock criteria method has developed a set of questions that are functional in establishing the preventability of ADRs. If a patient can answer “yes” to one or more of the following questions, the ADE might have been prevented (Hakkarainen *et al*., 2012):

1. “Was the drug involved in the ADR **not** considered appropriate for the patient’s clinical condition”?

2. “Was the dose, route and frequency of administration **not** appropriate for the patient’s age, weight and disease state”?

3. “Was required therapeutic drug monitoring or other necessary laboratory tests **not** performed”?

4. “Was there a history of allergy or previous reaction to the drug”?

5. “Was a drug interaction involved in the reaction”?

6. “Was a toxic serum drug level documented”?

7. “Was poor compliance involved in the reaction”?

When healthcare professionals report ADRs, the above criteria of the Schumock method and the DAIDS AE grading table (DAIDS, 2017) should be examined to determine the preventability, severity and causality of the ADRs. These systems are crucial and can be used to ease the developmental process of ADRs.

2.2.3 Medication errors

The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) (2001) defines a medication error as “*any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer*”. Such events may be related to “professional practice, healthcare products, procedures and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use” (NCCMERP, 2018). The definition is broad and suggests that medication errors are preventable at various levels. Table 2-7 describes factors which can cause medication errors and how these errors can be prevented. A study done by Dornan (2009) identified various types of medication errors. The higher result of errors was an omission on admission, under-dosing, over-dosing, strength/dose missing, wrong administration times, duplication, incorrect formulation and unintentional prescription of a drug(s).

A medication error has also been defined by the WHO (2016) as ”*a reduction in the probability of treatment being timely and effective, or an increase in the risk of harm relating to medicines and prescribing compared with generally accepted practice*”. There are a number of different approaches to classify medication errors (Dornan, 2009; Mekonnen *et al*., 2018; NCCMERP, 2001).

Table 2-7: **Factors influencing medication errors and how to prevent these errors**

Factors influencing medication errors	Interventions/Preventability
Healthcare professionals: • Lack of therapeutic training. • The decrease in drug knowledge and experience. • Not enough knowledge of the patient. • Overworked. • Emotional and physical health issues. • Lack of communication among healthcare professionals.	• Education and training on causes of medication errors. • Medication reviews and reconciliation. • Specialist outpatient clinics to be considered for routine monitoring. • Further research on medication errors.
Patients: Characteristics: • Difficult clinical case (polypharmacy, high-risk medication, multiple health conditions).	• Educating patients in medicine management.
Work environment: • Workload and time pressure. • Interruptions and distractions. • Lack of protocols. • Not enough resources. • Physical work environment (ventilation, temperature).	• Time management and working schedules. • Develop the necessary standard operationg procedures the work environment. • Regulatory authorities to investigate work environment conditions.
Medicines: • Medication names. • Labelling and packaging.	• Medicine reconciliation systems.
Computerised information systems: • Level of difficulty to process first prescriptions. • Accuracy of patient records. • Human error because of difficulty in design.	• Automated information systems.

Developed from: WHO. 2016. Medication Errors: *Technical Series on Safer Primary Care*. Geneva.

2.2.3.1 Medication errors classified according to their level of severity

The NCCMERP's (2001) approaches are not complete and there is no secure evidence to support specific methods of defining or classifying errors, especially in primary care. These approaches depend on the situation and the motivation of the classification.

Figure 2-4 classifies medication errors according to their severity (NCCMERP: 2001). According to the Agency for Healthcare Research and Quality (AHRQ) (2012) and the NCCMERP (2001), when a medication error causes harm it can cause emotional, psychological or physical impairment which results in discomfort. Medication errors may need monitoring of the patient, the patient needs to be observed and psychological signs need to be recorded. As soon as the medication error causes harm to the patient, intervention is needed. Possible interventions can include changing therapy or medical treatment. It may be necessary for more serious intervention, such as in the case of category H (figure 2-4), which includes respiratory (e.g., CPR, defibrillation and intubation) and cardiovascular support.

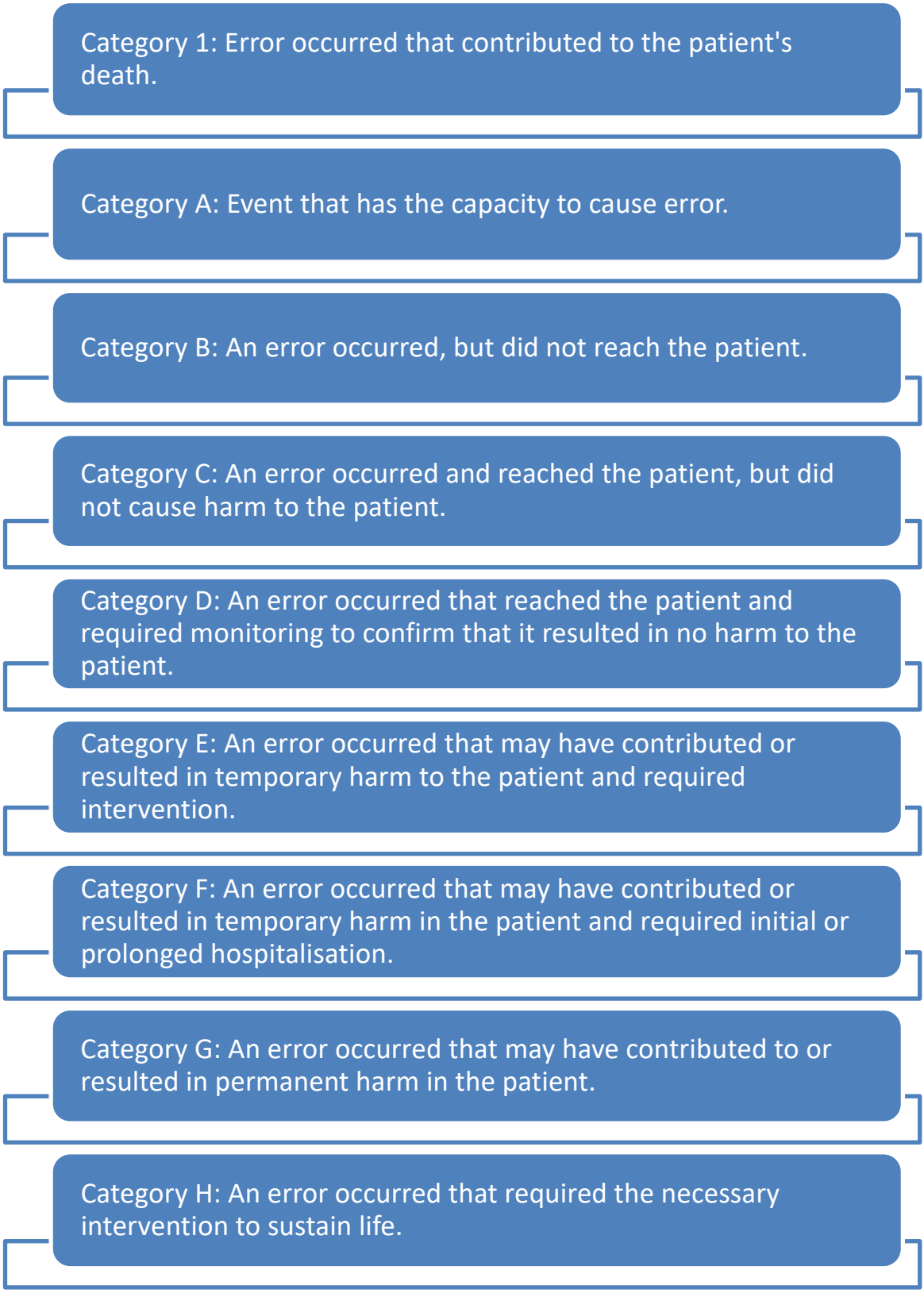

Figure 2-4: Classification of medication errors according to severity

Adapted from: National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP, 2001).

2.2.3.2 Skill-based errors

Another approach arranges errors by whether they occur from errors made when planning actions (knowledge-based or rule-based mistakes) or mistakes in the implementation of appropriately planned actions (action-based errors, known as “slips”, or memory-based errors, known as “lapses”) (Dornan, 2009; NCCMERP, 2001).

One of the most common action-based errors is rushing while prescribing (Dornan, 2009). This is due to heavy workloads and being under pressure. This medication error demonstrates the importance of good prescribing by all doctors. Figure 2-5 illustrates some of the mistakes identified by Dornan (2009):

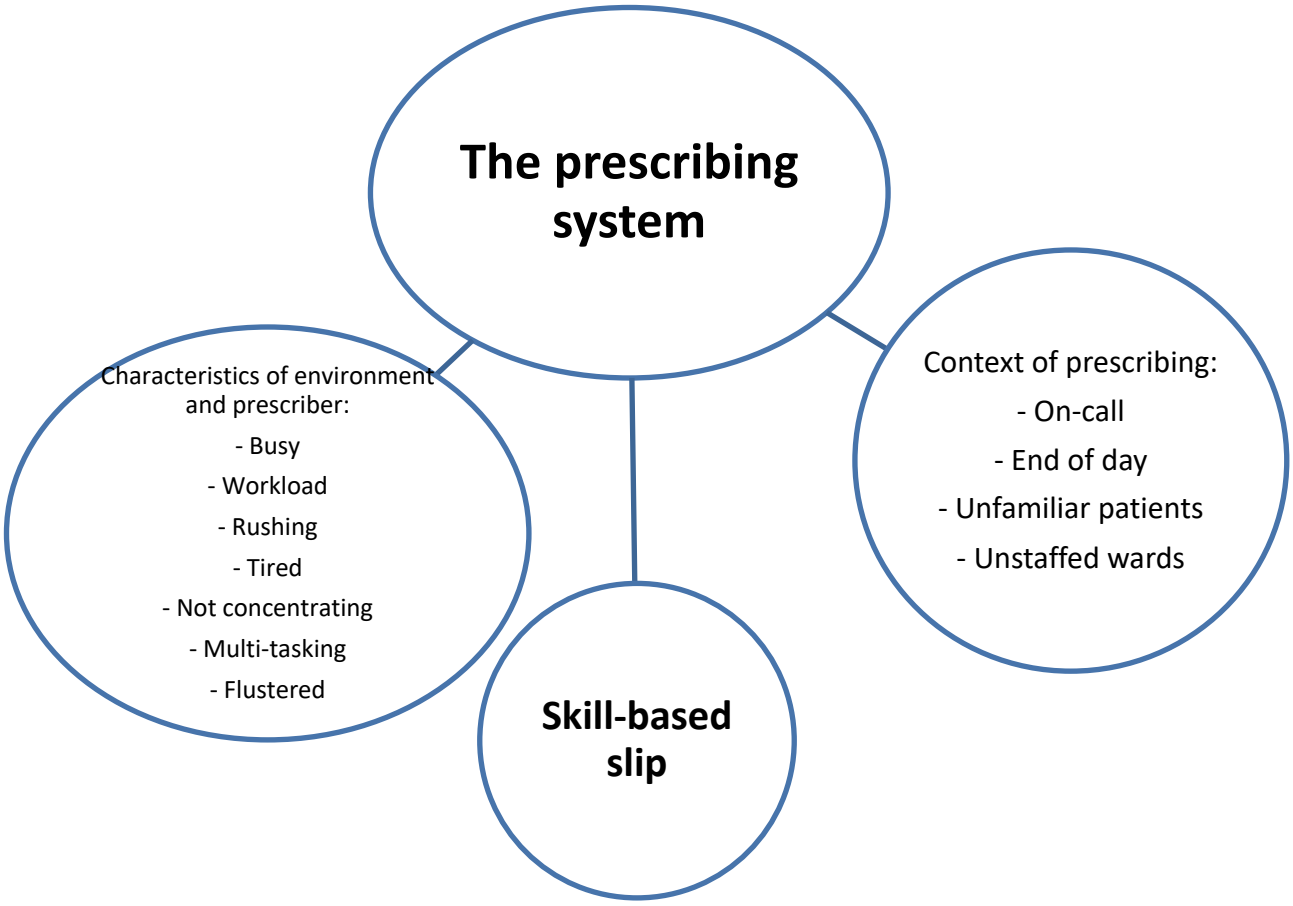

Figure 2-5: Skill-based errors – “Slips” or mistakes

Adapted from: Dornan, T. 2009. An in-depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education. Manchester.

Prescribing errors are often seen, which lead to incorrect dispensing by pharmacists. Jones (1978:543; Mohan *et al*., 2014:149) identified four different prescribing errors by doctors, namely:

- Errors of dose, where the dose is either too large or too small. Confusion between milligrams and micrograms were among the incorrectly prescribed errors.
- Errors of quantity, where the prescriber forgets to state the number of tablets, liquid or ointment. This is where the dispenser gives the wrong number of tablets.
- The error of naming drugs where the preparation is unreadable.
- Responsibility for errors. These errors occur when the doctor's staff member writes down the prescription.

A recent study in African hospitals found a median prescribing error rate of 57.4% of all prescriptions and 40% of medication errors using the Dornan (2009) clinical significance tool (Mekonnen *et al*., 2018). Another study conducted in Egypt using the NCCMERP (2001) clinical significance tool found that 85% of observations had at least one medication error (Tehewy *et al*., 2016).

Memory-based errors are the result of the design of the drug card, differences in hospital charts, no senior support and also heavy workloads of healthcare professionals. Figure 2-6 illustrates the context and environmental characteristics for memory lapses as described by Dornan (2009):

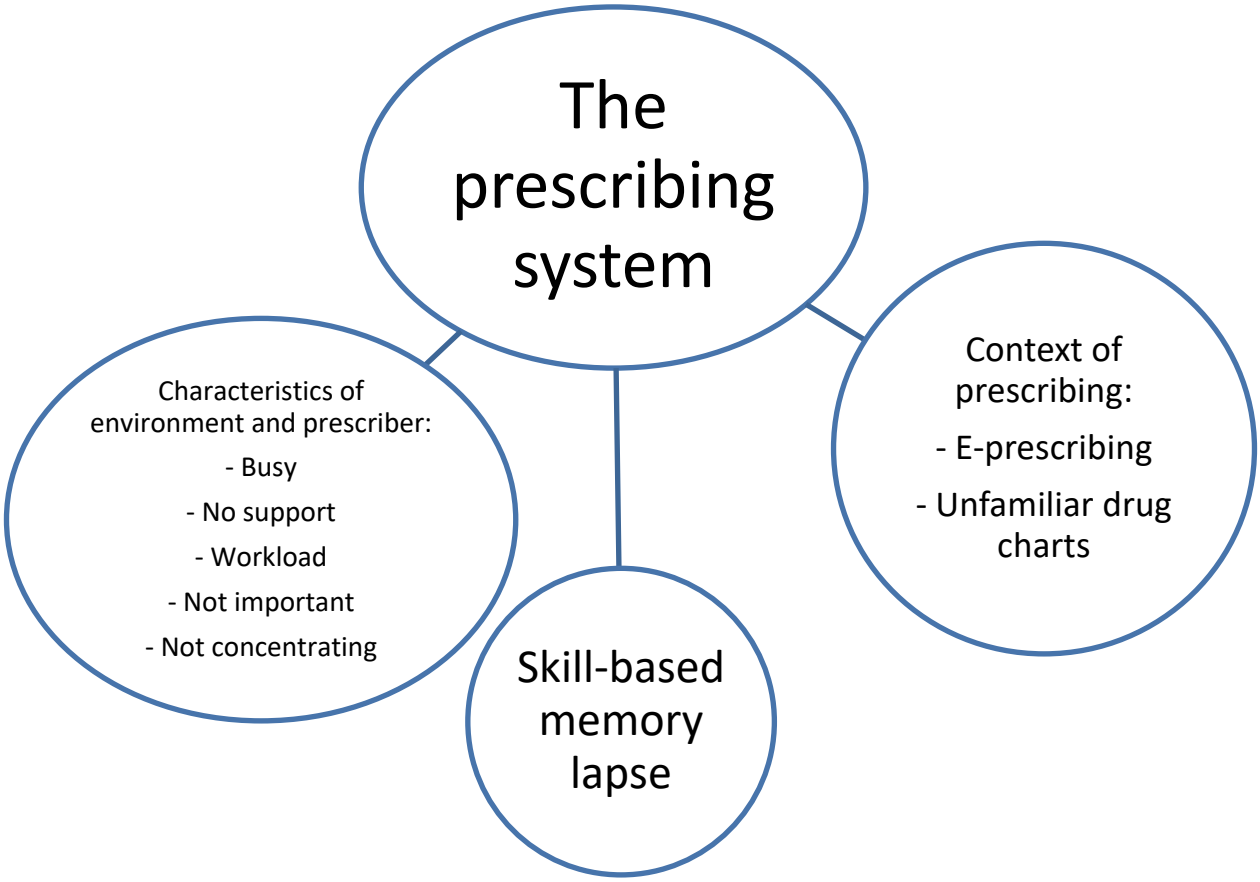

Figure 2-6: Memory-based lapse

Developed from: Dornan, T. 2009. An in depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education. https://www.gmc-uk.org/-media/documents/FINAL_Report_prevalence_and_causes_of_prescribing_errors.pdf_28935150.pdf Date of access: 22 May 2019.

2.2.4 Inappropriate drug use

The irrational use of medicine is a big problem worldwide (WHO, 2012b). Appropriate or rational use of medicine can be described as patients who receive medication that is appropriate for their clinical needs, in doses that meet their requirements for an appropriate timeframe at the lowest cost possible (WHO, 1985). The WHO presented examples of the irrational or inappropriate use of medicine as follows:

- Poly-pharmacy -- the usage of too many drugs per patient.
- Inappropriate use of antimicrobials -- this might be in insufficient dosages for non-bacterial infections.
- The use of too many injections when oral medicine would be sufficient.
- Failure to prescribe according to clinical guidelines.
- Improper use of self-medication.

- Non-adherence to dosing regimes.

The number of prescribed medications are often high and may introduce a risk for ADRs (Rausch *et al*., 2017). These risks may be due to either specific medication such as opioids, inappropriate combinations of drugs or the total number of prescribed drugs (Rausch *et al*., 2017). Poly-pharmacy can be defined as the use of multiple drugs by a single patient and includes improper medicine use (Hemraj & Suleman, 2015). A study done by Hemraj and Suleman (2015) on poly-pharmacy in geriatric patients in KwaZulu-Natal, South Africa, determined that the average number of medicines used by patients was 7.2 drugs and a total of 75% patients received five and more medicines during a six-week period from July 2014 to August 2014. A study conducted among 1 346 709 patients older than 65 years who were community-dwelling and institutionalised in Sweden, revealed that 38% of those patients were exposed to potentially inappropriate drug use, 16% using the Norwegian General Practice (NORGEP) criteria and 24% using the Beers criteria (Morin *et al*., 2015:315). Another study conducted in Sweden among 5 336 patients older than 50 years revealed that 50% of patients had been exposed to inappropriate drug usage because of unintentional poisoning (Rausch *et al*., 2017). Both these studies used the Beers criteria tool and the Norwegian General Practice (NORGEP) criteria to determine the improper use of drugs.

A study by Van Heerden *et al*. (2016) in South Africa, using pharmaceutical benefit management (PMB) data in 2013, revealed that 68.9% of patients older than 65 years were given inappropriate prescriptions, with the most inappropriately prescribed medicine to be oestrogen (12.4%) to women. The 2012 Beers criteria used in this study determined that 37.2% of patients received one inappropriately prescribed drug and 16.2% received three inappropriately prescribed items.

2.2.4.1 Norwegian General Practice (NORGEP) criteria for inappropriate drug use

The NORGEP criteria is a relevance-validated list of medicines, with medicine dosages and drug combinations to be avoided in patients older than 70 years of age (Rognstad *et al*., 2009:153). According to Rognstad *et al*. (2009), general practitioners (GPs) use this list of 36 items as a general rule when prescribing to elderly patients so as to avoid potential inappropriate prescribing practices. This list refers to drug combinations like warfarin and non-steroidal anti-inflammatory drugs that should not be used together because of the possibility of intestinal bleeding.

2.2.4.2 Beers criteria

The goal of the Beers criteria is to refine the care of elderly patients by decreasing their exposure to potentially improper medications (Rognstad *et al.,* 2009:156). The Beers criteria was released by the American Geriatrics Society, improving the selection of drugs, evaluating the way drugs are used within a population, educating on the correct way of drug usage and evaluating health-outcomes, quality care and cost in elderly patients (Rognstad *et al*., 2009:155). The list contains 53 individual medications or

medication classes that are considered inappropriate for people aged 65 years and older (Fick *et al*., 2003).

2.2.5 Conclusion

Through the above definitions and categorisation of ADRs, ADEs, medication errors and inappropriate drug usage, the relationship between these terms is evident. Medication errors and inappropriate drug use definitely lead to ADRs and ADEs. Healthcare professionals should be more aware of these ADRs and use the clinical criteria to decrease these reactions.

Medicine use in patients should be appropriate and evaluated on a regular basis. Strategies for pharmacists to manage ADRs, ADEs, medication errors and inappropriate drug use can include communication with the prescriber and patient, medicine review and reduction in the total number of medicines prescribed. The role of pharmacovigilance is particularly important in the detection of ADRs due to inappropriate medication use, as such ADRs are potentially preventable.

2.3 Burden of adverse drug reactions globally and in South Africa

According to Mosby's Medical Dictionary (2009), a burden can be defined as a heavy, oppressive load and a disabling clinical load.

After studying different explanations of the burden of ADRs, it has been determined that a burden includes the prevalence thereof, cost implications (economic burden) and various health determents in order to realise the severity of ADRs on patients' health and the global economy (Akhideno *et al*., 2018; Mosby's Medical Dictionary, 2009 & Sultana *et al*., 2013).

The burden of ADR will be discussed as follow:

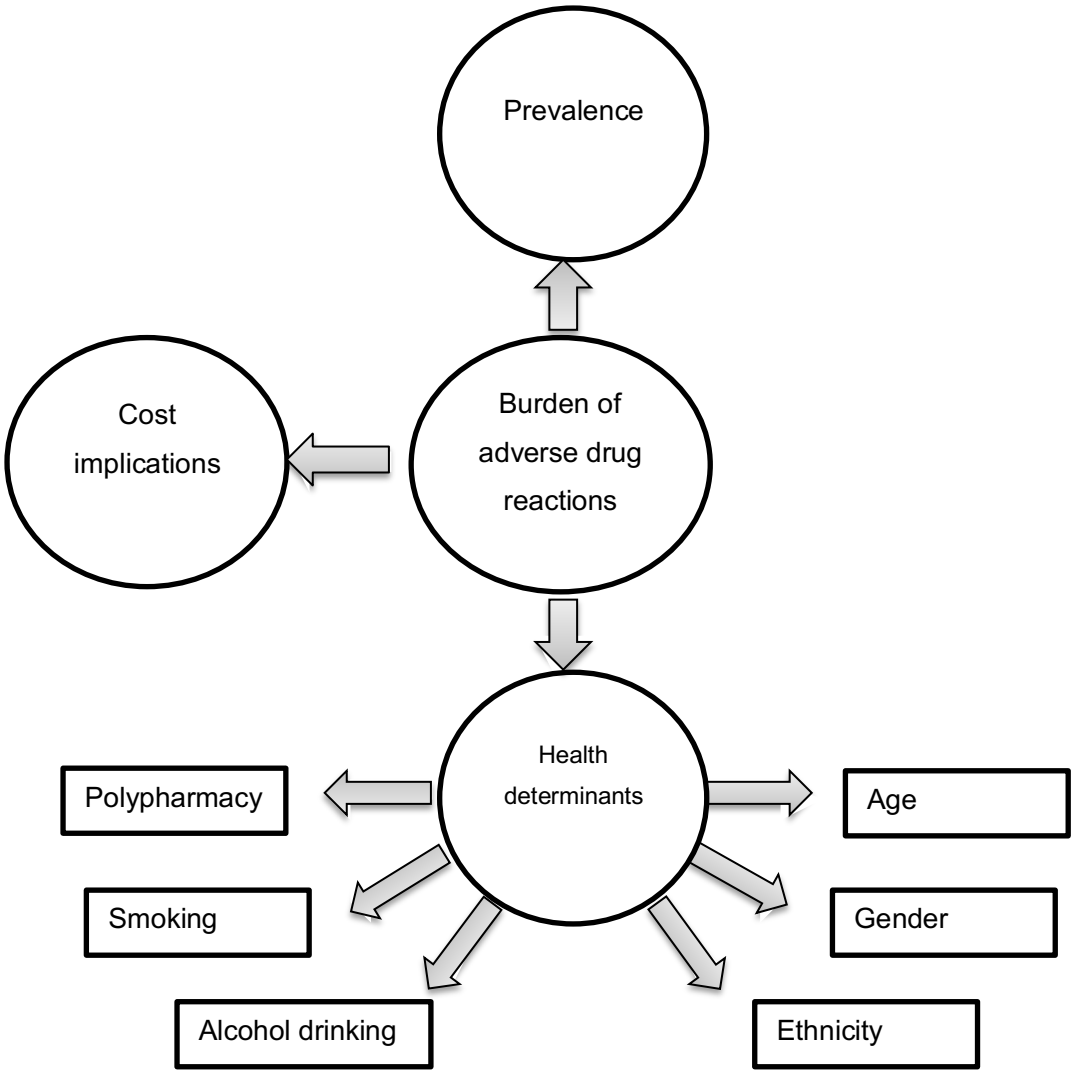

Figure 2-7: Discussion of burden of adverse drug reactions

2.3.1 Prevalence of adverse drug reactions

The National Institute of Mental Health (NIMH) (2017) describes prevalence as the proportion of individuals in a population having a specific disease or characteristic. Point prevalence is the number of cases of a disease that presents itself in a certain population at a specific time (NIMH, 2017). Factors contributing to ADR prevalence include: increase in the number of marketed drugs, increase in ageing population, gender, pregnancy, disease state, genetics, ethnicity and polypharmacy (Angiji, 2017; Holm *et al.,* 2017:335 & Lucca *et al.,* 2017:84). A media report from the WHO (2007), focusing on developing countries, called for more research to be done, as an estimated 7% to 10% of patients in acute care experience an ADE, where 28% to 56% of these reactions is avoidable.

A number of studies have been conducted that give an indication of the prevalence of ADRs and the cost implications thereof in relation to healthcare in clinical practice (Lucca *et al*., 2017; Lund *et al*., 2010; Smith-Marsh, 2016; Roughead *et al*., 2016b & Shepard *et al*., 2012). Countries used in this dissertation will be from the USA, Asia, Europe, Australia, Africa and South Africa.

2.3.1.1 United States of America

In the USA, one of the top ten causes leading to death, is ADRs (Montanari-Vergallo, 2013:2). A study conducted in Chicago revealed that 3% to 7% of all hospitalisations were due to ADRs; ADRs occurred during 10% to 20% of hospitalisations and 10% to 20% of those ADRs were severe (Smith-Marsh, 2016). An annual death rate of 0.0058 was determined during an 8-year study period in die USA, were 2 341 deaths were recorded as a result of ADRs (Shepard *et al*., 2012:169). More than 50% of these ADRs were classified as type A, which means these ADRs could have been prevented.

An online-based study conducted in 2010 using search engines like Cochrane, CINAHL, EMBASE, IPA, Medline, PsycINFO and Web of Science was done by means of a meta-analysis to determine the percentage of patients with ADRs. The study divided participants into outpatients and inpatients and found that among adult outpatients, 2.0% had preventable ADRs and 52% of ADRs were preventable (Hakkarainen *et al.,* 2012:1). The results further indicated that 1.6% of inpatients had ADRs and 45% of these ADRs were preventable (Hakkarainen *et al.,* 2012:1). A study was done on veterans who visited a primary care clinic to determine, by using the medicine appropriateness index (MAI), whether an implicit measure of improper prescribing can predict ADE risks. Of 236 patients, 14.4% experienced an ADE (Lund *et al*., 2010957).

A report done from 2011 to 2018 by the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) revealed an increase in the reporting of ADRs by pharmacists and physicians; although, in March 2019, a reduction in the number of ADR reports was noticed (FAERS, 2019). Only 5% to 10% of ADRs are being reported (Rania *et al*., 2017:875).

2.3.1.2 Asia

A study done in Singapore in 2016 determined the prevalence and characteristics of ADRs at admission to a large tertiary-care hospital. The prevalence of all ADRs at admission was 12.4% and ADRs causing admission was 8.1% (Chan *et al*., 2016:1636). Most of these ADRs were gastrointestinal-related and the most common type of drugs involved were cardiovascular drugs. At admission, 30% of the ADRs could have been predicted by pharmacogenetics testing, as at least one drug had a clinical annotation in the Pharmacogenomics Knowledge Base (PharmGKB) (Chan *et al*., 2016:1637).

A study conducted in China revealed that 2 739 patients experienced an ADR with an ADR rate of 0.81% (Qing-ping *et al.,* 2014:73). The most commonly implicated drug in the above-mentioned study was antibiotics (34.94%). In India, a study was conducted in a mental health department of a tertiary-care hospital, revealing that out of a total of 775 patients, 426 patients experienced ADRs with an incidence rate of 35.5% (Lucca *et al.,* 2017:84).

Most studies in Asia are based on the knowledge and perceptions of pharmacists on the reporting of ADRs, which will be discussed in chapter 2.4.

2.3.1.3 Europe

In 2008, data from The European Commission (2008:52) revealed that 5% of all hospital admissions were due to ADRs; 5% of all hospitalised patients experienced an ADR; and on average, ADRs caused a minimum of 1.91 extra days in hospital. In Birmingham, a study was done to determine whether patients should be allowed to report ADRs after patients reported 5.2% life-threatening ADRs and 2.3% cases of significant disability because of ADRs in 2009 (Cox, 2009:16). A systematic review done on the quality of life in children with ADRs was done in 2014. In this study they found that children with epilepsy constituted the largest group and included the highest number of patients. The study concluded that ADRs, including side-effects, had a negative impact on the patients' quality of life (Del Pozzo-Magana *et al*., 2017:827).

An online article on Medical News (2015) about 'promising new innovations in drug development, health monitoring to improve drug safety in the future', stated that one-in-seven patients are currently at risk of an ADR. Adverse drug reaction related emergency room visits and hospital admissions were 3% in the Netherlands and Germany, 6.5% to 8.8% in the UK (Ahern *et al*., 2014:24), 5.8% in Italy (Franceschi *et al.,* 2008:545) and 12.8% in Greece (Alexopoulou *et al*., 2008:505).

In 2010, a study on paediatrics revealed that half of the registered ADRs occurred in children younger than four years of age, and the risk of ADRs among children under five years of age was four times higher than those of children who attended schools (Napoleone, 2010:4). In Italy, about 15 out of 1 000 children developed ADRs (Clavenna, 2009:503).

The off-label use of drugs in children is a major factor contributing to ADRs. In hospital wards, 36% to 67% of children received off-label prescriptions and in clinical practice, the outpatients' prescriptions of off-label drugs represented 11% to 37% of the cases (Napoleone, 2010:2).

2.3.1.4 Australia

The Therapeutic Goods Administration (TGA) at the Department of Health and Ageing in Australia released data in 2011 on the reporting of ADRs. The TGA's database contains data dating back to 1972, where 233 300 reports of suspected ADRs have been reported. In 2010 alone, 14 200 reports were received: 43%

from pharmaceutical companies, 10% from hospitals, 9% from general practitioners and the rest from members of the public and pharmacists (TGA:2018:4). By 2015 approximately 312 000 reports of ADRs were in the database. Figure 2-8, developed from statistics at the Department of Health and Ageing, shows the number of reports received per year by the TGA:

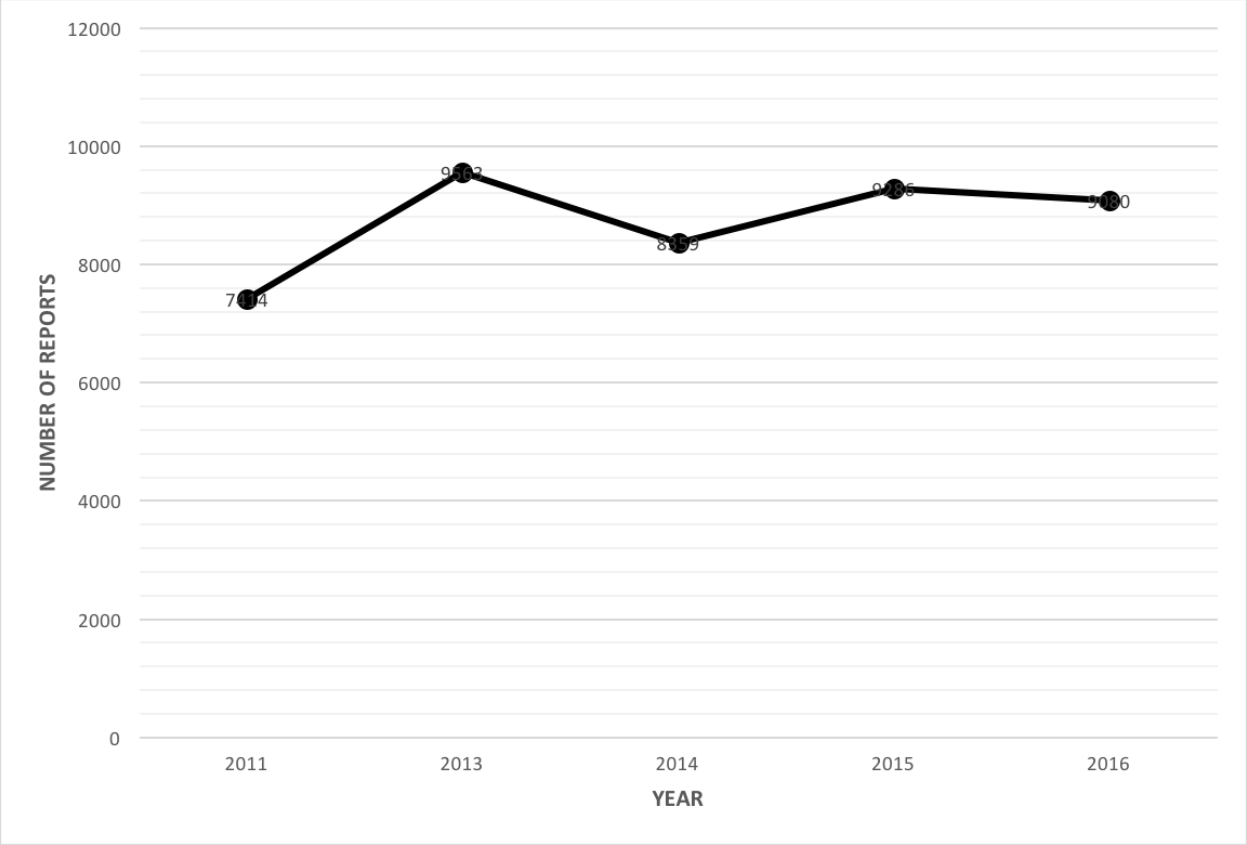

Figure 2-8: Reports received per year by TGA

Adapted from: The Therapeutic Goods Administration (TGA). 2018. Adverse drug reaction reporting.

The TGA received 17 000 ADR reports of which 54% came from sponsors, 17% from State and Territory Health Departments, 11% from hospitals and hospital pharmacists, 6% from consumers, 5% from community pharmacists, 4% from general practitioners and 3% from other sources (TGA:2018:5). The largest increase in ADR reports over the years was from State and Territory Health Departments (from 2 516 in 2015 to 2 824 in 2016) and consumers (from 654 in 2015 to 969 in 2016). The reason for the increase in ADR reports was due to the addition of the National Immunisation Programme in 2016. The importance of the reporting of ADRs following immunisation was significantly promoted (TGA:2018:5).

Evidence from a study conducted from 2008 to 2013 revealed that medication errors occurred in 9% of medication administrations in hospitals (Roughead *et al*., 2016a:113). At hospital discharge, errors in medication documentation may have occurred at a rate of two errors per patient (Roughead *et al*., 2016a:113).

2.3.1.5 Africa

In Nigeria, a study was conducted on 2 400 paediatric patients (Oshikoya *et al*., 2011). The results indicated that 12% of paediatric patients were admitted to hospitals due to ADRs and 23% of paediatric patients admitted to hospital developed ADRs (Oshikoya *et al*., 2011:153). In a regional hospital in Uganda, 4.5% of the 728 patients were admitted with a suspected ADR, and an ADR was the reason for 1.5% of the hospital admissions (Tumwikirize *et al*., 2011:72). According to an article, *Safety of medicines in sub-Saharan Africa: Assessment of pharmacovigilance systems and their performance,* published in 2012, 6.3% of hospital admissions were a direct consequence of ADRs (SPS, 2011:22).

A recent study conducted in nine different African countries revealed that the median percentage of patients experiencing ADRs at hospital admission was 8.4%, while ADRs causing admission were 2.8% (Mekonnen *et al*., 2018:4). A total of 42.5% of these ADRs were deemed preventable. In the study by Mekonnen *et al*. (2018:1), the most common cause of ADRs was medication errors at 57.4%.

2.3.1.6 South Africa

Although data on ADR reports in South Africa is limited, a few studies that were conducted revealed the trends of ADRs (Masenyetse *et al.,* 2015; Metha *et al*., 2008; Mouton *et al*., 2014 & Truter *et al*., 2017). A study at the Groote Schuur Hospital, Edendale Hospital, Cecilia Makiwane Hospital and Frere Hospital revealed that ADRs were the reason for 2.9% of hospital admissions and 16% (n=56) patients died where 43% of these deaths were considered preventable (Mouton *et al*., 2014:818). In the study by Mouton *et al.* (2014:819) one in 12 hospital admissions were due to an ADR. Of the 56 patients whose ADRs resulted in death, four had at least one 'certain' ADR, eight had one 'probable' ADR and the remaining 44 had 'possible' ADRs, according to the WHO-UMC method. In 2018, approximately 7,52 million people in South Africa were living with HIV with an HIV prevalence rate of 13,1% of the South African population (STATS SA, 2018). Antiretroviral (ARV) drugs, anti-tuberculosis (TB) drugs and co-trimoxazole were the most commonly implicated drugs in ADR-related deaths (Mouton *et al*., 2014:824).

Another study done on the use of ARVs in a community hospital revealed that 41 (6.3%) patients were admitted because of an ADR and 41 (6.3%) patients developed an ADR during hospitalisation, where 46.2% of those ADRs were considered preventable, 84.8% were type A reactions and seven patients' ADRs resulted in death (Metha *et al*., 2008:396). The most frequently implicated drugs causing ADRs were cardiovascular medicines (n=22), oral hypoglycaemic agents (n=7) and non-steroidal anti-inflammatory drugs (n=7) (Metha *et al*., 2008:398). According to a study by the Medunsa National ARV Pharmacovigilance Surveillance System, 590 HIV/AIDS patients were registered onto the programme, starting on the same regimen: stavudine, lamivudine and efavirenz. Of these 590 HIV/AIDS patients, 67% started antiretroviral therapy (ART) between 2009 to 2011, where 37% had experienced at least one ADR (Masenyetse *et al.,* 2015:6).

Statistics published in the Pharmacovigilance bulletin by the Department of Health in 2016, revealed that they received 251 ADR reports from 1 October 2016 to 31 December 2016. Figure 2-9 represents the total number of reports received per province in South Africa during the stated period. (NDoH, 2017).

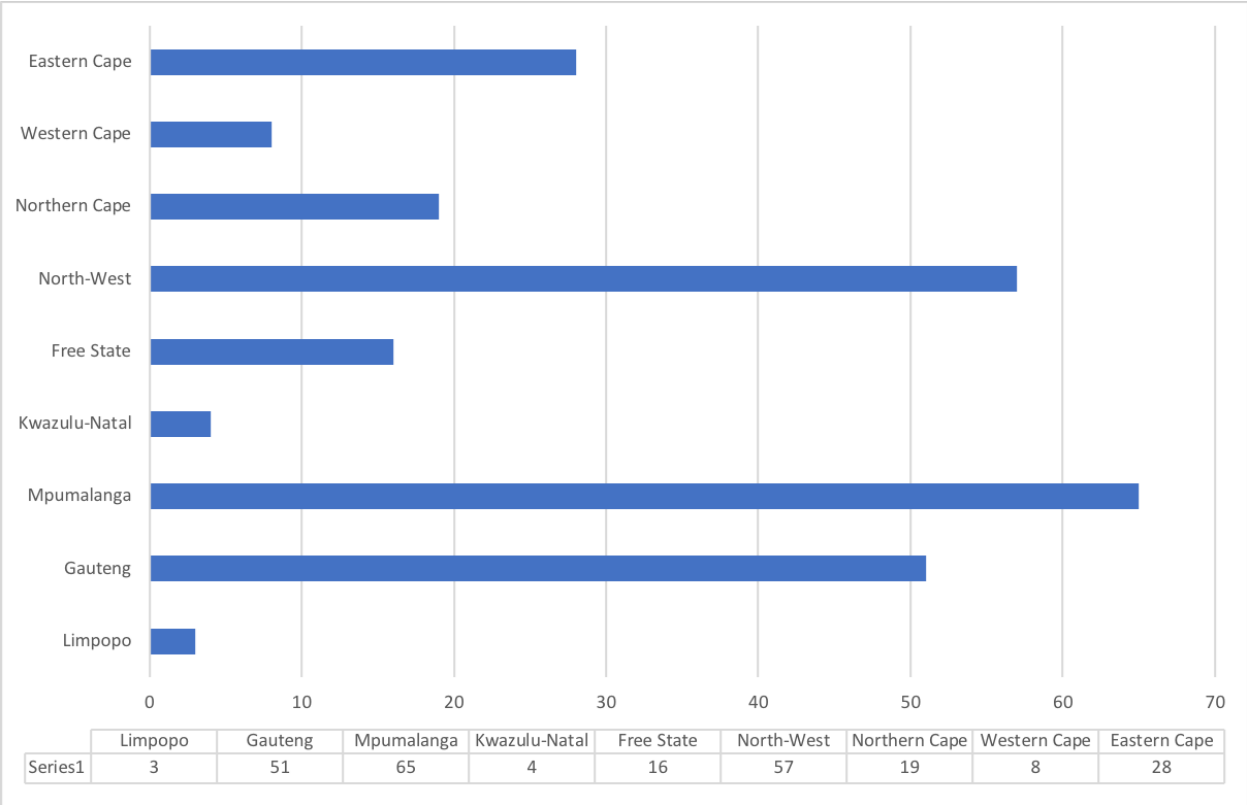

Figure 2-9: Number of ADR reports received on ARVs from October to December 2016
Adapted from: National Department of Health (NDoH). 2017. Pharmacovigilance bulletin.

The most common ADR affecting patients in these facilities were virologic failure, psychosis/hallucinations, renal failure and Steven Johnson syndrome. The ADR reports received on antiretroviral therapy increased drastically from 2009 to 2016 (from two in 2009 to
6 325 in 2016) (NDoH:2017).

In March 2017, a study on medication errors in a neonatal intensive care unit and paediatric wards in a tertiary-academic hospital, revealed a total of 663 medication errors in 227 patients over a period of 16 weeks (Truter *et al*., 2017:5). In the study, 78% of these patients had one or more medication error(s), 51% were administration errors and 47% prescribing errors (Truter *et al*., 2017:5). The drugs mostly involved in the ADRs were anti-infective drugs (43%) and analgesics (25%). Another study on medication errors conducted in 2014 in a paediatric intensive care unit tested the staff members on their ability to complete medication calculations accurately (Gokhul *et al.,* 2016:1222). The study revealed that 2.7% of medication errors due to incorrect calculations resulted in ADRs (Gokhul *et al.,* 2016:1222). A study done

by Schwendimann *et al*. (2018:521) in 27 countries revealed that medication errors were the second most frequent cause of ADRs, which accounted for 19.3% of these reactions.

2.3.2 Cost implications of adverse drug reactions

Various factors contribute to the economic burden of ADRs. These factors put economic strain on both patients and the economy of each country mentioned. Adverse drug reactions lead to an extended length of hospital stay, additional laboratory tests and more medication in and out of hospital. Many countries spend between 15% to 20% of their hospital budgets to treat drug complications (Mahan *et al*., 2011; Qing-ping *et al*., 2014; Rajakannan *et al*., 2013; Roughead *et al*., 2016b & Sultana *et al*., 2013).

2.3.2.1 United States of America (USA)

In the USA, the management and impact of ADRs may cost up to 30.1 billion dollars annually (Sultana *et al*., 2013:73). Increased costs due to ADRs cause increased hospitalisation, prolonged hospital stay and clinical investigation in serious cases. Adverse drug reactions that are unrecognised can allow new medications to be prescribed. Out of incident ADRs that resulted in hospitalisation, the cost per preventable ADR was estimated to be higher than for non-preventable ADRs (Sultana *et al*., 2013:4). In the USA, venous thrombosis lead to a majority of hospital-acquired ADRs, with annual hospital costs of $7.5 to $39.5 billion (R48.75 to R256.75 billion in May 2011) or 6% of public hospital spending, of which $2.5 billion was deemed preventable (Mahan *et al*., 2011:405).

2.3.2.2 Asia

The study by Qing-ping *et al*. (2014:73) revealing an ADR rate of 0.81% indicated a total socio-economic loss of ¥817 401.69 (R1 594 432.35 in 2014), with an average of ¥7032.29 (R13 717.26 in 2014) per patient. Costs in the mentioned study included treatment fees, inspection fees, laboratory fees, material fees, bed charges, drug charges and meals.

A study in South India assessed 317 patients in a tertiary-care teaching hospital and revealed that 246 patients had experienced an ADR (Rajakannan *et al.,* 2013:559). This study found the total cost to the hospital due to ADRs to be INR (Indian Rupee) 1 567 397 ($27 202.12, R241 936.12) and the average price per patient with an ADR to be INR 4 945 ($87.39, R763.28).

2.3.2.3 Europe

The economic burden of ADRs is enormous. In the UK alone, the costs associated with ADRs in 2004 were £466m (€706 million, $847 million) per year (Pirmohamed *et al*., 2004:15). A study done in Germay by Hoogervorst-Schilp *et al*. (2015:531) identified that hospital patients with an adverse drug event (ADE)

had an extended stay of 5.11 more days in hospital. The cost of these patients with ADEs came to €2 600 more per patient (R33 702 in April 2015) compared to patients not suffering from an ADE. Hospital-acquired ADRs place a big economic burden on healthcare systems in Europe, with an overall cost of $2 401 (R24 883 in December 2013) per patient with an ADR, which is equivalent to a 19.86% increase in the total cost of care and an increase in the average length of hospital stay by 8.25% (Khan, 2013a:96). Fever, bleeding, diarrhoea and cardiac arrhythmia, in decreasing order, have been identified by drug surveillance studies to have the greatest economic burden in hospital settings (Sultana *et al*., 2013:5).

An average length of extra days spent in hospital due to ADR-related admissions was eight days (Pirmohamed *et al.* 2004:15). It has been reported that in-hospital incidents as a result of ADRs caused a 9% increase in the length of stay as well as a a 20% increase in the cost of care, including bed usage, laboratory and treatment costs (Khan, 2013a). Additional expenditure included the use of blood products which are needed in up to 20% of all ADR-related hospitalisations for the treatment of gastrointestinal bleeding. By preventing those ADRs, a reduction in the demand for blood products would be possible and it could also impact the mortality rates (Rottenkolber *et al.,* 2012b:240). The study by Pirmohamed *et al.* (2008:15) also revealed that 20 of 28 deaths were due to gastrointestinal or intracranial bleeding out of 1 225 ADR-related hospital admissions (Pirmohamed *et al.,* 2004:16). A study conducted in German hospitals determined the mean inpatient length of stay to be between 6.8 and 8.7 days. During the study period the total cost for patients admitted as a result of ADRs was €1.12 million (Rottenkolber *et al*., 2012a:868).

2.3.2.4 Australia

In 2013, a study conducted by the Health Policy Analysis in Australia revealed that patients who acquired ADRs during their hospital stay accounted for 12% to 16% of hospital expenditure, which calculated to AU$634 million (Health Policy Analysis, 2013).

In Australia, there is an estimate of 230 000 medicine-related hospital admissions per year, which leads to an annual cost of AU$1.2 billion (R135 billion) or 3.95% of the public hospital spending (Roughead *et al*., 2016b:113).

2.3.2.5 Africa

The previously mentioned study in Nigeria on paediatric patients showed that approximately 1.83 million Naira ($15 466; R109 960 in June 2011) was spent per hospital stay (±7days) to be able to manage all the admissions due to ADRs (Oshikoya *et al*., 2011:153).

2.3.2.6 South Africa (SA)

There is not much data available on the cost of ADR admissions in South Africa, but a recent study conducted in SA revealed that ADRs cost 483,000 ZAR for just two of the country's medical wards (Frenk & Hoffman, 2015:234). This means that 1.9 million ZAR is not spent on effective interventions. The main costs of ADRs in a hospital are wages, disposable goods and drugs (Wasserfallen *et al*., 2001:447). Apart from the direct economic costs, there are also indirect costs for patients and their caregivers that are caused by ADRs, such as absent days from work and/or morbidity such as anxiety due to the ADRs (Wu & Pantaleo, 2003:253).

2.3.3 Health determinants

In this section, various health determinants, which have an influence on the burden of ADRs, will be discussed. Age, gender, ethnicity, polypharmacy, smoking and alcohol drinking all have effects on the body to metabolise drugs. Drugs react differently in different body compositions.

2.3.3.1 Age

Older patients generally use more drugs than younger people (Jackson *et al*., 2004:231). Elderly people are prone to taking disproportionate amounts of over-the-counter drugs (Wakaskar, 2017). Elderly and paediatric patients are particularly prone to develop ADRs, because drugs are less likely to be studied in these age groups (Alomar, 2014:83). Pharmacokinetic and pharmacodynamics changes (including drug absorption and metabolism) increase the risk of ADRs in old age (Jackson *et al*., 2004:231; Alomar, 2014:83). Examples include excessive sedation and confusion with morphine, warfarin causing an increased anticoagulant effect, and a higher sensitivity of the nervous system to anticholinergic drugs (Lavan & Gallagher, 2016:11). Aspirin, diuretics, warfarin and non-steroidal anti-inflammatory drugs are the most common drugs associated with ADR-related admissions (Pirmohamed *et al.,* 2004:15). These pharmacodynamics responses can be predictable and minimised by starting to give the lowest dose possible and titrating to response (Lavan & Gallagher, 2016:12).

In the USA, a study on patients 65 years and older revealed that ADRs accounted for 48.1% of hospitalisations out of 100 000 hospitalisations per year (Budnitz *et al*., 2011:2002).

A study in Korea on the reports of ADRs by community pharmacists compared clinical manifestations and their causative drugs by age group. The study revealed that among children, diarrhoea from antibacterials were the most common ADRs, whereas dizziness was most common among the elderly (Yu *et al.,* 2015:1). The study by Yu *et al*. (2015:1) also comprised mostly adults (64%), followed by the elderly (32.5%) and children (3.5%) with the median age of 58 years.

Table 2-8 includes studies focusing on the incidence of ADRs among different age groups as well as gender (Chan *et al*., 2016:1636; Lucca *et al*., 2017:84; Mouton *et al*., 2016:818; Oshikoya *et al*., 2011:153; Truter *et al*., 2017:5 & Tumiwikirize *et al*., 2011:72).

From the different studies in the table, it can be determined that most ADRs occur in the elderly and paediatric patients. The ADR incidence rate reveals the rate at which ADRs occur while being hospitalised and during hospitalisation (including medication errors).

Table 2-8: Studies revealing ADR incidence rate according to age and gender

Author, Year	Country	Study setting	Study design	Sample size	Sample age	Sample gender	ADR incidence rate (%)
Chan, 2016	Singapore	Medical ward	Prospective, observational	1 000	Median age: 62,8 years	Females: 47,4%	12,4% had an ADR. 8,1% ADRs contributed to hospitalisation.
Metha, 2008	South Africa	Medical ward	Prospective, observational	665	Adults	Females: 51%	6,3%
Mouton, 2016	South Africa	Medical ward	Cross-sectional	1 904	Adults	Females: 56%	8,5%
Oshikoya, 2011	Nigeria	Paediatric ward	Prospective, observational	2 004	Paediatric: 3-12 years	Males: 61%	1,8%
Qing-ping, 2014	China	Medical ward	Retrospective, descriptive	2 739	Median age: 46-60 years	Females: 52,3% Males: 47,7%	0,85%
Truter, 2017	South Africa	Paediatric ward	Prospective, quantitative	227	Neonates (47), paediatric (180)	Females: 40% Males: 60%	663 medication errors.
Tumiwikirize, 2011	Uganda	Medical ward	Longitudinal, observational	728	Mean age: 37 years	Females: 56%	4,5% had an ADR, 1,5% ADRs contributed to hospitalisation.
Lucca, 2017	India	Psychiatric ward	Prospective, observational	1 200	Median age: 34 years	Females: 49,7%	35,5%

						Males: 50,3%	
Yu, 2015	Korea	Medical ward	Descriptive	9 705	Median age: 58 years	Females: 66,9%	Serious ADRs: 0,54%
Stavreva, 2008	Bulgaria	Medical ward	Observational, prospective	485	30-70 years: 76,26% >70: 18,42%	Females: 41,3% Males: 58,7%	4,54%
Vijaishri, 2017	India	Medical ward	Prospective	1 138	45-65 years: 41,96%	Females: 48,25% Males: 51,75%	Hospitalisation: 14,68%

2.3.3.2 Gender

Women have an increased risk of developing ADRs compared to men due to differences in immunological and hormonal physiology which also influences the pharmacodynamic and pharmacokinetic responses (Lavan & Gallagher, 2016:11). The anatomical and physiological differences include body weight, body composition, gastrointestinal factors, liver metabolism and renal functions (Alomar, 2014:85). Women have lower organ size and bodyweight, more body fat and different gastric motility which can affect the way the body deals with medication (Alomar, 2014:85).

A study done by Lucca *et al*. (2017:84) in India, giving an incidence rate of ADRs at 35.5%, revealed the incidence in females as 45.9% and in males as 33.6%. The average number of ADRs per male was 1.6 and 1.7 per female (Lucca *et al*., 2017:84). According to Lucca *et al*. (2017:85), the explanation for the higher number of ADRs in females might be due to lower body size, weight in females, change in absorption, volume of distribution, the metabolism of drugs and gender-specific hormones that change physiological function.

A study conducted in Sweden among adults to determine the seriousness of ADRs and drug utilisation revealed that the reporting rate in females was higher than in males (Holm *et al*., 2017:335). In contrast to women having reported more ADRs than men, women reported more non-serious reactions and men reported more serious ADRs (Holm *et al.,* 2017:336). Table 2-8 lists different studies that compare gender against the ADR incidence rate. In this table it can also be seen that females represent the higher number of affected patients with ADRs.

2.3.3.3 Ethnicity

Evidence shows that ethnicity plays an important role in drug response and action (Alomar, 2013:86). Genetic factors control the ethnic background, which influence the inter-individual changes due to polymorphisms in genes that encode medication metabolising enzymes, drug transporters and drug receptors (Sexton *et al*., 2000:745).

A study on epidemiological risk factors found the Caucasian race as a risk factor for ADRs due to hypersensitivity reactions to abacavir (Lyssenko *et al*., 2008:2220). Another study showed that the experience of moderate to severe bleeding following thrombolytic therapy was 17% with black patients versus 11% with non-black patients (Coleman *et al.,* 2006:1177). A study conducted over an 8-year period in the USA evaluated 2 313 902 patients and 2 341 ADR-related deaths were identified (Shepherd *et al.,* 2012:169). The study by Shepherd *et al*. (2012:170) revealed that the deaths varied by race and ethnicity and were highest among black people, with the most common drug classes to be anticoagulants, opioids and immunosuppressants.

An interesting study done by McDowell *et al*. (2006:1177) using MedLine and Embase to identify studies, used 564 studies containing ethnicity and ADRs as inclusion criteria. The study revealed that 17% of black patients experienced headaches as a result of using hydrochlorothiazide, compared to 2% non-black patients experiencing the same effect. Adverse drug reactions after using antihypertensive drugs among white and Asian patients were 13% and 26% respectively. In the United States patients experienced atrial fibrillation after using ibutilide, where 15% of black patients and 2.63% of non-black patients experienced this ADR. Seventeen percent black patients and 11% non-black patients had moderate to severe bleeding after using thrombolytic treatment (McDowell *et al.,* 2006:1178).

According to a recent study by Baehr *et al.* (2015:527), using PubMed and MedBase to identify studies, revealed that Asian patients were identified as an increased risk for anticoagulant-related ADRs. The results also concluded that black patients were at higher risk for anticoagulant-related ADRs compared to white patients. The study also revealed that 14.4% of black patients compared to 9.9% of white patients experienced hypoglycaemia, whereas 37.3% of Asians and 45.6% of American Indians reported hypoglycaemia. More results from this online study showed that white patients (34.4%) experienced more ADRs (nausea, vomiting and pruritus) from the use of opioids than black patients (17.5%) and the Hispanic culture experienced the highest rate of 58% ADRs (Baehr *et al.,* 2015:530).

In South Africa a retrospective study was done on 227 patients with extensively drug-resistant (XDR) tuberculosis using capreomycin and para-aminosalicylic as the main drugs for treatment (Dheda *et al*., 2010:1798). This study by Dheda *et al*. (2010:1798) revealed that 66% of black patients, 0% of white patients and 34% mixed race patients died in hospital, where 55% of the patients were HIV-positive and 45% HIV-negative.

The above studies indicate that different diseases affect different races.

2.3.3.4 Polypharmacy

Older patients consume more medications than other age groups in most developed countries, as they have more chronic diseases and comorbidity that often require the use of more medication, which increases their risk of ADR development (Lavan & Gallagher, 2016:19; & Nguyen *et al.,* 2006:36). Polypharmacy is defined by the World Health Organization (WHO) as the use of too many medicines per patient (WHO, 2012). According to a study in the USA in geriatric nursing homes, a total of 207 ADRs were identified (Nguyen *et al.,* 2006:37). The study by Nguyen *et al.* (2006:36) revealed that 43 patients received nine or more drugs and experienced 53 ADRs, compared to the 292 patients who experienced 154 ADRs.

Polypharmacy can be categorised into 3 different categories. Table 2-9 illustrates these categories identified by various authors.

Table 2-9: Categories of polypharmacy

		Indicator name	Calculation	Sources
Polypharmacy	Simultaneous	One data at random	Total current prescriptions, one day taken at random during the year of study.	Kennerfalk *et al.,* 2002
		An average day, year	Total current prescriptions per day, annual average.	Bjerrum *et al*., 1997
		An average day. 20 days	Total current prescriptions per day, average over 20 days each with a 2-week interval.	Fincke *et al*., 2005
	Cumulative	Quarterly	Total number of medications prescribed over the quarter, average over 4 quarters.	Bjerrum *et al*., 1997
	Continuous	Prescribed at least 3 times during the year	Total number of medications prescribed at least three times during the year.	Carey *et al.,* 2008 & Cahir *et al*., 2010

Adapted from: Monegat *et al*., 2014. Polypharmacy: definitions, measurements and stakes involved. *Questions d'économie de la santé*, 204:1-8.

In the UK, the study by Kennerfalk *et al*. (2002:797) determined that the most frequent drug groups involved in polypharmacy were cardiovascular, central nervous and gastrointestinal system drugs. In the study they used simultaneous methods mentioned in Table 2-10 using two-time windows – the current use of individual drugs on a random day and one month following that particular day (Kennerfalk *et al*., 2002:797). Another study in Europe using the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database revealed the potentially inappropriate prescribing (PIP) prevalence to be 36% where the main determinant was polypharmacy (Cahir *et al*., 2010:543). Proton pump inhibitors prescribed at a maximum therapeutic dose for more than eight weeks gave a prevalence of 17%, non-steroidal anti-inflammatories prescribed for more than three months came to 9% and 5% prescribed duplicate drugs (Cahir *et al*., 2010:545).

Polypharmacy can be a result of many conditions. Older patients especially might suffer from more than one disease (Alomar, 2013:90). Patients are seeking more than one prescriber at the same time for different diseases. In Nigeria a study among 220 elderly patients in a rural tertiary hospital revealed a total of 837 drugs prescribed among these patients (Fadare *et al*., 2013:115). Each patient received an average of 3.8 drugs, where antihypertensive drugs accounted for most (30.6%) of the prescriptions (Fadare *et al*., 2013:116).

A study in KwaZulu-Natal, South Africa, on geriatric patients revealed that 859 medicines were prescribed to 120 patients, where the average number of medicines per patient was 7.2 (Hemraj & Suleman, 2015:) and 75% of these patients received five or more medicines (Hemraj & Suleman, 2015).

The lack of coordination between physicians, pharmacists and patients can lead to redundancy, using the same medication under different brands and increasing the risk of ADRs (Alomar, 2013:89). Polypharmacy should be looked at more seriously in order to prevent potential ADRs.

2.3.3.5 Smoking

Tobacco-related diseases kill more than 44 000 South Africans and 5.4 million people worldwide annually (National Council against Smoking, 2018). Smoking is known to be one of the major risk factors of diseases like peptic ulcers, cancer and cardiovascular diseases (Alomar, 2013:89). A study in Australia concluded that cigarette smoking affects drug metabolism via pharmacokinetic and pharmacodynamic mechanisms, putting patients at serious risk for ADRs (Lucas & Martin, 2013:102). A study done by Mohebbi *et al.* (2010:889) identified an ADR rate of 6.9%, revealing that patients with a history of smoking and concurrent diseases had a higher risk of experiencing ADRs. These reactions are due to the nicotine and not the tobacco.

Cigarette smoking induces the activity of cytochrome P450 and also CYP2B6 (Lucas & Martin, 2013:102). Cytochrome P450 and CYP2B6 metabolise drugs like antidepressants and antipsychotics and also procarcinogens (like those in cigarettes). The study by Lucas and Martin (2013:103) revealed that the metabolism of clozapine and olanzapine are induced by cigarette smoking and patients who smoke will require higher doses of fluvoxamine.

According to the Cancer Association of South Africa (CANSA, 2017), 90% of deaths among men and woman, due to lunch cancer are caused by smoking. Eighty percent of all deaths from chronic obstructive pulmonary disease (COPD) are caused by smoking (CANSA, 2017). A study in South Africa on the treatment outcomes and HIV status of patients with drug-resistant tuberculosis revealed that 16% of patients who died had a history of smoking and 24% of patients who are still alive had a history of smoking (Dheda *et al.,* 2010:1798).

2.3.3.6 Alcohol drinking

The use of alcohol can interfere with the absorption, distribution, metabolism and excretion of medicine and can increase the risk of ADRs (Alomar, 2014:88). Acute alcohol consumption can lead to competition for drug-metabolising enzymes which increases the available drug supply to the body, increasing the risk of ADRs, while chronic alcohol consumption activates drug-metabolising enzymes which decreases the availability and effect of the medicine (Jones, 2003:395 & Tanaka, 2003:81). Because of the interactions

with alcohol, alcohol users may experience ADRs like drowsiness, nausea and vomiting as well as long-term side effects such as internal bleeding, gastrointestinal issues and liver damage (Jones *et al.,* 2014:881 & Moore *et al*., 2015:1061).

A study in the USA revealed that from 2005 to 2011, the incidence of patients experiencing ADRs with alcohol involvement came to an average of 25 303 visits annually, where central nervous system drugs were the most common (59.1%) with half of them being analgesics (Castle *et al*., 2016:1913). In this study by Castle *et al.* (2016:1913), 13.8% of the visits involved psychotherapeutic agents, including anti-depressants. A study in Italy, using the Italian Group of Pharmacoepidemiology in the Elderly (GIFA) database on 22 778 patients, identified 894 ADRs, of which the most frequent ADRs were recorded among non-drinkers [3.7% (393)] and among moderate drinkers with gastrointestinal complications [4.1% (511)]. (Onder *et al.,* 2002:385). In South-west Ethiopia, a study on 103 patients recorded 16.5% alcohol users admitted to hospital with ADRs and 24.3% alcohol users admitted to hospital with non-related ADRs (Angamo *et al.,* 2017:1).

An ADR can be caused by the intake of alcohol before, concomitant with or immediately after the intake of antiretroviral (ARV) drugs. ARVs and alcohol are both metabolised by CYP450 enzymes which means that ARVs can inhibit or induce the enzymes within the system (Schneider *et al.,* 2014:8). Efavirenz, for example, induces these enzymes, which may cause HIV drugs to be cleared faster than usual, undermining their effectiveness and leading to possible viral resistance (Schneider *et al.,* 2014:8).

2.3.3.7 Conclusion

Different factors can lead to the development of ADRs having different effects on various population groups. Giving more attention to the above factors will result in the prevention of ADRs. Healthcare providers should be more aware of current drug dosing, interactions, ADRs and other information needed to provide optimal care to patients. Healthcare providers should remember that benefits should always outweigh the risks in order to be able to provide the best care possible with the best economic price.

2.4 Pharmacovigilance practices

The pharmacovigilance system safeguards the public through efficient and timely identification, collection, assessment and communication of medicine-related adverse events.

2.4.1 Definition of pharmacovigilance

According to the WHO (2012a:1), pharmacovigilance can be defined as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems*". Voluntary reporting of ADRs is the foundation of pharmacovigilance (Mehta *et al*., 2013:104). According to the WHO (2012a), spontaneous (or voluntary) reporting can be explained as "*no active*

measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns". Reporting is entirely dependent on the initiative and motivation of potential reporters.

2.4.2 Aims of pharmacovigilance

A strong pharmacovigilance system is important for all medicine regulatory authorities to ensure the safe and effective use of medicine and to provide information regarding drug changes on the market (Maigetter *et al.,* 2015:295). The WHO initiated minimum requirements for an effective and practical national pharmacovigilance system (WHO, 2002).

The specific aims of pharmacovigilance according to the WHO (2002) are mentioned in Section 1.2.

A pharmacovigilance framework is an essential part of medicine safety and policy, including regulatory and independent needs both internationally as well as nationally (Metha *et al.,* 2017:125). Pharmacovigilance frameworks should consolidate and develop active and passive pharmacovigilance surveillance, modify existing programmes, prioritise post-marketing monitoring and focus on risk management in clinical practice environments through improved communication channels and feedback policies (Metha *et al.,* 2017:125).

When reporting ADRs, certain structural and functional aspects apply (Yadav, 2008:2) The idea of pharmacovigilance rests on three pillars:

(i) Collecting new data from scientific resources, healthcare professionals, journals and literature that is reliable.
(ii) Analysing and classifying the above data received.
(iii) Circulating information and data received to all health sectors.

2.4.3 Key elements of pharmacovigilance

The key element of pharmacovigilance of national governments is to provide good quality, safe and effective medicines to patients. To achieve this, national governments have to establish a medicine regulatory agency and a designated centre for the study of ADRs (WHO, 2014). Table 2-10 and 2-11 show the various countries' regulatory bodies they report to, as well as whether they have pharmacovigilance guidelines for the reporting of ADRs. These tables also reveal the various pharmacovigilance profiles as well as the number of reports received by them. According to the WHO (2014:5), the following elements apply to achieve a successful pharmacovigilance centre:

- *"Establishment of national pharmacovigilance systems for the reporting of adverse events, including national and, if appropriate, regional pharmacovigilance centres".*

- *"Development of legislation/regulation for medicine monitoring".*
- *"National policy development (to include costing, budgeting and financing)".*
- *"Continuing education of healthcare providers on safe and effective pharmacotherapy".*
- *"Provision of up-to-date information on adverse reactions to professionals and consumers".*
- *"Monitoring the impact of pharmacovigilance through process indicators and outcomes".*

2.4.4 Pharmacovigilance entities

The development of a pharmacovigilance system may depend on the organisation and the country's healthcare system, as government support is needed for national co-ordination (WHO, 2014). All ADR reports have to be sent to the WHO ADR Monitoring Centre at Uppsala, Sweden, which is responsible for updating the world data of information on this topic (Yadav, 2008:2). Countries discussed in this section are the USA, Australia, Asia, Europe, Africa and South Africa with focus on their main pharmacovigilance entities and regulatory bodies.

2.4.4.1 United States of America

In the United States of America (US), the Food and Drug Administration (FDA) is responsible for ensuring the safety of medication to the public (FAERS, 2018). Adverse drug reactions are reported to the FDA through a voluntary, consumer-friendly or mandatory reporting form. The FDA Adverse Event Reporting System (FAERS) is a database that contains ADE reports, medication error reports and product quality complaints that resulted in ADEs that were submitted to the FDA. The database is designed to support the FDA's post-marketing safety surveillance programme for drugs and therapeutic biologic products (FAERS, 2018). The FDA has accepted electronic submissions of both expedited and non-expedited Individual Case Safety Reports (ICSRs) for human and non-vaccine products (FAERS, 2018) since 2000.

2.4.4.2 Australia

The Therapeutic Goods Administration (TGA) has established a pharmacovigilance system for the collection and evaluation of medicine safety reports of registered medicinal products through the Adverse Drug Reaction Advisory Committee (ADRAC) (Yadav, 2008:1).

Consumers and healthcare professionals are able to report serious unexpected and expected ADRs or healthcare professionals and pharmaceutical companies are allowed to advise the TGA within 72 hours of any safety issue regarding a product (TGA, 2018:5). Medicine and vaccine ADRs are entered into the TGA Adverse Event Management System (AEMS) and medical device reports are recorded in the Incident Reporting and Investigation Scheme (IRIS) database (TGA, 2018:5). These reports are entered within two days and a letter of acknowledgement is sent to the reporter with a unique identification number. The data

is then entered into a publicly accessible Database of Adverse Event Notification three months after the report has been received (TGA, 2018:5).

2.4.4.3 Asia

As in developing countries, the importance of pharmacovigilance is recognised amongst the regulatory authorities in the Asia region (SIAPS, 2013). Most of these countries have post-marketing surveillance or pharmacovigilance units as part of their agency's structure (SIAPS, 2013). The Democratic Republic of Korea and Myanmar are the two countries who are not members of the WHO-UMC and Mongolia and Pakistan are only associate members (UMC, 2018).

In India, the National Pharmacovigilance Advisory Committee (NPAC) monitors zonal, regional and peripheral centres' performance (Yadav, 2008). The NPAC is divided into the Zonal Pharmacovigilance Centre, which includes large healthcare facilities with medical colleges in metro cities that function as first contact ADR data collection units, and the Regional Pharmacovigilance Centre (AIIMS, 2018). Figure 2-10 illustrates the division of the NPAC.

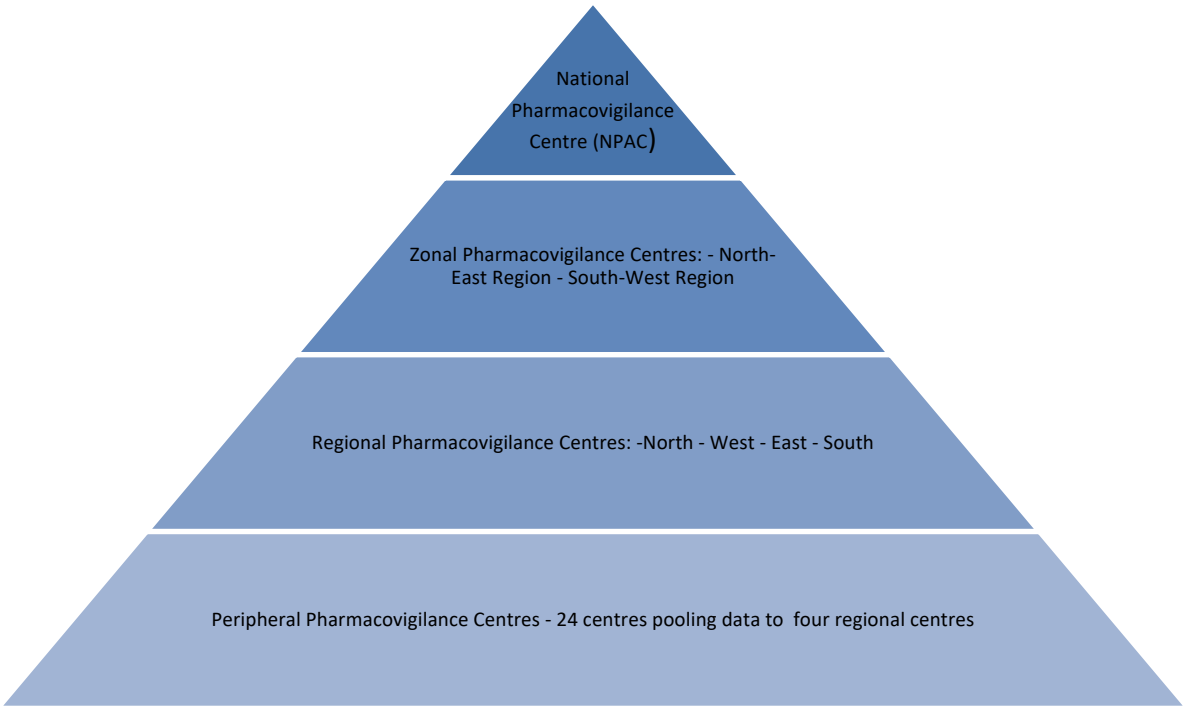

Figure 2-10: Division of the National Pharmacovigilance Advisory Committee in India

Adapted from: AIIMS (All India Institute of Medical Sciences). 2018. National pharmacovigilance programme. https://www.aiims.edu/en/national-introduction.html?id=166 Date of access: 4 Aug. 2018.

In Singapore, the Pharmaceutical Advisory Committee was established in 1993 and serves as the national centre for the review of ADRs (Yadav, 2008). This unit comprises experts in the field of medicine,

pharmacy, pharmacology and forensic science. They assess the impact of major drug safety issues and advise on the regulatory action to be taken to enhance drug safety (Yadav, 2008).

2.4.4.4 Europe

In the United Kingdom (UK), the European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU (EMA:2018). The spontaneous ADR scheme in the UK, monitored through the Medicines and Healthcare Products Regulatory Agency (MHRA), is commonly known as the Yellow Card reporting scheme and is the cornerstone of the ADR monitoring system (MHRA:2015). Since 1964, the Yellow Card Scheme (YCS) operated the spontaneous reporting of suspected ADRs by healthcare professionals and from 2005, patients have also been able to submit Yellow Card reports (McLernon *et al.,* 2010:33). The Yellow Card Scheme is essential in supporting the MHRA monitor the safety of all healthcare products in the UK to guarantee they are acceptably safe for patients and those who use them. Before a medicine is authorised for use, verification of its safety and efficacy is needed from the results of clinical trials. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is accountable for assessing and monitoring the safety of all human medicines. The EMA provides the PRAC with clinical data available for electronic health records or prescription databases (EMA, 2018).

The EMA developed and has been maintaining EudraVigilance since 2001. EudraVigilance is a system that manages and analyses information on suspected ADRs to medicines authorised in the European Economic Area (EEA) (EMA, 2018:4). This system is used by member states, the Agency and industry for the reports of ADRs seen in healthcare practice and clinical trials. The MHRA is required to send details of all serious UK ADR reports it receives from any health professional or pharmaceutical company to the EudraVigilance database within 15 days of receiving the report (MHRA, 2015). EMA is responsible for publishing the data from EudraVigilance in the European database of suspected ADR reports. In 2017, 1 471 596 ADR reports were received and managed in EudraVigilance, which gave a 19% increase from 2016 (EMA, 2018:8)

2.4.4.5 Africa

With an estimated pharmaceutical market size of 3.8 billion to 4.7 billion US dollars (USD) and local manufacturing ability in 80 percent of countries, the ability for regulating health products in sub-Saharan Africa is insufficient (SPS, 2011:30). Presently, 74% of these 46 countries have a national medicine regulatory authority (NMRA), 78% have a national medicine policy (NMP), five World Health Organization (WHO) prequalified quality control laboratories exist in the region, and 33 sub-Saharan countries are an official or associate member of the WHO Programme for International Drug Monitoring (SPS, 2011:32).

With increased access to new essential medicines in Africa, there is a larger need to monitor and endorse the safety and effectiveness of medicines. In 2011, the assessment report *Safety of Medicines in sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance* was published (SPS, 2011). The US Agency for International Development (USAID)-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) programme, implemented by Management Sciences for Health (MSH), was executing an interagency agreement between the USAID and US Food and Drug Administration (FDA) in 2011 (SPS, 2011:19). This agreement is directed at fostering collaboration between the two agencies to strengthen regulatory systems in order to certify the quality and safety of health products in the supply chain of developing countries (SPS, 2011). Tables 2-10 and 2-11 below featurethe pharmacovigilance profile of various countries in Africa.

Table 2-10 : Pharmacovigilance practices in African countries compared to South Africa

Country	Policy, laws and regulations	Name of regulatory authority	Joined the WHO programme	Type of reports in pharmacovigilance V database	Number of ICSRs in database
Burkina Faso	The Code of Public Health Act (23/94/ADP of 1994) regulates their pharmacovigilance practices.	Direction Generale de la Pharmacie, du Medicament et des Laboratoires (DGPML) 2010 (http://www.dgpml.sante.gov.bf/)	2010	Spontaneous reports, AEFI reports, active surveillance reports, reports from pharmaceutical companies	1 986 in 2010
Democratic Republic of Congo (DRC)	The Department of Pharmacy and Medicine. 2018. Mission (Chapter 7 of Decree 2018-270), viewed 3 Nov. 2019, https://www.dpm-congo.net/dpm/	Direction de la Pharmacie, Medicaments et Plantes medicinales (DPM) National Centre for Pharmacovigilance (CNPV) (https://www.dpm-congo.net/dpm/)	2010	Spontaneous reports	156 in 2010 1 432 in 2011
Ghana	The Ghana National Drug Policy 2004. The Food and Drug Act (Act PNDCL 3058 of 1992) regulates their pharmacivigilancy activities.	Food and Drug Board (http://www.moh.gov.gh/wp-content/uploads/2016/02/Ghana-National-Drug-Policy-2nd-edition.pdf)	2001	Spontaneous reports, AEFI reports, PSURs, reports from PHPs	1 190 (107 in 2008, 171 in 2009, 467 in 2010)
Kenya	The Kenya National Drug Policy 1994.	Pharmacy and Poison Board (PPB),	2010	Spontaneous reports, AEFI reports, product quality reports, active	1 490 (600 in 2010)

	National Pharmaceutical Policy 2010. The Pharmacy and Poisons Act (Act 244 of 2007) regulates their pharmacovigilance activities.	http://www.pharmacyboardkenya.org/		surveillance reports, PSURs	
Nigeria	The National Agency for Food and Drug Administration and Control Act (Act 15 of 1993) regulates their pharmacovigilance activities.. Good Pharmacovigilance practice regulations 2009.	National Agency for Food and Drug Administration and Control (NAFDAC), www.nafdac.gov.ng	2004	ADR reports, AEFI reports and reports from PHPs	8 757 (310 in 2008, 2 838 in 2009, 5 140 in 2010)
Senegal	National Pharmaceutical Policy 2006.	Direction de la Pharmacie et des Laboratoires (DPL). Le Centre Antipoison. https://www.dpml.ci/fr/liste-document-public-industrie	2009	Spontaneous reports, AEFI reports, PSURs, active surveillance reports, reports from PHPs, reports from clinical trials	120 in 2010 265 in 2011
South Africa	National Drug Policy for South Africa 1996. https://www.gov.za/sites/default/files/gcis_document/201409/drugpol0.pdf Medicines and Related Substances Control Act (101 of 1965).	The Medicines Control Council http://www.mccza.com/ National Adverse Drug Event Monitoring Centre (NADEMC)	1992	N/A	N/A

Tanzania	The Food, Drugs and Cosmetics Act (Act 1 of 2003). National Medicines Policy 1991.	Tanzania Food and Drugs Authority (TFDA) (http:// www.tfda.or.tz/)	1993	Spontaneous reports, AEFI reports	126 in 2010
Uganda	National Drug Policy and Authority Act (Act 206 of 1999). Uganda National Drug Policy, 2002.	National Drug Authority (http://www.nda.or.ug/)	2007	Spontaneous reports, PSURs, reports from clinical trials	75 in 2008 222 in 2009 180 in 2010 735 in 2011

*AEFI = adverse events following immunisation; PSUR = periodic safety update report; PHP = public health programme; ICSR = individual case safety report

Developed from: Strengthening Pharmaceutical Systems (SPS) Programme. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Programme. Arlington, VA: Management Sciences for Health.

2.4.4.6 South Africa

South Africa (SA) has been involved in pharmacovigilance for more thanr 40 years (Metha *et al*., 2017:125). Pharmacovigilance has developed from passive regulatory reporting to an active surveillance system. Metha *et al*. (2017) cited that in 1962 thalidomide was marketed as a sedative and anti-emetic drug in pregnancy, which led to severe birth defects, causing a major disaster (1962, cited in Metha *et al*., 2017). It was internationally known that the government had to intervene to regulate the manufacturing and selling of medicines to guarantee the safe and effective use of drugs. This is how the Medicines and Related Substances Control Act (101 of 1965) came into existence in South Africa in 1965. South Africa has a convincing policy, legal and regulatory framework and well-established systems and structures for pharmacovigilance. The Medicines Control Council (MCC) (now SAPHRA since 2019), under the Medicines and Related Substances Control Act (101 of 1965), oversees SA's regulation of medicines, including pharmacovigilance, and safeguards ethical standards in advertising and promotion of medicines (Metha *et al.,* 2017:125).

In 1987, the MCC established a National Adverse Drug Event Monitoring Centre (NADEMC) in collaboration with the University of Cape Town to monitor the safety of medicines by managing, collecting and reviewing the voluntary reporting of suspected ADEs by industry and health professionals in order to be able to detect poorly understood ADRs (Metha *et al*., 2017). Standard Operating Procedures (SOPs) are in place for expedited reporting of serious ADRs and submitting PSURs, which fulfil with the national regulatory requirements (SAHPRA, 2019:10).

South Africa became the first member of the WHO International Drug Monitoring Programme in 1992 (WHO, 2002). The national antiretroviral (ARV) treatment programme was launched in 2003, when the government started to provide ARVs to thousands of patients (NDoH, 2012). Since then, studies on the use of ARVs and their ADRs have increased in SA. Reports of maternal deaths caused by nevirapine in 2012 raised apprehensions about the safety of ARVs in pregnancy and the National Department of Health (NDoH) changed the first-line treatment to efavirenz (NDoH, 2012).

Pharmacovigilance in South Africa is categorised into **(i) regulatory pharmacovigilance,** covering quality and efficacy of all medicines, and **(ii) programmatic pharmacovigilance,** covering medicines used in public health programmes. Regulatory pharmacovigilance is then divided into two categories, namely passive and active surveillance (Metha *et al*., 2017:130).

a. **Passive surveillance i**ncludes the spontaneous reporting of ADRs to the NADEMC by health professionals to ensure safe data collection of local medicines. Passive surveillance is useful to

identify new signals or ADR trends, but are unable to quantify the risk of particular harm. Therefore, passive systems need to be supported by active surveillance approaches (Metha *et al.,* 2017:128).

b. **Active surveillance** by means of well-sourced settings, require pharmaceutical manufacturers to submit risk management plans, which include conducting post-marketing studies as part of their registration for license applications.

In South Africa, the pharmaceutical industry's efforts to identify safety signals and evaluate the risks are still insufficient (SPS, 2011:106). A study by Roux (2014) among HCPs in a private sector in the country revealed that 92% of the participants have never reported an ADR to a pharmaceutical company. The study also revealed that 89% of the HCPs have never reported a new or strange side-effect to a pharmaceutical company (Roux, 2014:39). Roux (2014:40) reported that inadequate education and knowledge to identify risks of medication, due to the lack of awareness created by pharmaceutical companies, could be a major setback in terms of reporting ADRs. Most of the surveyed companies did not stipulate or implement a process to identify safety signals from change in rigorousness, features or occurrence of expected ADRs. For instance, the systematic review of reported safety data was seldom performed and none of the surveyed companies had statistical or mathematical tools (i.e., data mining software such as the WHO's Vigibase) at the local level (SPS, 2011:107).

Data gathering, risk assessment, and decision-making are usually carried out by multinational company headquarters or barely incorporated into the routine pharmacovigilance activities of local companies (SPS, 2011:108). However, South Africa shows some reassuring trends in pharmacovigilance development in the pharmaceutical industry. Interestingly, multinational companies require local affiliates in SA to coordinate pharmacovigilance activities within the companies located in other African countries (SPS, 2011:109). South African industry can play a significant role to enhance regional capacity for pharmacovigilance in the industry. (Metha *et al.,* 2017:127).

The following features should be considered to improve the current pharmacovigilance system in South Africa's pharmaceutical industry by:

- refining the policy;
- improving SOPs;
- improving internal processes to meet the local requirements and regulations;
- strengthening the technical capacity of the local pharmacovigilance unit or designee to carry out all facets of pharmacovigilance activities;
- developing a formal information sharing and tracking process among different units in the company and among consumers and other stakeholders;
- developing a process to gather, review and assess local safety data, publications and medicine information queries;

- enriching the scope of pharmacovigilance, including all other ADEs; and
- developing a strategy or procedure to ensure passivity with pharmacovigilance requirements internally (i.e., self-audit) (SPS, 2011:108).

Fifty percent of all ADR reports from Africa are from South Africa; however, there are wide dissimilarities in reporting between different regions/provinces (Joubert & Naidoo, 2016:239). Pharmacovigilance system challenges include:

- The government of South Africa does not meaningfully acknowledge the significance of pharmacovigilance.
- There is a deficiency of appropriate collaboration with the pharmaceutical industry.
- There is reduced synchronisation and collaboration in data management, i.e. the national pharmacovigilance database does not include data from all sources.
- The Ministry of Health and the National Medicines Regulatory Authority (NMRA) lack capacity for pharmacovigilance (SPS, 2011).

Figure 2-11 explains that although ADR reports were still very low in 2015, there had been an increase in the number of reports since 2010 (Metha *et al*., 2017:127). Since 2013 there had been a clear increase in the reporting of ADRs from manufacturers, although reports from the reporters directly had decreased.

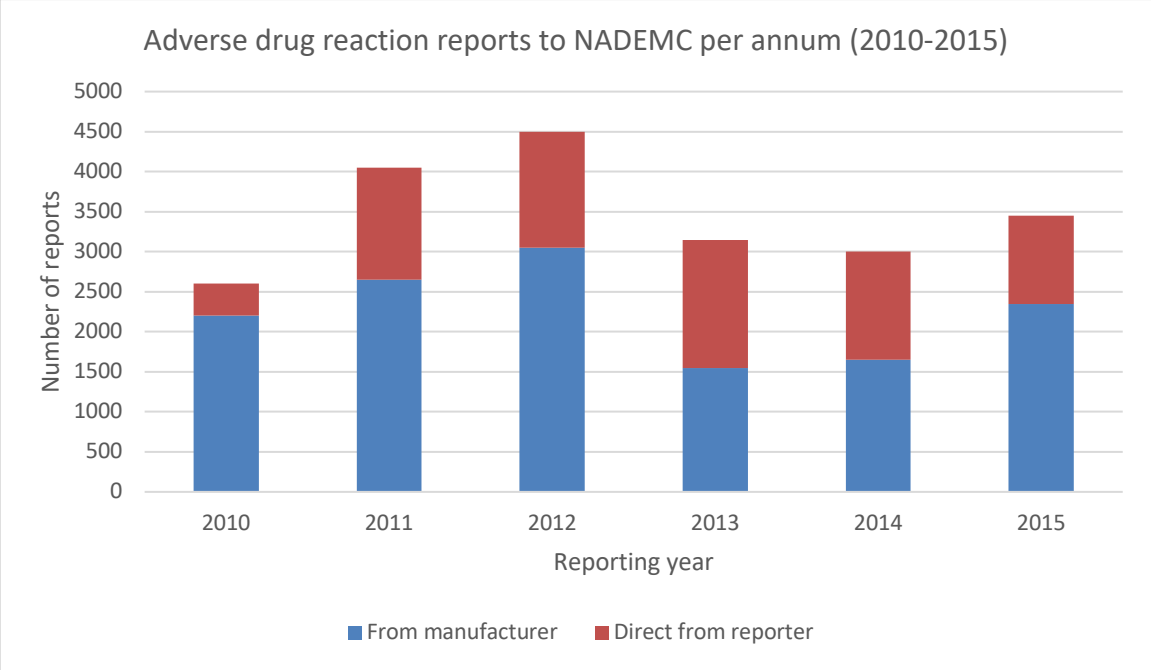

Figure 2-11: Number of ADRs reported per annum to the NADEMC (2010-2015)

Adapted from: Metha *et al.,* 2017. Pharmacovigilance: a public health priority for South Africa. South African health review: 20 year anniversary edition: SA.

2.4.5 Conclusion

Adverse drug reactions (ADRs) have the potential to cause serious harm to patients. There is an increase in the awareness of the impact of ADRs on patient health and care. Healthcare workers need to develop an appreciation of the benefits and dangers of medication prescribed to their patients. Pharmacovigilance includes the evaluation of marketed medicine, risk evaluation, communication, promoting rational drug usage and being prepared for crises. All healthcare professionals will benefit from training in all of these mentioned activities. ADR forms should always be available. Regulatory authorities should acknowledge receipt of ADR forms to avoid duplicated reports. Pharmacovigilance centres should be encouraged to interact with the Uppsala monitoring centre in Sweden.

Table 2-11: Pharmacovigilance profiles in African countries compared to South Africa

	National Pharmacovigilance policy exists	National Pharmacovigilance guidelines exist	WHO membership	Spontaneous reporting of ADRs	Coordination and collation of PHARMACOVIGILANCE data from all sources in the country (see key below*)	No. of ADR reports per million population in 2010
Angola	No	No	Associate	Yes	2	0
Botswana	Yes (2002)	Yes (2009)	Official (2009)	Yes	2	32
Cameroon	No	N/A	Official (2010)	Yes	2	N/A
Congo (DRC)	Yes	No	Official (2010)	Yes	2	2
Ethiopia	Yes (2009)	Yes (2008)	Official (2008)	Yes	1	2
Lesotho	N/A	N/A	Non-member	N/A	N/A	N/A
Mozambique	No	Yes (2004)	Official (2005)	Yes	2	2
Namibia	Yes (2010)	Yes (2010 – draft)	Official (2009)	Yes	2	135
South Africa	No	Yes (2010)	Official (1992)	Yes	3	N/A
Swaziland	N/A	N/A	Non-member	N/A	N/A	N/A
Uganda	Yes (2002)	Yes (2009)	Official (2007)	Yes	2	6
Zimbabwe	Yes (1998)	Yes	Official (1998)	Yes	2	5

*1) No database 2) Database exists, containing partial sources of information 3) Database exists, containing all sources of information. N/A: Not applicable.

Table 2-12: Status of pharmacovigilance initiatives in international countries compared to South Africa

Country's status	Australia	Brazil	India	Jordan	Malaysia	Singapore	South Africa	Ukraine
Present ADR reporting system	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of commencement	1968	2001	2003	2001	1990	1993	1997	2000
Regulatory body	ADRAC	NDMC, PVU	NPAC	JPC	MADRAC, NDSMC	PVU	NADEMC, MCC	SPC, MoH
Available guidelines	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Investigation reporting time for spontaneous ADRs	≤15 days	≤15 days	≤15 days	≤15 days	≤15 days	≤15 days	≤15 days	≤15 days
Reporting of non-serious ADRs	No	-	Yes	-	Yes	No	No	No
Reporting to the WHO centres (mandatory)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

ADR: Adverse drug reaction; ADRAC: Adverse Drug Reaction Advisory Committee; NDMC: National Drug Monitoring Centre; PVU: Pharmacovigilance Unit; NPAC: National Pharmacovigilance Advisory Committee; JPC: Jordanian Pharmacovigilance Centre; MADRAC: Malaysian Adverse Drug Reaction Advisory Committee; NDSMC: National Drug Safety Monitoring Centre; NADEMC: National Adverse Drug Event Monitoring Centre; MCC: Medicines Control Council; SPC: State Pharmacovigilance Centre; MoH: Ministry of Health.
Adapted from: Yadav, S. 2008. Status of adverse drug reaction monitoring and pharmacovigilance in selected countries. *Indian journal of pharmacology*, 40:4-9.

2.5 Adverse drug reaction (ADR)reporting

2.5.1 The importance of adverse drug reaction reporting

The reporting of ADRs is important to detect safety information regarding the use of medicine (Shapiro, 2013:1401). Clinical trials are used to detect and monitor unwanted effects with the participation of patients, which are then analysed (Shapiro, 2013:1401). These ADRs are then reported to the FDA for further investigation (Shapiro, 2013:1401). One of the methods to increase the number of ADR reports is by means of marketing strategies (Anderson *et al*., 2011:808). According to data collected by Anderson *et al.* (2011:810), ADR reporting is important to improve information leaflets that will improve the safe and effective use of medication. The study also revealed that the reporting of ADRs could activate the necessity to withdraw unsafe medication from the market, which will encourage more studies to be done on the specific drug (Anderson *et al.,* 2011:810).

2.5.2 Different types of adverse drug reaction reporting

Various methods exist for the reporting of ADRs. In this section the methods used to report ADRs are discussed and compared to one another for South Africa, the USA, Europe and Australia.

2.5.2.1 South Africa

In South Africa there are various methods of ADR reporting (MCC, 2012:18). Post-registration reports and pre-registration reports are discussed in Table 2-13 and Table 2-14 respectively. Reporting entities, what to report and who are responsible for reporting ADRs are indicated in Table 2-16.

Table 2-13: Post-registration adverse drug reaction reports in South Africa

Type of reports	What to report	Time frame for reporting	Format of ADR reporting
Reaction occurring in South Africa	Serious (expected & unexpected)	15 days	ADR form
	Non-serious (unexpected)	15 days	ADR form
	Non-serious (expected)	No report	Not required
	Pregnancy-related reports		

Reaction occurring outside South Africa	Serious Pregnancy-related reports	On request	As appropriate
Periodic Safety Update Reports (PSURs)	Condition of registration for a new medicinal product	30 days	Not applicable
Case reports from published scientific literature	Published suspected ADRs related to active substances	As needed	A copy of the relevant published article
Reports from post-registration studies	According to 4.1 on reports of clinical epidemiological investigations	As needed	As per 4.1

Adapted from: MCC (Medicines Control Council). 2012. Reporting adverse drug reactions in South Africa. *Registrar of Medicines,* 1(2):4-17.

Adverse drug reaction reporting is done by using the adverse reaction report form that is available from SAHPRA (Annexure C) or applicants may use their report forms from their company of work (SAHPRA, 2019). According to the SAHPRA (2018:6), a periodic safety update report (PSUR) is *"an update of the world-wide safety experience of a medicine at defined times post-registration, as determined from the international birth date. Each safety update report should cover the period of time since the last update report".*

Consumer reports are also a type of ADR reporting method used by a consumer through his/her general practitioner, pharmacist, nurse or dentist (SAHPRA, 2018).

During pre-registration, a serious adverse event/reaction (SAE) reporting form is used for the reporting of pre-registration clinical trial adverse event/reaction reports (SAHPRA, 2018).

Table 2-14: Pre-registration adverse drug reaction reports in South Africa

Type of report	What to report	Time frame for reporting	Format of ADR reporting
Clinical trials	Fatal and life-threatening, unexpected ADRs. Serious, unexpected ADRs that are not	7 days 15 days	ADR form ADR form

	fatal or life-threatening. Suspected serious and unexpected ADRs.	6 monthly	Line-listing
Reaction occurring in South Africa	Fatal or life-threatening (unexpected). Other serious (unexpected).	7-8 days 15 days	SAE form SAE form
Reaction occurring outside South Africa	Serious (unexpected and expected). Non-serious (unexpected).	6 monthly 6 monthly	Line-listing Line-listing

Adapted from: MCC (Medicines Control Council). 2012. Reporting adverse drug reactions in South Africa. *Registrar of Medicines,* 1(2):4-17.

2.5.2.2 United States of America

Adverse drug reactions are reported to the Food and Drug Administration (FDA) in various forms (FDA, 2018). The FDA accepts PDF format forms as well as online reporting forms. The PDF format forms are used for voluntary reporting, voluntary reporting for consumers and mandatory reporting (FDA, 2018).

Voluntary reporting is one of the methods on which the FDA relies to keep effective medical products available (FDA, 2018). Consumers and healthcare professionals use this form of reporting ADRs. Consumers are encouraged to take a reporting form to their healthcare professional once they experience an ADR in order, for the healthcare professional to be able to use medical records to help the FDA to evaluate the report, although it is not required to take the form to the healthcare professional (FDA, 2018). To report ADRs voluntarily, the FDA Form 3500 should be used by healthcare professionals and FDA Form 3500B by consumers (FDA, 2018). Information on reporting is available in Table 2-15.

Mandatory reporting is done by manufacturers and importers of medicinal products. The mandatory reporting process is discussed in Table 2-15.

Table 2-15: Mandatory reporting of adverse drug reactions

Reporter	What to report	Reporting form	To whom	When
Manufacturers	30-day reports of the following events: • death	Form FDA 3500A	FDA	Within 30 days of being aware of a reaction.

	• serious injuries • malfunctions 5-day reports for a reaction indicated by the FDA. A reaction that needs remedial action to prevent an unreasonable risk of extensive harm to the public health.			Within 5 working days of being aware of a reaction.
Importers	Reports of the following: • death • serious injuries • malfunctions	Form FDA 3500A	FDA and the manufacturer	Within 30 days of being aware of a reaction
User facility	Reports of the following: • Device-related death • Device-related serious injury	Form FDA 3500A	FDA and the manufacturer	Within 10 working days of being aware of the reaction.
	Yearly summary of death and serious injury reports	Form FDA 3419	FDA	January 1 for the current year

Adapted from: The Food and Drug Administration (FDA). 2018. Reporting serious problems to FDA. https://www.fda.gov/safety/medwatch/howtoreport/default.htm Date of access: 10 Aug. 2018.

2.5.2.3 Europe

The European Medicines Agency is in charge to develop, maintane and coordinate EudraVigilance, a system developed for the reporting of suspected side-effects (EMA, 2018). EudraVigilance is there to manage and analyse data of suspected adverse reactions to medication that have previously been authorised or that are currently being studied in clinical trials in the European Economic Area (EEA). The European Union (EU) medicines regulatory network are being operated by The EMA (EMA, 2018).

The reporting of adverse reactions are being defined by certain EU legislation set up by the European Parliament and the Council, which are the following:

- Regulation (EC) No 726/2004

- Directive 2001/83/EC as amended
- Directive 2001/20/EC
- Regulation (EU) 536/2014 (EMA, 2018).

Reporting entities, what to report and how to report is illustrated in Table 2-16.

2.5.2.4 Australia

In Australia, the Therapeutic Goods Administration (TGA) which forms a part of the Australian Government Department of Health and is in charge to regulate therapeutic goods which includes vaccines, prescription medicines, vitamins and minerals, sunscreens, medical devices and blood products (TGA, 2018). Most products for which therapeutic claims can be made needs to be entered into the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia (TGA, 2018). Reporting entities, what to report and how to report are illustrated in Table 2-16.

Table 2-16: ADR reporting processes in various countries compared to South Africa

Country	Reporting entity	Reporting method	Who can report	What to report	What to include
South Africa	Reportable safety information associated with registered human medicines needs to be reported to: The Medicines Regulatory Affairs in Pretoria – SAHPRA 012 395 8000 http://www.mccza.com/Contact NADEMC in Cape Town: National Adverse Drug Event Monitoring Centre Medicines Control Council, C/o Department of Pharmacology, University of Cape Town. Reportable Safety Information associated with medicines used under section 21 of the Medicines and Related Substances Act no 101 of 1965 and in clinical trials involving unregistered medicines should be sent to: Office of the Registrar of Medicines Pharmacovigilance Unit	Online/ PDF format: (As discussed in Table 4-4 and Table 4-5) - ADR form - SAE form	Medical practitioners Dentists Pharmacists Nurses (Patients are advised to report to a medical practitioner)	Suspected adverse experiences.	Medicines and vaccines. Medical devices. Complementary medicines. Traditional and herbal medicine. Homeopathic medicines.
				Suspected product quality problems.	Contamination. Stability problems. Defective components. Poor packaging or labelling.
				Therapeutic failure.	

	Private Bag X828, Pretoria.				
United States	FDA MedWatch https://www.fda.gov/	PDF reporting forms: Voluntary reporting & Voluntary reporting for consumers. -- complete Voluntary Form FDA 3500 online. Call 1-800-FDA-1088 to report by telephone. Mandatory reporting Medical Device Reporting (MDR) regulation (21 CFR 803). Online reporting form	Healthcare professionals. Consumers. Patients. Manufacturers. Distributors. Importers. User facilities personnel.	Serious adverse events. Prescription or OTC medicines. Biologics. Cosmetics. Medical devices. Food/beverages.	Human medicinal product. Product quality problems. Therapeutic failure. Medication errors. Blood components. Cellular and tissue-based products. Allergic reactions. Infant formulas and medical foods.

Europe	European Medicines Agency (EMA) responsible for coordination of EudraVigilance. http://www.adrreports.eu/en/eudravigilance.html	Electronic reporting: Individual case safety reports (ICSRs). Product reports.	Sponsors of clinical trials. Marketing authorisation holders [Regulation 726/2004 (Article 57(2)].. National competent authorities.	Suspected unexpected serious adverse reactions. Suspected serious adverse reactions.	
Australia	Therapeutic Goods Administration (TGA) https://www.tga.gov.au/	Online electronic reporting at https://aems.tga.gov.au/report-create/ Emailed reports. Telephonic reports: defect with a medicine or vaccine, contact the TGA on **1800 020 653**.	Sponsors (pharmaceutical companies and medical device suppliers). State and Territory health departments, hospitals, health professionals and consumers.	Suspected adverse events to new therapeutic goods. Suspected medicine and/or vaccine interactions. Unexpected adverse events. Serious adverse events, such as those suspected of causing: Death, danger to life,	Medicine or vaccine. A problem with a medical device. A counterfeit medicine or medical device. An issue with packaging or storage of a medicine.

		report about a problem with a medical device, phone **1800 809 361**.		admission to hospital, prolongation of hospitalisation, absence from productive activity, increased investigational or treatment costs, birth defects.	

Adapted from: MCC (Medicines Control Council). 2012. Reporting adverse drug reactions in South Africa. *Registrar of Medicines,* 1(2):4-17. The Food and Drug Administration (FDA). 2018. Reporting serious problems to FDA. https://www.fda.gov/safety/medwatch/howtoreport/default.htm Date of access: 10 Aug. 2018. European Medicines Agency (EMA). 2018. Eudravigilance: electronic reporting. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000686.jsp&mid=WC0b01ac0580a69261 Date of access: 10 Aug. 2018. Therapeutic Goods Administration (TGA). 2018. Reporting problems. https://www.tga.gov.au/reporting-problems Date of access: 10 Aug. 2018.

2.6 Adverse drug reaction (ADR) reporting form

An ADR report is a "*detailed record of all relevant data associated with the use of a medicine in a subject or patient*" (SAHPRA, 2018). There are different Case Report Forms in different countries, which have at least four sections that should be completed (WHO, 2002:13 & SAHPRA, 2018:6). These four sections are the following:

- Information identifying the patient who is experiencing the ADR.
- Description of the ADR or product problem.
- Medication involved in the suspected ADR.
- Information identifying the reporter of the ADR.

Table 2-17: Minimum information appearing on ADR reporting form compared to South Africa

	Information	South African ADR report form*	WHO ADR report form**
Patient information	Patient identifier.	✓	✓
	Age at time of event or date of birth.	✓	✓
	Gender.	✓	✓
	Weight.	✓	✓
Adverse event or product problem	Explanation of event or problem.	✓	✓
	Date of event.	✓	✓
	Date of this report.	✓	✓
	Relevant tests/laboratory data (if available).	✓	✓
	Other applicable patient information/history.	✓	✓
	Consequences attributed to adverse event.	✓	✓
Suspected medication (s)	Name (INN and brand name).	✓	✓
	Dose, occurrence & route used.	✓	✓
	Therapy date.	✓	✓
	Diagnosis for use.	✓	✓
	Event decreased after use stopped or dose reduced.	✓	✓
	Batch number.		

	Expiration date. Event re-emerged after reintroduction of the treatment. Concomitant medical products and therapy dates.	✓ ✓ X ✓	✓ ✓ ✓ ✓
Reporter	Name. Address. Telephone number. Speciality and occupation.	✓ X ✓ ✓	✓ ✓ ✓ ✓

*Adapted from MCC (Medicines Control Council). 2012. Reporting adverse drug reactions in South Africa. *Registrar of medicines,* 1(2):4-17.

**Adapted from WHO (World Health Organization). 2002. Why health professionals need to take action. Safety of medicines – a guide to detecting and reporting adverse drug reactions. Geneva.

2.6.1 Implementation of adverse drug reaction reporting in the private and public sector in South-Africa

2.6.1.1 Regulatory sector – private and public

South Africa established a medicines regulatory authority with internationally recognised standards over the past few years (MCC, 2018). The South African Health Products Regulatory Authority (SAHPRA) laid down standards according to the Medicines and Related Substances Act (101 of 1965), which oversees manufacturing, distribution, sales and the marketing of medicines (SAHPRA, 2018). SAHPRA considers whether medicine is safe and appropriate to use for its intended purpose by assessing the risks and benefits of the drug. All medicines used by humans are subject to this law (SAHPRA, 2018).

According to the Medicines and Related Substances Act, (101 of 1965) SAHPRA shall include a member with the knowledge in the study of ADRs (South Africa, 1965). The law also states that (i) an applicant or holder of a certificate of registration should inform the Council, within the determined time frame, of any suspected ADR reported to him/her; (ii) the certificate holder should inform SAHPRA of the steps taken to address the ADR and (iii) inform SAHPRA of other pharmacovigilance data, as well as (iv) keep and maintain records of all ADR data (South Africa, 1965).

2.6.1.2 Public and private patient level

There are a number of institutions that have established ADR and medication error surveillance systems in the country (NDoH, 2017; SASQC, 2016; SAQA, 2014 & SAMRC, 2018). ADR monitoring is being recognised as a crucial quality assurance activity with accreditation agencies such as the National Policy on Quality in Healthcare which provides ways to improve the quality of care in both the public and private sectors (NDoH, 2017:2), the South African Society for Quality Control (SASQ) (SASQ:2016), the South

African Qualifications Authority (SAQA) (SAQA, 2014) and the South African Medical Research Council (SAMRC) (SAMRC, 2018). Their aims to improve quality are described in Table 2-18:

Table 2-18: Quality assurance entities' objectives

Quality assurance entities	Objectives
National Policy on Quality in Healthcare	The objective of this entity is to address access to healthcare to patients to be able to reduce main causes of illness, injury and disability. This policy wants to prevent disease and promote a healthy lifestyle. They participate in research on the effectiveness of medicine to ensure the appropriate use thereof. By participating in these activities, they are reducing adverse drug events (NDoH, 2017:2).
South African Society for Quality Control (SASQC)	SASQC's objective is to stimulate quality healthcare by creating awareness on the quality in indutry and commerce. The entity wants to improve the quality of healthcare through continuous training, and through this develop practitioners in the health and safety environment (SASQC, 2016).
South African Qualifications Authority (SAQA)	To be in charge of overseeing the continous development of the National Qualifications Framework (NQF), to be able to develop professionals social environment as well as the economy of the nation. The objectives of the NQF is to create a framework for learning achievements, to facilitate access and progression in career paths and also improve the quality of education and training (SAQA, 2014).
South African Medical Research Council (SAMRC)	Operate in a socially (community and staff) and environmentally (fauna and flora) responsible manner, to maintain an environment that is safe and without risk to the health and safety of the nation. Another objective is to provide enough resources to be able to support SAMRC's efforts to comply with its Health, Safety and Environment (HSE) obligations. Ensure that health and safety is not sacrificed for the sake of expediency, and ensure that

	unacceptable health and safety performance is not tolerated (SAMRC, 2018).

In 2003, at the Sefako Makgatho Health Sciences University (SMU), the South African Vaccination and Immunisation Centre (SAVIC) was established (SAVIC, 2018). This centre serves as a guide in the field of vaccination and immunisation to strenghten collaborations between universities, the NDoH, the vaccination industry and other stakeholders, to be able to support immunisation services in order to prevent morbidity and martality (SAVIC, 2018).

In 2004, the KwaZulu-Natal's (KZN) pharmacovigilance committee initiated its ARV programme, because of the increased prevalance of HIV/AIDS and the increasing number of patients being initiated on ARV treatment (Fyzoo, 2014:2). The KZN Department of Health instituted a spontaneous reporting system for ARVs. The mandatory reporting system required clinicians to submit an ADR report when toxicity prompted variations in ARV treatment regimens (Fyzoo, 2014:2). In 2007, 3 923 reports were collected, which increased to 34 209 reports in 2012, specifying useful information on the medicine usually implicated in ADRs and demanding treatment substitution (Fyzoo, 2014:3).

On 25 November 2015, the National Department of Health (NDoH) officially launched the mobile application of the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for the primary healthcare level (NDoH, 2018a). The application was designed to promote clarity on the revised edition of the Primary healthcare STGs and EML (NDoH, 2018b). One can click from one guideline and be taken directly to another related guideline or query. The application also comprises of a directory service of all the healthcare facilities in the country. It offers the phone numbers and GPS location of every public health facility in South Africa. Table 2-19 describes the useful tools of the applications as well as the benefit thereof for pharmacovigilance (NDoH, 2019b).

Table 2-19: Mobile application benefits for pharmacovigilance in South Africa

Tools	Description	Benefit for pharmacovigilance
Search function	A healthcare professional can type a keyword or a symptom and locate a list of related guidelines.	This will simplify proficient access to correct information.

Cardiovascular Risk Assessment Tool	Healthcare professioanals can calculate a patient's percentage risk of having a cardiovascular event such as a stroke or a heart attack in the next 10 years.	A decrease in medication errors.
Paediatric Drug Dosage Calculator	Healthcare professioanals are able to calculate the weight or age-based dosage for the most usual medications on the medicine list.	This will decrease errors in prescriptions and reduce frustration from healthcare professionals.
Medicine Stock-Out Tool	Users are able to report medication shortages and stock-outs directly to the NDoH.	The decrease in prescribing errors and polypharmacy.
The Adverse Drug Reaction Tool	It permits healthcare professionals to report serious reactions to medicines.	Increase in ADR reports with easy and less time-consuming methods.
ICD10 Codes	The recording of medical diagnosis information according to the international ICD10 standard is becoming essential in healthcare management and will be a requirement for National Health Insurance. This tool offers a searchable database of ICD10 codes.	A decrease in prescribing and dispensing errors by HCP's, which will lead to a decrease in medication errors.

Adapted from: NDoH (National Department of Health). 2018a. Launch of mobile application. http://www.health.gov.za/index.php/gf-tb-program/295-launch-of-mobile-app-for-primary-health-care-standards Date of access: 12 Sep. 2018.

2.6.1.3 Academia

South Africa has a total of 25 universities and nine schools of health sciences (SAPC, 2018). The following universities offer programmes in pharmacovigilance with various objectives. Table 2-20 illustrates these universities along with their objectives:

Table 2-20: South African pharmacy schools and courses

Institution	Type of programme
North-West University of Potchefstroom (NWU)	Post-graduate programme: Master of Pharmacy in pharmacovigilance and pharmacoepidemiology (NWU, 2019:98)
University of the Witwatersrand (WITS)	BSc (Honours) in Pharmacology (WITS, 2017): Research areas include: *Toxicology *Clinical pharmacology *Pharmacovigilance *Drug utilisation
University of the Western Cape (UWC)	MSc. in Pharmacy Administration and Pharmacy Policy. Programmes aiming toward ADR reporting are as follow: • _Pharmacovigilance • _Health economics • _Regulatory sciences for generics and biosimilars , complementary/traditional medicine and medical devices. • _Research project (UWC, 2018)
Rhodes University	PharmD in Pharmacy Practice: This programme focus on pharmacuetical care and the role of the pharmacist in management of the pharmacy. The programme assists with primary healthcare and focus on providing safe and effective medicine to patients (Rhodes University, 2017).
Sefako Makgatho Health Sciences University	Master of Pharmacy: This postgraduate programme include studies in the following fields:

	• clinical, • industrial, • public health pharmacy • public health pharmacy management, and • radio-pharmacy (SMU, 2018).
University of Kwazulu-Natal (UKZN)	Masters in Health Sciences: Pharmacovigilance: This programme focus on the reporting of ADRs as well as pharmacovigilance. This course look at drug safety, post-marketing surveillance, ADRs, event reporting; pharmacoepidemiology, and health legislation in the field of ADR reporting. The program also focus on current reporting systems in South Africa and internationally (University of Kwazulu-Natal, 2018).

The undergraduate BPharm degree in South African universities does not cover the reporting of ADRs extensively. For this reason, postgraduate studies and supplementary training are provided by providers to support education in pharmacovigilance. Short courses such as professional development and good manufacturing practices are provided by the Health Science Academy (HSA), the University of Stellenbosch and the International Council for Harmonisation (ICH) endorsed by the Pharmaceutical Industry Association of South Africa (PIASA) to teach pharmacists the importance of drug safety, ADRs and legislation the the pharmaceutical field (HSA, 2015; University of Stellenbosch, 2018; PIASA, 2012).

2.7 Barriers and facilitators of adverse drug reaction reporting

From what has been discussed thus far, it is evident that there are still barriers and facilitators toward ADR reporting in many countries, resulting in underreporting and thereby hindering the progress that needs to be made in pharmacovigilance. Some of the barriers include: time management, compensation, no adequate training and limited feedback from the pharmacovigilance units. In this section barriers experienced by pharmacists in their pharmaceutical sector in SA will be discussed.

2.7.1 Barriers and facilitators influencing the implementation of pharmacovigilance

Adverse drug reactions can cause harm to patients; but are being underreported in many countries, including South Africa (SA) (Joubert & Naidoo, 2016:241; Van Graan *et al*., 2017:31). The foundation of pharmacovigilance is the voluntary reporting of ADRs (Mehta *et al*., 2013:104). Adverse drug reaction reporting is completely reliant on the initiative and enthusiasm of potential reporters.

A retrospective clinical analysis of ADRs correlated with antiretroviral therapy in the Tlokwe district (public healthcare sector) in SA revealed that 98.8% of the reported ADRs came from doctors and 0.9% from nurses in 2017 (Van Graan *et al*., 2017:31). During the period 2010-2014, no pharmacists reported ADRs (Van Graan *et al*., 2017:32). A study done in North-West Province in the public healt sector on South African pharmacists' knowledge and perceptions of pharmacovigilance in 2015 revealed various attitudes towards the reporting of ADRs (Joubert & Naidoo, 2016:241). Forty-four percent of pharmacists indicated that they had not reported an ADR and 50% of respondents were not satisfied with the South African pharmacovigilance system. The foremost barrier to reporting ADRs is a lack of knowledge about the reporting process (Elkalmi *et al*., 2011b:71). In the study of Joubert and Naidoo (2016:241), 62.75% of the pharmacists were familiar with the term pharmacovigilance, but only 45.10% could define pharmacovigilance. Only 10.78% could identify the pharmacovigilance unit, NADEMC (Joubert & Naidoo, 2016:240). Table 2-21 indicates their attitudes and perceptions towards pharmacovigilance and the reporting of ADRs.

Table 2-21: Attitudes and perceptions of pharmacists towards pharmacovigilance

Attitudes and perceptions	Yes n(%)	No n(%)
Medicine Control Council is remote.	63 (61.8)	27 (26.5)
NADEMC is remote.	57 (55.9)	22 (21.6)
Not responsible to report ADRs.	7 (6.9)	92 (90.2)
Do not report ADRs on older medicine.	6 (5.9)	92 (90.2)
Do not report rare ADRs.	6 (5.9)	93 (91.2)
Pharmacovigilance is an unrealistic tool.	9 (8.8)	81 (79.4)
Receive pharmacovigilance notifications from manufacturers that are clear.	82 (80.4)	11 (10.8)

In the study by Joubert and Naidoo (2016), pharmacists also revealed certain barriers keeping them from reporting ADRs. Fifty percent of the pharmacists in the study felt that reporting ADRs is time-consuming and 38.24% did not know how to report an ADR (Joubert & Naidoo, 2016:242). Pharmacists had trouble with the ADR form, where 27.45% felt the form was not user-friendly and 20.59% felt that the form is too complicated to complete (Joubert & Naidoo, 2016:242). Not gaining financial incentive was mentioned by 17.65% of respondents (Joubert & Naidoo, 2016:242).

Underreporting is a common problem in many countries such as Saudi Arabia, Pakistan, Bangalore, the United Kingdom and South Africa (Joubert & Naidoo, 2016; Khan, 2013b; Suleman, 2010) . According to a study done in Saudi Arabia, only 30% of pharmacists were willing to report ADRs (Khan, 2013b:48).

These pharmacists also believed that it was not necessary to report ADRs occurring from OTC medication. It is important to create awareness and a positive attitude among pharmacists to report ADRs. Pharmacovigilance and the reporting of ADRs should become a routine responsibility among pharmacists. Many recent studies reveal the knowledge, attitude and barriers to the reporting of ADRs. Table 2-22 illustrates some of these studies, which focus on the barriers for underreporting of ADRs by pharmacists in various countries (Almandil, 2016; Green *et al*., 2001; Joubert & Naidoo, 2016; Khan, 2013b; Nagaraju *et al*., 2015 & Shamim *et al*., 2016).

A study in South Africa, at the National Department of Health (NDoH) Pharmacovigilance Centre for Public Health Programmes, showed that ART and TB drugs had a total of 251 ADR reports for the period 1 October 2016 to 31 December 2016 (NPC, 2016:2). According to a systematic review by Varallo *et al.* (2014:743), the main cause for underreporting of ADRs in Europe includes ignorance and insecurity. The study identified that ongoing education for healthcare professionals will be effective in improving attitudes towards noticing ADRs. Another cause of underreporting identified by Varallo *et al.* (2014:744) included the lack of interest in completing the ADR form and shortage of time.

Pharmacists have the need to be educated about the reporting of ADRs in pharmacies (Suleman, 2010:57). A study conducted in South Africa on barriers of ADR reporting indicated that healthcare professionals, which included pharmacists, had a need to understand what should be reported, as well as a shortage in skills and knowledge to classify or identify ADRs (Ruud *et al*., 2010:5). An important aspect of pharmacovigilance is the importance of ongoing under- and post-graduate education of healthcare professionals (WHO, 2000:16). The WHO (2000:18) emphasises that education will improve knowledge and awareness of ADRs, and lead to reporting. Pharmaceutical companies, national pharmacovigilance centres and academia can all contribute to the education and knowledge of pharmacovigilance and the ADR reporting skills of healthcare professionals.

Definitions used in the field of pharmacovigilance need to be understood by pharmacists. Pharmacists should be able to explain the specific ADRs to ensure reliability and extensive understanding of data obtained through the ADR reporting systems. An important aspect is to encourage recognition of drug safety problems and the importance of appropriate use of drugs among healthcare professionals and the public.

In Table 2-22 it can be seen that pharmacists in South Africa have less knowledge of the term pharmacovigilance than in Saudi-Arabia and Pakistan, although South Africans have a higher awareness of ADRs. Overall, pharmacists have not attended ADR or pharmacovigilance courses in all the countries mentioned in Table 2-22. The awareness of ADR reporting and how to obtain the forms in South Africa is also much lower than other countries (Almandil, 2016; Green *et al.,* 2001; Joubert & Naidoo, 2016; Khan, 2013b; Nagaraju *et al.,* 2015 & Shamim *et al*., 2016).

These statistics reveal that further education is needed in the field of pharmacovigilance and the reporting of ADRs.

Table 2-22: Pharmacists' knowledge, attitudes and barriers to the reporting of ADRs

Different studies						
Study design **Country** **Reference**	Cross-sectional **Saudi-Arabia** Almandil, (2016)	Prospective study **Bangalore** Nagaraju *et al.* (2015)	Cross-sectional **Pakistan** Shamim *et al.* (2016)	Cross-sectional **South Africa** Joubert & Naidoo, (2016)	Cross-sectional **United Kingdom**Green *et al.* (2001)	Cross-sectional **Saudi-Arabia** Khan, (2013b)
Participating pharmacists (%)	39 (8.48%)	100%	106 (29.7%)	102 (68.9%)	305	71.43%
Knowledge and awareness						
Understood the term pharmacovigilance	60.5%	N/A*	43.4%	46.1%	N/A	N/A
Definition of ADR	46.1%	91%	43.4%	N/A	N/A	92.0%
Awareness of pharmacovigilance centre in country	37.8%	N/A	16%	60.8%	97.0%	10.0%
Attended courses/workshop	10.1%	N/A	24.5%	N/A	37.9%	N/A
Perception and attitude						
Believe it is an obligation	75.9%	53%	53.8%	8.8%	86.1%	N/A
Barriers						
Not aware of reporting system in sector	44.9%	31%	35.8%	39.2%	3.0%	90.0%

Do not know where to find the forms	N/A	N/A	23.6%	35.29%	N/A	88.0%
Reporting forms are too complicated	N/A	N/A	N/A	20.59%	9.5%	18.0%
Reporting is time consuming	N/A	N/A	65.1%	50.0%	45.2%	34.0%
I fear legal liability of the reported ADR	10.3%	N/A	N/A	N/A	N/A	12.0%
There is no motivation for me to report	17.5%	N/A	N/A	17.65%	5.0%	38.0%
I do not know how to report	43.8%	99%	N/A	38.24%	N/A	44.0%
I am not confident about whether it is an ADR	N/A	N/A	42.5%	N/A	40.9%	2.0%
I do not have the knowledge of pharmacotherapy to detect an ADR	N/A	N/A	N/A	N/A	32.3%	2.0%
Reporting ADRs is not part of my job	9.9%	N/A	N/A	6.9%	N/A	N/A
I understand that only safe drugs are marketed	N/A	N/A	15.1%	N/A	N/A	2.0%

*N/A: Not applicable.

CHAPTER SUMMARY

Chapter 2 explained the rationale for the research with focus and explanation of the term ADR, adverse drug event, medication error and inappropriate drug usage in different countries. The need for the study is

explained through the burden that these terms have on the various countries and how these countries maintain and manage it. Relevant previous studies were used to reach the objective of the research.

CHAPTER 3: RESULTS

As mentioned in the preface, this chapter contains the results of the empirical study. Results are presented in two articles which were prepared for publication. Table 3-1 presents the article titles, their correlation between each other, the different parts of the structured questionnaire used and the objectives of the empirical study.

Table 3-1: Obejectives, manuscripts and structured questionnaire

Article title	Objective	Manuscript	Sections of the structured questionnaire
Pharmacists' perceptions towards the past and future of adverse drug reaction reporting in South Africa.	Objective 1: Determine pharmacists' past experience with the reporting of ADRs, stratified by pharmaceutical sector and demographic information. Objective 2: Assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographic information.	1	Section A, B, C
Pharmacists' pharmacovigilance and adverse drug reaction reporting perception and barriers affecting the reporting rates: A South African online survey.	Objective 3: Determine from the perceptions of pharmacists' possible factors that influence the successful implementation of pharmacovigilance in different	2	Section A, C, D

	pharmaceutical sectors in South Africa. Objective 4: Identify pharmacists' additional training needs regarding ADR reporting and pharmacovigilance.		

3.1 Manuscript 1

The article titled: "Pharmacists' perceptions towards the past and future of adverse drug reaction reporting in South Africa." is presented in this chapter. The article was prepared for submission to the *Journal of Research in Pharmacy Practice*, as an original research article. This article was prepared according to the specific guidelines by the authors for this journal (See Annexure F).

Instructions to the author can be viewed at the following link:

http://www.jrpp.net/contributors.asp

Manuscript 1 addresses the first and second objective of the empirical study:

> Objective 1:Determine pharmacists' past experience with the reporting of ADRs, stratified by pharmaceutical sector and demographic information.
>
> Objective 2:Assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographic information.

Title: Pharmacists' perceptions toward the past and future of adverse drug reaction reporting in South Africa

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Pharmacists' perceptions toward the past and future of adverse drug reaction reporting in South Africa

Abstract

Objective: Adverse drug reactions (ADRs) have become a major health concern worldwide. These reactions are vastly underreported in South Africa (SA). The aim of the study was to investigate pharmacists' past experiences toward ADR reporting and to determine their current attitudes and abilities to report ADRs in SA.

Methods: A cross-sectional research design was implemented by using an online structured questionnaire that was emailed to 11 732 pharmacists on the Register of Pharmacists of the South African Pharmacy Council (SAPC) in 2018. The questionnaire consisted of 34 questions that evaluated pharmacists' past experience, their current attitude and ability to report ADRs in South Africa.

Findings: Of the 656 pharmacists who responded (response rate of 5.6%), the majority were female (n = 464, 70.7%) and practicing in the private healthcare sector (n = 380, 57.9%). A third (n = 232, 35.4%) of the respondents had received additional training in ADR reporting. Most respondents (N = 561) (n = 537, 95.7%) had heard about ADR reporting, 60.9% (n = 342) and noticed a suspected ADR in the past 12 months, although 52.8% (n = 296) had never reported an ADR in their professional career. The majority of pharmacists (N = 656, n = 493, 75.2%) understand the reporting system, 60.8% (n = 399) pharmacists would be willing to report ADRs and 58.2% (n = 382) believe they have the ability to report ADRs. Twenty percent (n = 137) of pharmacists knew they should report an ADR to the National Adverse Drug Event Monitoring Centre (NADEMC).

Conclusions: The attitude among pharmacists toward ADR reporting is promising, but the actual reporting of ADRs is inadequate and needs improvement. Educational programmes should be initiated to strengthen the knowledge and attitudes of pharmacists toward pharmacovigilance and ADR reporting.

Key messages: Pharmacists have a positive attitude toward ADR reporting and have the ability and willingness to report ADRs in South Africa, but pharmacists are still not reporting these reactions sufficiently.

Key-words:

adverse drug reaction reporting, pharmacist, pharmacovigilance, South Africa

Introduction:

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "a *response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function".* [1] Healthcare professionals have begun to realise that morbidity and mortality that are related to ADRs, which are caused by medicine, bring about significant grief and are among the leading healthcare problems in South Africa (SA).[2] ADRs contribute to 2.9% of deaths in SA, where 43% of these ADRs are considered preventable. [3] In the private hospital sector, 18.9% of pharmacists and nurses previously reported an ADR and 22.3% stated that they 'don't know' if they had ever encountered an ADR. [4]

Most pharmacists see ADR reporting as part of pharmaceutical care and acknowledge the importance thereof, although the reporting of ADRs is still uncommon. [5] On-going education regarding ADR and the reporting process will improve healthcare professionals' attitudes and insecurity toward the process. [6]

The aim of this study was to determine pharmacists' approach to the reporting of ADRs and whether further education is needed in the field of ADR reporting. This is the first study focusing on pharmacists' attitudes and perceptions toward ADR reporting in all pharmaceutical sectors in a developing country.

Methods:

This was a cross-sectional study, conducted amongst pharmacists from all sectors of pharmacy (community, public- and private institutional-, manufacturing, wholesaler, academia and consultancy pharmacies) in South Africa. All pharmacists on the 2018 Register of Pharmacists of the South African Pharmacy Council (SAPC) were included. [7] The target population consisted of 14 511 pharmacists. Pharmacists with no email address or an invalid email address were excluded as well as pharmacists older than 65 years of age or not practicing anymore, giving a study population of 11 732 pharmacists. A total of 656 pharmacists completed the questionnaire, resulting in a response rate of 5.6%.

A structured online questionnaire, with both open and closed-ended questions, was used and emailed to each potential participant. Various policy documents [8, 9] and structured questionnaires assessing knowledge, perception and attitude toward ADR reporting from different studies, were also examined to draft the questionnaire.[2, 10-14] The questionnaire was developed in both English and Afrikaans, as these are two of the official languages in South Africa. The content and face validity of the questionnaire were assessed by subject specialists and a statistician. The questionnaire consisted of two sections. The first section consisted of 14 questions, which included demographic information such as age, gender, area of practice and qualification of the participant. The second section had 20 questions that were used to measure the training, experience and perception of pharmacists regarding the reporting of ADRs.

The questionnaire was distributed by a survey mediator, who completed a confidentiality agreement to ensure the anonymity of participants and their information. The questionnaire was distributed with a title page that explained the purpose of the study. An informed consent form was also included in the online questionnaire. The questionnaire took up to 30 minutes to complete and was voluntary. Participants could withdraw from the study at any stage.

The IBM SPSS® software was used to analyse the data. The study population was characterised by using descriptive statistics, including frequencies (n) interpreted as percentage (%) values, arithmetic means and standard deviations (SDs). Pearson's chi-square test (x^2) was used to determine whether a statistically significant association exists between two or more categorical variables, for example, to determine the statistically significant association between the age group and gender of respondents within their current area of practice. The chi-square test was also used to determine statistically significant associations between pharmacists who received additional training, their highest qualification and years of experience against which ADRs and product stability problems to report.

Cramér's *V* statistic was used to test the practical significance of these associations, where a value of 0.1 was regarded as a small effect, 0.3 as a medium effect, and 0.5 as a large effect.[15] The Binomial test was used to compare two proportions and to determine whether the difference between the two proportions was of statistical significance. The Binomial test was also used to determine whether the differences

between the proportion of pharmacists who responded positively and those who responded negatively toward the reporting of ADRs and product stability problems were of practical or statistical significance. The results were seen as statistically significant when the *p*-value was $p \leq 0.05$.[15]

The following equation was used to calculate the effect size:[16]

$$\delta_{\frac{1}{2}} = 2\left(\frac{x}{n}\right) - 1$$

where x = number of people who responded positively and n = sample size. The following guideline was used to evaluate the results:

$\delta_{\frac{1}{2}}$ = 0.1: small effect (non-significant)

$\delta_{\frac{1}{2}}$ = 0.3: medium effect (observable)

$\delta_{\frac{1}{2}}$ = 0.5: large effect (statistically significant)

Ethical approval for the study was obtained from the Health Research Ethics Committee of the North-West University in South Africa (NWU-00137-17-S1).

Results:

The average age of the respondents was 41.55 years (SD±10.89). The majority of respondents were females (N = 656, n = 464, 70.7%, p<0.001). Among the pharmacists (N = 603) who responded, the majority were practicing in the private healthcare sector (n = 350, 58.0%) and 173 (28.7%) in the public healthcare sector. Pearson's chi-square (x^2) and effect size (Cramér's V) indicated a statistically significant association between both gender- x^2 (1, N = 656) = 27.6, p=0.001 (Cramér's V=0.205) and age group x^2 (1, N = 656) = 55.6, p=0.020 (Cramér's V=0.146) of respondents with their current area of practice. Both male (n = 90, 46.9%) and female (n = 166, 35.8%) pharmacists are more likely to practice healthcare in a community, corporate and mail order pharmacy. Pharmacists in the age group 55 years and older (n = 63, 53.8%) are more likely to practice healthcare in a community, corporate and mail order pharmacy. Demographic characteristics of the study respondents are shown in Table 3-2.

Table 3-2 Demographics of the study population (N = 656)

	Characteristics	Number n (%)	*p*-value	$\delta_{\frac{1}{2}}$
Gender	Female	464 (70.7)	<0.001	0.414
	Male	192 (29.2)		
	Age (years) [mean (SD)]	41.55±10.89		
	≤31	138 (21.0)		
	32-36	125 (19.1)		
	37-43	143 (21.8)		
	44-54	133 (20.3)		
	≥55	117 (17.8)		
Highest qualification	BPharm degree	477 (72.7)		
	MPharm degree	120 (18.2)		
	PhD	20 (3.0)		
	Diploma in Pharmacy	22 (3.3)		
	Specialist pharmacy degree	3 (0.4)		
	Other	14 (2.1)		
			Average years of experience	
Current area of practice*	Community, Corporate and/or Mail order pharmacy	256 (39.0)	5.1±5.1	
	Private hospital pharmacy	83 (11.6)	5.5±6.0	
	Public hospital pharmacy	112 (17.1)	5.2±5.9	
	Medical aid environment	12 (1.8)	4.8±4.9	
	Clinical research	24 (3.7)	6.0±6.7	
	Academia	35 (5.3)	6.3±7.6	
	Wholesale/Distribution pharmacy	23 (3.5)	4.6±6.3	
	Manufacturing/Production	32 (4.9)	6.1±7.4	
	Medicine registration and/or Quality control	76 (11.6)	5.7±5.5	
	Military services and/or Correctional services	10 (1.5)	2.3±2.5	

*More than one answer was excepted. Data presented as number (%), or mean±SD, where applicable. SD=Standard deviation

A large number of respondents (N = 604, n = 198, 32.8%) have more than 20 years of experience as a practicing pharmacist (Table 3-3). The majority of respondents (N = 654, n = 421, 64.4%) have not received any additional training in the reporting of ADRs. Additional training was received by pharmacists in pharmacovigilance (N = 656, n = 191, 29.1%), ADRs and drug-related problems (n = 165, 25.2%) and toxicology (n = 37, 5.6%) and is presented in Table 3-3. The Binomial test indicated that most respondents (N = 412, n= 383, 92.9%, p <0.000, δ½=0.859) reacted positively toward believing that they have the ability to report ADRs.

Table 3-3: Pharmacists training regarding ADR reporting

		Number n (%)	*p*-value	$\delta_{\frac{1}{2}}$
Highest qualification	BPharm degree	477 (72.7)		
	MPharm degree	120 (18.2)		
	PhD	20 (3.0)		
	Diploma in Pharmacy	22 (3.3)		
	Specialist pharmacy degree	3 (0.4)		
	Other	14 (2.1)		
Years of experience as a practicing pharmacist	Less than 5 years	88 (14.5)		
	5-10 years	126 (20.9)		
	11-15 years	97 (16.0)		
	16-20 years	94 (15.5)		
	More than 20 years	198 (32.8)		
Ever received ADR reporting training	Yes	232 (35.5)	<0.000	0.289
	No	421 (64.4)		
Area where training was received *	University level	37 (15.9)		
	Additional degree	5 (2.1)		
	Additional diploma	7 (3.0)		
	Pharmaceutical company	91 (39.2)		
	In-service training	143 (61.6)		
	Other	39 (16.8)		
Additional training received*	Pharmacovigilance	191 (29.1)		
	Adverse drug reactions	165 (25.2)		

	Toxicology	37 (5.6)		
	None	367 (55.9)		
Ability to report ADRs	Yes	383 (92.9)	<0.000	0.859
	No	29 (7.0)		

Data presented as number (%) *Multiple responses were allowed, ADR=Adverse drug reaction

The Binomial test and the effect size ($\delta_{½}$) were used to determine whether the differences between the proportion of pharmacists who responded positively and those who responded negatively are of statistical significance. The results in Table 3-4 indicate that the vast majority of respondents (N = 561, n = 537, 95.7%) have heard about ADR reporting and the result is of statistical significance (p<0.001, $\delta_{½}$=0.914). A total of 21.6% (n = 121) of pharmacists do not know where to find ADR reporting forms, and the Binomial test indicated the result to be of statistical significance (p<0.001, $\delta_{½}$=0.568). Almost forty percent (N = 656, n = 257, 39.2%) of respondents rely on their workplace to have the ADR reporting forms; 16.5% (n=108) have their own personal files and 46.0% (n = 302) believed that they could find the reporting forms on the South African Health Products Regulatory Authority's (SAHPRA) website. A high number of respondents (N = 561, n = 342, 61.0%) had noticed a suspected ADR in the previous 12 months and 33.5% (n = 188) of respondents noticed an ADR in the past three months.

The majority of respondents (N = 412, n = 344, 83.5%, p<0.001, $\delta_{½}$=0.669) believe that ADR reporting should be compulsory (Table 3-4) and 75.2% (n = 310, p<0.001) responded that they understand the reporting system. The Binomial test also indicated statistical significance (p<0.001) with a large effect size of 0.669 and 0.504 respectively, with the above mentioned. Most respondents (n = 261, 63.4%) have standard operating procedures available in their workplace for the reporting of ADRs. When asked whether the respondents (N = 412) would be willing to report ADRs, 97.0% (n = 400) of respondents said they would be willing to report ADRs 92.9% (n = 383). The Binomial test also indicated statistical significance (p<0.001) with a large effect size of 0.941 and 0.859 respectively.

Regarding the number of ADRs reported in their careers, 52.7% (N = 561, n = 296) of the respondents have not reported any suspected ADRs. Only 29.1% (n = 163) have reported between one and five ADRs in their careers. The respondents (N = 249) indicated that 42.6% (n = 106) were working in the public healthcare sector, 37.0% (n = 92) in the private healthcare sector and 20.5% (n = 51) in a pharmaceutical company at the time of reporting.

Table 3-4: Pharmacists' education and experience regarding ADR reporting (N=561)				
	Response	**Number n (%)**	***p*-value**	$\delta_{½}$
Have heard about ADR reporting †	Yes	537 (95.7)	<0.001	0.914
	No	24 (4.3)		
Noticed an ADR in their professional career*	During the past 3 months	188 (33.5)		
	During the past 3 to 6 months	198 (35.3)		
	During the past 6 to 12 months	232 (41.4)		
	More than 12 months ago	342 (61.0)		
Number of ADRs reported in a professional career †	None	296 (52.8)		
	1-5	163 (29.1)		
	6-10	25 (4.5)		
	More than 10	77 (13.7)		
Know where to obtain ADR reporting form †	Yes	440 (78.4)	<0.001	0.568
	No	121 (21.6)		
Where to obtain ADR form* (N=656)	Current work environment	257 (39.2)		
	Own personal files	108 (16.5)		
	Head office of the current work environment	90 (13.7)		
	SAHPRA website	302 (46.0)		
	Medicines Act (101 of 1965) hard copy	75 (11.4)		
	SMU website	21 (3.2)		
	Bloemfontein PV Centre	23 (3.5)		
	I do not know	50 (7.6)		
Willingness to report ADR ‡	Yes	400 (97.1)	<0.001	0.941
	No	12 (2.9)		

Belief of ADR reporting ‡	Voluntary	68 (16.5)	<0.001	0.669
	Compulsory	344 (83.5)		

*More than one answer was accepted.

†N=561 (missing frequency of n=5, 0.7%)

‡N=412 (missing frequency of n=244, 37.1%)

Data presented as number (%), SAHPRA=South-African Health Products Regulatory Authority, SMU=Sefako Makgatho Health Science University, PV=Pharmacovigilance, ADR=Adverse drug reaction.

Twenty-three percent (n = 137) of respondents (N = 589) knew they should report an ADR to the National Adverse Drug Event Monitoring Centre (NADEMC); 21.6% (n = 127) of respondents would report to the pharmaceutical company involved and 4.8% (n = 28) of respondents did not know where to report the suspected ADR. More than half (N = 656, n = 375, 57.2%) of the respondents think the patient should report an ADR directly to the physician who prescribed the medication and 43.8% (n = 287) think the patient should report the ADR to their pharmacist. The most frequently ADRs observed by respondents (N = 488) were allergic skin reactions (n = 372, 76.2%), followed by hospitalisation (n = 195, 40.0%), the death of a patient (n = 56, 11.5%) and a congenital abnormality (n = 18, 3.7%).

Table 3-5 illustrates pharmacists' perceptions to which ADRs and product stability problems they believe should be reported. Generally, pharmacists are aware of which ADRs and product stability problems to report, but there are still a few outliers.

As illustrated in table 3-5 the Binomial test and effect size ($\delta_{½}$) were used to determine whether the differences between the proportion of pharmacists who responded positively and those who responded negatively toward which ADR or product stability problem to report are of practical or statistical significance. Most respondents (N = 488, n = 480, 98.4%) believe that all serious reactions (p<0.001, $\delta_{½}$ =0.967) should be reported, but still 40.0% (n = 193) thought that known ADRs (p<0.001, $\delta_{½}$=0.209) does not have to be reported. Both these results are of statistical significance as p<0.05. Pharmacists (n = 429, 87.1%) also reported that they would report poor product packaging and labelling as an ADR, which was also seen as statistically significant with a large effect (p<0.001, $\delta_{½}$=0.733)

Pearson's chi-square (x^2) indicated a statistically significant association between respondents who received additional training and the reporting of well-known ADRs x^2(1, N = 488) = 22.6, p<0.001, (Cramér's V=0.216), ADRs caused by OTC medication x^2(1, N = 488) = 9.9, p=0.002, (Cramér's V=0.143) and ADRs caused by herbs and traditional medication x^2(1, N = 488) = 15.1, p<0.001, (Cramér's V=0.176). Pharmacists who received additional training in ADR reporting (n = 232, 35.5%) are more likely to report reactions toward well-known ADRs, OTC medication and traditional medicine that cause ADRs. There was no statistically significant association between the highest qualification and the years of experience as a pharmacist and which ADRs or product stability problems (p>0.05) to report. Pearson's chi-square indicated a statistically significant association between practice sector and the reporting of well-known ADRs x^2(1, N = 488) = 29.9, p<0.001 (Cramér's V=0.248) and ADRs caused by over-the-counter (OTC) medication x^2(1, N = 488) = 7.6, p=0.022 (Cramér's V = 0.125). Pharmacists working in the public healthcare sector (n = 107, 78.7%) are more likely to report well-known ADRs and pharmacists in the private healthcare sector (n = 255, 88.5%) are more likely to report ADRs caused by OTC medication. Table 3-5 illustrates pharmacists' perceptions to which ADRs and product stability problems they believe should be reported.

Table 3-5: Pharmacists' perceptions about which ADRs and product stability problems need to be reported in practice

(N=488)

	Yes* *n* (%)	No* *n* (%)	*p*-value	$\delta_{½}$
Adverse drug reaction				
All serious reactions	480 (98.4)	8 (1.6)	<0.001	0.967
Unexpected / unknown reactions	482 (98.8)	6 (1.2)	<0.001	0.975
Well-known adverse drug reactions	295 (60.0)	193 (40.0)	<0.001	0.209
Unexpected therapeutic effects	452 (93.0)	36 (7.0)	<0.001	0.852
Reactions caused by over-the-counter medicine (unscheduled)	446 (91.4)	42 (8.6)	<0.001	0.827
Reactions caused by over-the-counter medicine (schedules 1 & 2)	464 (95.1)	24 (4.9)	<0.001	0.901
Reactions caused by prescription medication (schedules 3 to 6)	477 (97.7)	11 (2.3)	<0.001	0.954
Adverse reactions to vaccines	475 (97.3)	13 (2.7)	<0.001	0.946
Reactions toward herbal and traditional medicine	415 (85.0)	73 (15.0)	<0.001	0.700
Adverse reactions not indicated in the package insert	481 (98.6)	7 (1.4)	<0.001	0.971
A reaction caused by an interaction between drugs	462 (94.7)	26 (5.3)	<0.001	0.893
A reaction caused by a food-drug interaction	452 (92.6)	36 (7.4)	<0.001	0.852
The adverse reaction caused due to medication error	390 (79.9)	98 (20.1)	<0.001	0.598
Product stability problems				
Product contamination because of uncleanness that occurred during production or packaging and storage of the product	462 (94.7)	26 (5.3)	<0.001	0.893
Defective components that are harmful to the patient and could result in a defect	476 (97.5)	12 (2.5)	<0.001	0.950
Possible product stability (chemical and physical appearance at the time of packaging and storage)	465 (95.3)	23 (4.7)	<0.001	0.905

Poor packaging and labelling of a product	423 (86.7)	65 (13.3)	<0.001	0.733

Data presented as number (%) *Multiple responses were allowed.

Only 10.8% (N = 434, n = 47) of respondents claimed to have received an ADR reporting form in their career from a patient and a third (n = 471, 89.0%) have received at least one reporting form from a physician. Some respondents (n = 8, 10.5%) have received five ADR reporting forms from a physician. Pharmacists (N = 656) responded that all healthcare professionals, including general practitioners (n = 469, 71.5%), pharmacists (n = 466, 71.0%), registered nurses (n = 445, 67.8%), dentists (n = 448, 68.3%) and physiotherapists (n = 323, 49.2%), should report ADRs.

When asked about the steps to follow after identification of a suspected ADR, pharmacists responded (N = 434) as follows:

- A total of 292 (67.3%) respondents (N = 434) agreed to contact the patient's physician to report the ADR; 295 (68.0%) agreed to send the patient back to the doctor and 352 (81.1%) of pharmacists agreed to complete the ADR reporting form and send it to SAHPRA.
- A few respondents (N = 434) (n = 34, 7.8%) believed that the patient should complete the form themselves and 392 (90.3%) of respondents would report the ADR and make a note thereof on the patient's file.
- Only six (1.4%) respondents believed that nothing needs to be done and 342 (78.8%) pharmacists would phone the physician to change the therapy.

There was one question assessing the knowledge of pharmacists regarding the information needed to complete the ADR reporting form. Respondents indicated that most of the information (product causing ADR, reaction observed, dosage taken, duration of treatment, time of onset, outcome of ADR, batch number, expiry date) regarding the medication causing the ADR is needed, although 42.7% (N = 656, n = 280) of respondents believe it is not necessary to include laboratory results of the ADR caused.

Discussion:

The study gives relevant information regarding the attitude and perception of pharmacists toward ADR reporting and training associated with reporting. However, the study revealed that even though most pharmacists have a positive attitude toward ADR reporting, reporting still remains low in South Africa (SA). The reason could be limited training and understanding among pharmacists due to a shortage of training in the field. In 1992, SA became the first country in Africa to become a member of the World Health Organization (WHO) International Drug Monitoring Program to coordinate international pharmacovigilance activities.[17] The foundation of pharmacovigilance is based on voluntary reporting of ADRs. [17] In SA, SAHPRA uses the National Adverse Drug Event Monitoring Centre (NADEMC) for the voluntary reporting of suspected ADRs.[8]

The study had mostly female respondents (70.7%), which are in line with the statistics of the South African Pharmacy Council (SAPC), where the female to male ratio is currently 1.72:1.[18] The attitude of pharmacists toward ADR reporting was promising. The study revealed that most of the respondents (N = 412, n = 400, 97.1%) believed that ADR reporting is necessary and that they are willing to report. The majority of respondents (83.5%) agreed that ADR reporting should be compulsory and this is also confirmed by the following previous studies. In Pakistan, 93% of pharmacists and physicians agreed that ADR reporting should be mandatory because of their well-established pharmacovigilance centre.[19] The reporting of ADRs was below expectation. Only 29.1% respondents have reported between one and five ADRs in their professional career and 52.8% have never reported an ADR. These results are in line with the study conducted in Pakistan where 88.3% of pharmacists never reported an ADR.[19] In a South African study in the private hospital sector, the results revealed that 18.9% of participants previously reported an ADR.[4] These results, however, are in contrast with a study in Sweden, which revealed that 60% of healthcare professionals report ADRs and the reason behind this might be an increase in training among respondents (pharmacists, nurses and doctors).[20] Li *et al* reported that only a third (31%) of community pharmacists received enough training to report ADRs.[21] Most of the pharmacists (98.8%) stated that unexpected ADRs should be reported, while 60% reported that well-known ADRs do not have to be reported. More than 90% of the pharmacists believe that ADRs toward over-the-counter (OTC) medication should be reported. These results are in contrast with a study from Saudi-Arabia, where only 30% of pharmacists are willing to report ADRs and also believe that it is not necessary to report ADRs regarding OTC medication.[14] It is a concern that pharmacists do not know which type of ADRs to report.

A large number (n = 421, 64.2%) of pharmacists stated that they had not received training regarding the reporting of ADRs. Similar results were found in a study conducted among healthcare professionals in Saudi-Arabia and South Africa, where 78.5% and 76.2% respectively had never received training on ADR reporting.[4,22] This indicates that a portion of healthcare professionals have had no proper training regarding ADR reporting. A study conducted in Nigeria revealed that 89.9% of respondents believe that

physicians are responsible to report ADRs, which is in line with the present study, where the majority of respondents (67.2%) also stated that they "would contact the patient's physician to report the ADR".[23]

Study results revealed that pharmacists have poor knowledge of ADR reporting practices in all pharmaceutical sectors in South Africa. Although a positive attitude toward ADR reporting is evident, the lack of knowledge on how to report, what to report and whom to report ADRs to, is still discouraging. Based on the findings of the study, the following recommendations are made:

- Increased training in ADR reporting is needed.
- ADR reporting forms should be freely available to all pharmacists in all sectors.
- ADR reporting should be made compulsory.

One limitation in this study that could be addressed in future studies is the length of the questionnaire and the time required to complete it. The questionnaire could have had fewer questions for the participants to be able to complete the questionnaire in 15 minutes. This might have resulted in a higher response rate.

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3.2 Manuscript 2

The article titled: “Pharmacists’ pharmacovigilance and adverse drug reaction reporting perception and barriers affecting the reporting rates: A South African online survey.” is presented in this chapter. The article was prepared for submission to the *International Journal of Pharmacy Practice*, as an original research article. This article was prepared according to the specific guidelines by the authors for this journal (See Annexure G).

Instructions to the author can be viewed at the following link:

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Manuscript 2 addresses the third and fouth objective of the empirical study:

> Objective 3: Determine from the perceptions of pharmacists’ possible factors that influence the successful implementation of pharmacovigilance in different pharmaceutical sectors in South Africa.
>
> Objective 4: Identify pharmacists’ additional training needs regarding ADR reporting and pharmacovigilance.

Title: Pharmacists' pharmacovigilance and adverse drug reaction reporting perception and barriers affecting the reporting rates: A South African online survey

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Author	Contribution to the study
Ms PH Jordaan	Planning and design of the study Conducting the literature review Interpreting of results Conclusion Write the manuscript
Prof MS Lubbe	Supervisor: Study concept and design Guidance for result interpretation Revision of the manuscript
Ms I Kotzé	Co-supervisor: Study concept and design Guidance for result interpretation Revision of the manuscript

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Abstract

Objectives

This study was carried out to:(1) determine factors that influence the successful implementation of pharmacovigilance in South African healthcare sectors focusing on the reporting of adverse drug reactions (ADRs) by pharmacists and (2) to identify the need of training in ADR reporting and pharmacovigilance in South Africa (SA).

Method

An online-based, cross-sectional survey was conducted from July to October 2018 among 11 732 pharmacists recruited from the South African Pharmacy Council Register of Pharmacists. A structured questionnaire was developed using previous quantitative studies and literature. The questionnaire consisted of three sections, containing 11 demographic questions, 5 questions to acquire information regarding facilitators and barriers toward ADR reporting, and 5 questions obtaining information regarding pharmacists' knowledge toward pharmacovigilance.

Key findings:

The response rate was 5.6% (656/11 732). Four hundred (N=412, 97.1%) pharmacists responded that they are willing to report ADRs and 383 (92.9%) believe they have the ability to report ADRs in their sector of current practice. Although pharmacists understood the importance of ADR reporting, uncertainty toward the reporting process remains. The term "pharmacovigilance" is familiar (N = 336, n = 211, 62.8%) to most respondents, but only 15 (N = 268, 5.6%) pharmacists could define pharmacovigilance correct. The three main factors discouraging pharmacists (N = 412) to report ADR are: (1) the reporting form being too time consuming (n = 235, 57.0%), (2) a lack of clinical knowledge to detect ADRs (n = 206, 50.0%), and (3) the lack of feedback (n = 218, 52.9%) from the National Pharmacovigilance Centre (NADEMC). Almost all the respondents (N = 336, n = 308, 91.7%) agreed to undergo additional ADR training to improve the reporting statistics in South Africa.

Conclusion

The main reason for underreporting is a lack of pharmacovigilance and adverse drug reaction reporting knowledge of pharmacists. Training needs to be provided on an on-going basis as well as follow-ups by authorities to improve pharmacovigilance activities in South Africa.

Key words: adverse drug reaction, adverse drug reaction reporting, pharmacist, pharmacovigilance, South Africa

Introduction

Globally, adverse drug reactions (ADRs) remain a major socioeconomic burden.[1-4] The World Health Organization (WHO) ranks ADRs as the sixth leading cause of death in the United States of America (USA),[5] with a reporting rate of only 1-6%.[6] In Australia, the prevalence of ADRs has been increasing, reaching 16.6% in both community and hospital environments.[7] A South African study reported that one in twelve hospital admissions are due to an ADR.[8] To reduce these outcomes of ADRs, which are mortality, morbidity and healthcare costs, the identification and reporting of ADRs to the regulatory authorities need to be done more efficiently. Pharmacovigilance programmes are initiated for the effective reporting of ADRs.[5,9,10] Pharmacovigilance is defined by the WHO as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".[5] All healthcare professionals (HCPs) from all healthcare sectors need to be actively involved in the detection and reporting of ADRs to ensure the safe use of medicines. Pharmacists play a vital role in the spontaneous reporting of ADRs, as they are able to identify signals of risk when issuing medication.

The FDA Adverse Event Reporting System (FAERS) received a total of 1 1163 920 ADR reports from HCPs in 2018, growing from 382 054 reports in 2011.[11] In 2015, South Africa had only 28 609 ADRs reported to VigiBase® since 1992 when the PV system began functioning.[12] This number is seen as very low, since 13.1% of the South African population (7.52 million in 2018) is HIV positive and also considering tuberculosis (TB) and other communicable and non-communicable diseases in the country.[13]

ADR reporting does rely on HCP's to report spontaneously.[4,14] Various barriers have been identified in studies,[3,4,14-16] which might explain the low reporting rates: (i) inadequate knowledge toward ADR reporting, (ii) awareness around which entity to report to, (iii) ignorance, (iv) attitude toward professional activities, and (v) time management. Pharmacists' need to be motivated and encouraged to participate in pharmacovigilance activities. Participation will assist in ensuring patient safety and medicine efficacy.

This study highlights the importance of an effective pharmacovigilance system in South Africa. HCP's knowledge and education need to be developed on an on-going basis by regulators and policy-makers. The study also adds data regarding ADR and pharmacovigilance knowledge of pharmacists in all pharmaceutical sectors in South Africa. This is the first study in South Africa focusing on all the pharmaceutical sectors with regard to the view of a pharmacist toward ADR reporting.

Methodology

Study design

A cross-sectional, online-based survey was conducted between July and October 2018 among registered pharmacists working in all pharmaceutical sectors in South Africa.

Ethical approval

Ethical approval for this study was granted by the Health Research Ethics Committee (HREC) of the North-West University in South Africa (NWU) (NWU-00137-17-S1).

Study setting and participants

Survey participants included all pharmacists on the Register of Pharmacists on 31 October 2018. The research was conducted in all the pharmaceutical sectors in South Africa using the list of email addresses of all pharmacists as included in the South African Pharmacy Council Register of Pharmacists. The following exclusion criteria were used to compile the study population:

- Pharmacists with an invalid, inactive or absent email address on the Register of Pharmacists of the SAPC.
- Pharmacists who act as supervisors or reviewers of the study.
- Pharmacists older than 65 years of age, or pharmacists who are not practising anymore.

The 2018 Register of Pharmacist of the South African Pharmacy Council consist of 14 511 pharmacists. After applying the exclusion criteria, the structured questionnaire was sent to a study population of 11 732 pharmacists.

Questionnaire development

Previous quantitative studies and literature [14,17-20] were used to develop the questionnaire. Questions were included to evaluate the participants' perceptions and knowledge toward pharmacovigilance and ADR reporting. Questions were also developed to determine the barriers and facilitators respondents experience toward ADR reporting. The structured online questionnaire went through face- and content validity by subject experts. The online survey contained an introduction stating the purpose and objectives of the study. The questionnaire consisted of three sections. Section one included 11 demographic questions, such as age, gender, qualifications obtained and area of practice. The second section had 5 questions, to acquire information regarding facilitators and barriers toward ADR reporting. The last section had 5 questions obtaining information regarding pharmacists' knowledge toward pharmacovigilance. The online survey also contained an informed consent page that explained that each participant has a free choice to participate in the study and that they can withdraw from the study at any time.

Data collection

A structured questionnaire was developed and sent out by an independent survey mediator who signed a confidentiality agreement to ensure confidentiality and anonymity of participants' information. The online survey was sent out via email using Survey Monkey® software. One month after the initial email was sent out; a reminder was sent to potential participants. A third and final reminder were sent out again another month later.

Data analysis

Data collected in the study were exported from Microsoft Excel® spreadsheet to IBM SPSS® software for data analysis. Descriptive statistics such as frequency, mean and standard deviation (SD) were used to analyse demographic variables. Inferential statistics included the chi-square test (x^2) to determine the relationship between two variables. Likert scale questions containing 5-point data were rescaled into three categories (strongly disagree/disagree, uncertain and strongly agree/agree). Cramér's V was used to determine statistically significant associations (V=0.1: small effect, V =0.3: medium effect & V =0.5: large effect) [21] where a p-value of <0.05 was considered statistically significant.

Results

Response rate

A total population size of 11 732 pharmacists was emailed to participate in the study. Using a 5% margin of error at a 95% confidence level, a sample size of 373 pharmacists was needed. A total of 656 pharmacists responded to the questionnaire, giving a response rate of 5.6%.

Participant demographics

The sample population (N = 656) consisted of 70.7% (n = 464) females and 29.3% (n = 192) males. The mean age of the respondents was 41.55 years (SD±10.89). The majority of the respondents were in the age group 37 to 43 years (n = 143, 21.8%).The qualification obtained by most pharmacists were a Baccalaureus Pharmaciae (BPharm) degree (n = 477, 72.71%). Additional training in ADR reporting was received by 35.5% (n = 232) pharmacists, mostly by the means of in-service training (N = 232, n = 143, 61.6%).Most pharmacists (N = 603) had more than 20 years of experience (n = 198, 32.8%) as a practising pharmacist. Pharmacists current practice environment/sector is presented in Table 1.

Table 1: Pharmacists current healthcare sector of practice (N = 656)

Healthcare sector	Number of pharmacists n (%)	
Community; corporate and mail order pharmacy	256	39.0
Private hospital pharmacy	76	11.6
Public hospital pharmacy	112	17.1
Medical aid environment	12	1.8
Clinical research	24	3.7
Academia	35	5.3
Wholesale and distribution pharmacy	23	3.5

Production environment	32	4.9
Medicine registration and quality control	76	11.6
Military and correctional services pharmacy	10	1.5

Barriers toward ADR reporting

A total of 400 (N = 412, 97.1%) respondents are willing to report ADRs in their pharmaceutical sector. Responses received from pharmacists (N = 412) who were not willing to report ADRs (n = 12, 2.91%) followed a trend: (i) it's not the pharmacist's responsibility (n = 3, 25.0%), (ii) no time available to report (n = 6, 50.0%) and (iii) a lack of clinical knowledge to report ADRs (n = 3, 25.0%).

The majority of pharmacists (n = 383, 92.9%) believe they have the ability to report ADRs. Responses received from pharmacists who believe they are not able to report ADRs (n = 29, 7.1%) followed the following trend: (i) a lack of adequate training received (n = 16, 55.2%) (ii) no practical experience gained (n = 8, 27.6%) and (iii) interaction with physicians are required (n = 5, 17.2%).

Pharmacists reported that they are aware of the importance of ADR reporting in healthcare facilities (n = 249, 60.6%), although they are uncertain (n = 113, 27.4%) about the process to follow when reporting an ADR. Pharmacists mostly reported (n = 232, 73.4%) that they do not receive feedback from the National Pharmacovigilance Centre after reporting an ADR (See Table 2). There was a statistically significant association between pharmacists responding that they received enough training on ADR reporting x^2 (1, N= 360) = 84.8, $p < 0.001$, (Cramér's $V = 0.243$) and having the necessary standard operating procedures in their work environment x^2 (1, N =535) = 50.7, $p < 0.001$, (Cramér's $V = 0.308$) and their current healthcare sector of practice. Pharmacists practicing in the medicine and quality control sector (N = 54, n = 39, 72.2%) are more likely to "agree" that they received enough training in the reporting of ADRs. Pharmacists practicing in the community, corporate and mail-order pharmacies (N = 135, n = 131, 97.0%) are more likely to "agree" to having the necessary SOP's in their work environment. Refer to Table 2 for detailed results on pharmacists' perceptions toward ADR reporting.

Table 2: Pharmacists perception toward ADR reporting

Statements	Responses*			*p*-value	Cramér's *V*	*p*-value	Cramér's *V*	*p*-value	Cramér's *V*
	SD/D n (%)	**U n (%)**	**SA/A n (%)**	**Additional training received**		**Years of experience**		**Area of practice**	
Pharmacists are aware of the importance of ADR reporting in healthcare facilities.	92 (22.4)	70 (17.03)	249 (60.6)	0.016[a]	0.172	0.936	0.071	0.461	0.157
Pharmacists are aware of the process to follow for the reporting of ADRs in healthcare facilities.	153 (37.1)	113 (27.43)	146 (35.4)	0.997	0.020	0.987	0.061	0.255	0.168
You have been provided with ADR reporting forms.	144 (36.7)	24 (6.11)	225 (57.3)	0.002[a]	0.209	0.727	0.088	0.001[b]	0.224
You have received enough training to be able to identify an ADR.	99 (24.6)	57 (14.18)	246 (61.2)	0.000[a]	0.305	0.348	0.105	0.181	0.174
You have received enough training on how to report ADRs.	170 (42.2)	41 (10.17)	192 (47.7)	0.000[a]	0.626	0.594	0.093	0.000[b]	0.243
The pharmacy you currently practice in have the necessary standard operating procedures to report an ADR.	66 (19.0)	51 (14.70)	230 (66.3)	0.180	0.052	0.914	0.040	0.000[b]	0.308
You have previously received feedback from the National Pharmacovigilance Centre regarding a reported ADR.	232 (73.4)	31 (9.81)	53 (16.8)	0.798	0.010	0.119	0.110	0.022[b]	0.190

*SD = Strongly disagree, D = Disagree, U = Uncertain, A = Agree, SA = Strongly agree. Data presented as number (%).

[a] There is a statistically significant association between the statement and whether the respondent received additional training in ADR reporting.

[b] There is a statistically significant association between the statement and the respondent's area of current practice.

Respondents (N = 412) **strongly agreed** to all the encouraging factors leading to ADR reporting questioned:

- Half of the pharmacists (n = 207, 50.2%) are encouraged by the statement that ADR reporting should be compulsory.
- Pharmacists responded positively to being encouraged to report ADRs, provided they receive training (n = 211, 51.2%) from the National Pharmacovigilance centre and receive feedback (n = 229, 55.6%) from NADEMC.
- Pharmacists responded that a less complicated ADR reporting form (n = 183, 44.4%) or an electronic reporting system (n = 258, 62.6%), would encourage them to report ADRs more efficiently.
- Pharmacists (n = 203, 49.3%) would be more encouraged and believe the ADR reporting would benefit from a pharmacovigilance specialist working in their pharmacy environment.

There was no statistically significant association between encouraging factors toward ADR reporting and the respondents' pharmaceutical sector of current practice ($p > 0.05$). A statistically significant association exist between additional training received in ADR reporting $x^2(1, N = 412) = 10.7$, $p = 0.03$ (Cramér's $V = 0.161$) and pharmacists being encouraged to report ADRs, provided they received feedback. Pharmacists (n = 238, 57.8%) who did not receive additional training in ADR reporting would feel more encouraged to report ADRs if they received feedback from NADEMC.

The main factors discouraging respondents (N = 412) to report ADRs are the lack of clinical knowledge to detect an ADR (n = 206, 50.0%) and ADR reporting being too time-consuming (n = 235, 57.0%). Table 3 presents detailed results, as well as statistically significant associations, determined through the Pearson's chi-square test (x^2), between additional ADR training received, pharmaceutical sector of current practice as well as years of experience as a practicing pharmacist. Other barriers mentioned by pharmacists (n = 53, 12.9%) included: a lack of support from regulatory authorities and work environments.

Table 3: Barriers experienced toward ADR reporting

Statements	Responses*			*p*-value	Cramér's *V*	*p*-value	Cramér's *V*	*p*-value	Cramér's *V*
	D	**N/A**	**A**	**Additional training received (N = 412)**		**Years of experience (N = 412)**		**Area of practice (N = 366)**	
	n (%)	**n (%)**	**n (%)**						
Lack of clinical knowledge on how to detect an ADR	158 (38.4)	48 (11.7)	206 (50.0)	0.017	0.141	0.338	0.105	0.117	0.186
Lack of confidence to know when to report an ADR	166 (40.3)	38 (9.2)	208 (50.5)	0.001	0.184	0.060	0.135	0.056	0.197
I do not know where to obtain an ADR form to enable me to report the ADR	234 (56.8)	45 (10.9)	133 (32.3)	0.011	0.148	0.407	0.100	0.376	0.162
After reporting an ADR, I do not receive feedback from NADEMC.	58 (14.1)	136 (33.0)	218 (52.9)	0.005	0.161	0.701	0.082	0.161	0.180
Reporting ADRs are time-consuming	134 (32.5)	43 (10.4)	235 (57.0)	0.004	0.165	0.123	0.124	0.040	0.202
ADR forms are complicated, which increases my workload	144 (34.9)	63 (15.3)	205 (49.8)	0.000	0.242	0.233	0.113	0.020	0.210
ADR reporting is not part of my healthcare practice	320 (77.7)	47 (11.4)	45 (10.9)	0.021	0.137	0.004	0.165	0.189	0.177
I believe that drugs on the market are safe	281 (68.2)	32 (7.8)	99 (24.0)	0.029	0.131	0.618	0.087	0.039	0.202
I fear legal liability following the reported ADR	295 (71.6)	43 (10.4)	74 (17.9)	0.129	0.100	0.055	0.136	0.040	0.201
I fear that the ADR is caused by a medication error made by me	311 (75.5)	34 (8.3)	67 (16.3)	0.703	0.041	0.975	0.051	0.020	0.210
There are no ADR reporting forms available in my work environment	258 (62.6)	85 (20.6)	69 (16.8)	0.001	0.183	0.096	0.128	0.000	0.248
I feel that ADR reporting is not compulsory	292 (70.9)	31 (7.5)	89 (21.6)	0.678	0.043	0.524	0.093	0.076	0.193
There is no incentive involved for the reporting of ADRs	205 (49.8)	93 (22.6)	114 (27.7)	0.102	0.105	0.108	0.126	0.010	0.218
I experience other challenges	187 (45.4)	172 (41.8)	53 (12.9)	0.133	0.099	0.053	0.136	0.149	0.182

N/A: Not applicable, A: Agree, D: Disagree

Pharmacists who **did not** receive additional training in ADR reporting experience a lack of confidence in knowing when to report x^2 (1, N = 412) = 13.9, p = 0.001 (Cramér's V = 0.184) an ADR as well as a lack of clinical knowledge on how to detect x^2 (1, N = 412) = 8.1, p = 0.017 (Cramér's V = 0.141) an ADR. Pharmacists with more than 20 years of experience x^2 (1, N = 412) = 22.3, p = 0.004 (Cramér's V = 0.165) do not agree with the barriers that ADR reporting is not apart of their healthcare practice. Pharmacists practicing in the community, corporate, mail-order and public hospital environment do not agree that the fear of a medication error caused by them x^2 (1, N = 366) = 32.3, p = 0.020 (Cramér's V = 0.210), should be perceived as a barrier toward ADR reporting.

Knowledge toward pharmacovigilance

Most respondents (n = 211, 62.8%) are familiar with the term pharmacovigilance, although only 32 (N= 268, 11.9%) pharmacists could define pharmacovigilance correct. A statistically significant association exist between knowledge toward the term pharmacovigilance and the respondent's current area of practice x^2 (1, N = 299) = 95.3, $p < 0.001$ (Cramér's V = 0.282) and whether the respondent received additional ADR training x^2 (1, N = 336) = 56.3, $p < 0.001$ (Cramér's V = 0.409). Pharmacists practicing in the medicine registration and quality control environment have more knowledge of the term pharmacovigilance. Pharmacists who received additional training in ADR reporting are more likely to have knowledge of the term pharmacovigilance. Figure 1 presents pharmacists' responses (N = 337) to whom they think serves as South Africa's pharmacovigilance unit.

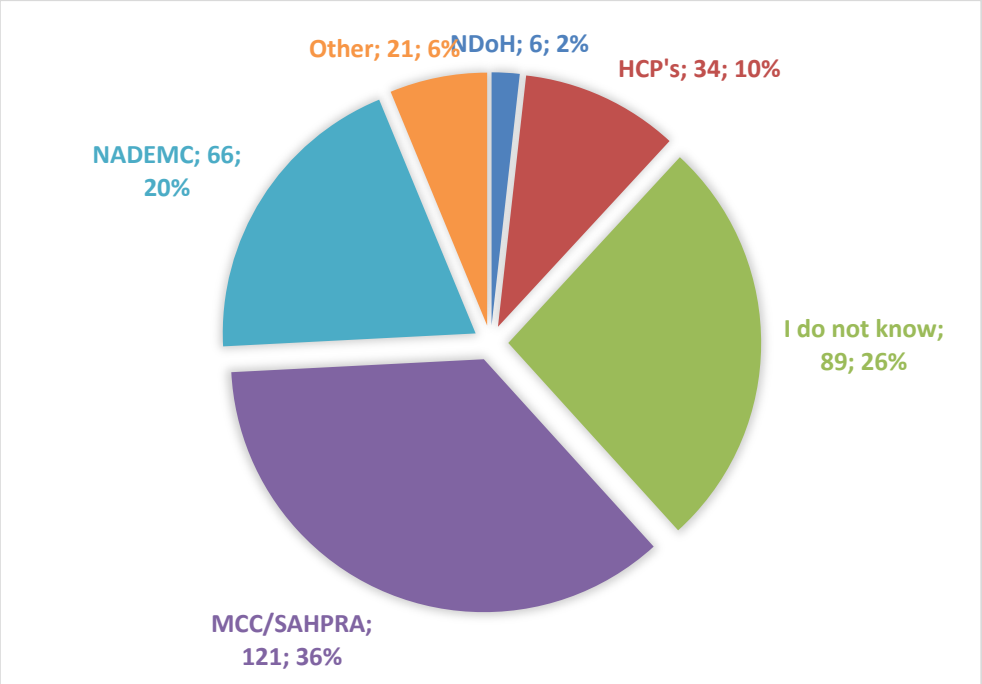

Figure 12: Reporting entity response by pharmacists

NDoH = National Department of Health, HCP's = Healthcare professionals, MCC = Medicines Control Council, SAHPRA = South African Health Products Regulatory Authority, NADEMC = National Adverse Drug Event Monitoring Committee

Regarding the perception of pharmacists, a statistically significant association exist between pharmacists who received additional ADR reporting training and the agreement (n = 186, 55.36%) that ADR monitoring ensures safe and effective medicines x^2 (1, N = 336) = 8.6, p = 0.070 (Cramér's V = 0.160). A statistically significant association exist between pharmacists who received additional ADR reporting training and that ADR reporting, national regulatory decisions, encourage x^2 (1, N = 336) = 13.8, p = 0.008 (Cramér's V = 0.203). Pharmacists with 16 to 20 years of experience agree that more education is needed in ADR reporting while studying towards the undergraduate pharmacy degree x^2 (1, N = 336) = 37.3, p = 0.002 (Cramér's V = 0.167), which is of statistical significance. When asked whether the current ADR reporting system in South Africa is sufficient, 106 (N = 336, 31.55%) respondents disagreed.

Discussion

Overall, pharmacists have a positive attitude towards ADR reporting but do experience the lack of training as a main barrier, discouraging them to report. Pharmacists regard the reporting of ADRs as very important and believe that it would make a difference in the current pharmacovigilance system of South Africa, as well as be of educational value. The result of our findings showed that pharmacists are willing (97.1%) and able (92.9%) to report ADRs, but still ADR reporting in South Africa remains low. Barriers mostly experienced by pharmacists were the lack of enough training received (42.2%), the lack of time with patients (57.0%) and no feedback being received from NADEMC (52.9%).

We consider this to be the first national survey that investigated pharmacists' perception and knowledge toward pharmacovigilance and ADR reporting in all the pharmaceutical sectors in South Africa. The initial idea of the study was to recruit enough participants to be representative of the pharmacist's population in South Africa to ensure statistical generalisation of the findings. It was not possible to obtain the email addresses of all the registered pharmacists as some might have been invalid, absent or inactive. The length of the survey could have been a discouraging factor in completing the questionnaire. A shorter questionnaire could have resulted in a higher response rate. Despite these limitations, this study provides various insights for future research to include a larger population of pharmacists specifically in need of training in ADR reporting. Also, future research should include other HCP's who also plays a vital role in the reporting of ADRs.

Pharmacists (60.6%) see ADR reporting as essential, which is consistent with different studies; 77.4% of HCP's in West Ethiopia,[19] 88.0% of pharmacists in the private hospital sector in South Africa,[22] and 97.0% in a study conducted in Australia.[9] Factors encouraging pharmacists to report ADRs include: training received from the National Pharmacovigilance Unit (51.2%), feedback from NADEMC (55.6%), and electronic ADR reporting forms (62.6%). These encouraging factors are also mentioned as barriers discouraging pharmacists to report ADRs. In Australia, it was reported that only 31.0% of pharmacists received enough training in ADR reporting,[9] which is in line with this study, as only 35.6% of pharmacists received additional training in ADR reporting. This indicated that most pharmacists have not had proper training in ADR reporting. A recent study by Joubert and Naidoo among

community and hospital pharmacists in South Africa revealed that 55.9% of pharmacists feel NADEMC is remote and the feedback received not to be sufficient (23.5%).[15] Reporting forms being too time-consuming is a barrier experienced in various studies,[9,15,19,22] as well as in this study. In Australia,[9] 43.5% experience time as a barrier, in Turkey, 9.7%[4] and 34% of pharmacists in Saudi Arabia.[14]

Although pharmacists' are familiar (62.8%) with the term "pharmacovigilance", only 11.9% could define the term correctly. A previous study in South Africa among community and hospital pharmacists' supports this finding, as 62.7% were familiar with the term, only 45.1% could define the term.[15] Various sections in the study confirm that pharmacists have poor knowledge of the ADR reporting process and pharmacovigilance activities in the country. On-going training needs to be offered by authorities to pharmacists to encourage the reporting of ADRs.

Conclusion

Overall, pharmacists showed a positive attitude toward ADR reporting in South Africa. However, pharmacists are experiencing various barriers, discouraging them to report ADRs. The same factors which encourage pharmacists to report ADRs are also, if not adequate, discouraging factors toward ADR reporting. These barriers, especially on-going training, need to be addressed by authorities, to ensure higher reporting rates. This study has provided many avenues for future research by including other HCP's in a study on their perception toward the reporting of ADRs. Adequate training as a barrier to ADR reporting, could change the curriculum of undergraduate studies and also open avenues to new courses and training methods.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflict of interest to disclose.

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3.3 Chapter summary

The objectives of the empirical study were reached and reported in the two manuscript which are discussed in this chapter. Pharmacists in South Africa believe they have the ability to report ADRs in their pharmaceutical sector, but still lack the necessary education to be able to report to their full abilities. Training is needed in pharmacovigilance and ADR reporting to improve the pharmacovigilance system in South Africa.

CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

The conclusions of the literature study and empirical investigation will be discussed in this chapter. Limitations of the study are discussed and recommendations for future studies are made.

4.1 Conclusions: Literature review

4.1.1 Objective 1: Describe the relationship between inappropriate drug use, medication errors, ADEs and ADRs by means of an extensive literature review.

Table 4-1 describes ADR, ADE, medication error and inappropriate drug use, as well as some characteristics of the terms.

The definitions and characteristics of these terms indicate the relationship between these terms. Medication errors made by either physicians who make prescribing errors, or by pharmacists who make dispensing errors, can lead to an ADR of an ADE (Doman, 2009). The inappropriate use of medicine by patients, either through poly-pharmacy or overdose could also lead to patients experiencing ADRs or ADEs (WHO, 2002). Interaction with the prescriber by pharmacists could prevent medication errors and inappropriate drug usage, preventing ADRs and ADEs. ADRs caused due to inappropriate medication prescribed and used could be prevented through early detection of prescribing errors. Pharmacovigilance plays a vital role in the detection of ADRs caused by inappropriate drug usage. This study indicate that pharmacists experience the lack of knowledge to identify an ADRs as a barrier toward reporting ADRs (See Manuscript 2:Table 2).

Medication errors, because of wrong calculations made, were the cause of 2.7% ADRs in a pediatric unit in South Africa (Gokhul *et al.,* 2016).

Clinical criteria could be used by healthcare professionals to prevent various ADRs (Fick *et al.,* 2003; Gallagher, 2011; Hakkarainen *et al.,* 2012; Naranjo, 1981; NCCMERP, 2001; Rognstad *et al*., 2009).

Table 4-1: Characteristics of ADRs, ADEs, medication errors and inappropriate drug use

Term	Definition	Example	Characteristics and assessment tool
Adverse drug reaction (ADR)	"An adverse drug reaction to a drug is one that is noxious, unintended and occurs at doses normally used in man" (WHO, 2002).	Allergic reactions toward medication.	There is a probability scale and a causality assessment tool to ensure simplicity and to save time when identifying ADRs (Gallagher, 2011; Naranjo, 1981).

Adverse drug event (ADE)	Any injury or illness that may occur during treatment with medicine , but has no relationship with the treatment regime (SAHPRA, 2019).	The patient having a road traffic incident while on a specific medication.	These reactions could be prevented as they are not necessarily caused by medication errors. The preventability of medication errors could be determined by the Schumock criteria (Hakkarainen *et al.,* 2012).
Medication error	An event that occurred, which was preventable, but could lead to patient harm or inappropriate medicine usage, while in the control of the physician or pharmacist (NCCMERP, 2001).	When medicine is dispensed to the wrong patient.	Medication errors do not necessarily cause harm to a patient. The severity of medication errors could be determined (NCCMERP, 2001).
Inappropriate drug use	Patients who receive medicine that is inappropriate for their clinical needs, in doses they do not require, for inappropriate timeframes (WHO, 1985).	When a patient takes a higher dose of a medicine than what is required.	The inappropriate use and prescribing of medication can be determined by using the NORGEP criteria as well as the Beers criteria. These lists indicated the safe use and prescribing of certain medications (Rognstad *et al*., 2009:153; Fick *et al.,* 2003).

4.1.2 Objective 2: Identify the current prevalence of ADRs and drug-related problems globally and in South Africa.

Prevalence can be described as, a specific disease or characteristics which occurs in a number of people in a population (NIMH, 2017). There are various factors which influence the prevalence of ADRs (Angji, 2017; Holm *et al.,* 2017; Lucca *et al.,* 2017):

- more drugs being released to the market,
- an increase in aging of the population,
- patients' gender, genetics, ethnicity or whether the patient is pregnant, and
- poly-pharmacy.

Various studies have been conducted indicating the prevalance of ADRs in different countries (See Table 4-2). Table 4-2 represents the results reported in these studies. Although this study did not focus on the patient, but on the healthcare professionals, the prevalence of ADRs in South Africa could not be identified. Still the study revealed that pharmacists are aware of the importance of ADR reporting when present in their sector of current practice.

It has been reported by The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) that an increase in ADR reports by pharmacists and physicians in the United States is noticed since 2011 (FAERS, 2019). In Australia, the Therapeutic Goods Administration (TGA) at the Department of Health and Ageing reported that an increase in ADR reports can be seen from 2010 to 2015, where 14 200 reports were received, increasing to 312 000 reports in 2015 (TGA, 2018:4). The largest increase in ADR reports over the years was from the State and Territory Health Departments (from 2 516 in 2015 to 2 824 in 2016) and consumers (from 654 in 2015 to 969 in 2016), due to the addition of the National Immunisation Programme in 2016 (TGA, 2018:5).

In 2004, an increased prevalence of HIV/AIDS occurred, leading to the initiation of the KwaZulu-Natal's (KZN) pharmacovigilance committee's ARV programme (Fyzoo, 2014:2). This programme instituted a spontaneous reporting system for ARVs, making it mandatory for clinicians to submit an ADR report when toxicity prompted changes in ARV treatment regimens (Fyzoo, 2014:2). In 2007, 3 923 reports were collected, increasing to 34 209 reports in 2012 (Fyzoo, 2014:3). In the Pharmacovigilance bulletin published by the Department of Health in 2016 in South Africa, statistics revealed a total of 251 ADR reports from 1 October 2016 to 31 December 2016 (NDoH, 2017).

Table 4-2: Studies indicating the prevalence of ADRs

Country	Prevalence of ADRs	Reference
United States of America (USA) Chicago	3% - 7% ADRs causes hospitalisation, ADRs occur during 10% - 20% of hospitalisations. These ADRs were considered severe.	Smith-Marsch (2016)
USA	In an 8 year period, an annual death rate of 0.0058 was determined as 2341 deaths were reported because of ADRs. Half of these ADRs were considered preventable.	Shepard *et al*. (2012:169).
Asia Singapore	Prevalenece of ADRs at admission was 12.4% and 8.1% ADRs caused admission to tertiary hospital care. Thirty percent of these ADRs could have been predicted prior to admission	Chan, *et al.* (2016:1636).
China	An ADR rate of 0.81% is experienced in China, with antibiotics (34.9%) being the most implicated drug.	Qing-ping *et al*, (2014:73).
Europe	ADRs were the cause of 5% of all hospital admissions in 2008 and 5% of patients experienced an ADR while hospitalised. In 2014 6.5% - 8.8% of	European Commision (2008); Ahem *et al.* (2014:24).

	ADRs caused emergency hospital visits in the United Kingdom.	
Australia	During 2008 – 2013 medication errors caused 9% of admissions in hospitals and at discharge, two medication errors were predicted to occur per patient.	Roughead *et al.* (2016a:113).
Africa Nigeria	Data revealed that 12% of children were admitted to hospital as the cause of an ADR and 23% of these patients developed an ADR while being admitted to the hospital.	Oshikoya *et al.* (2011:153).
Africa (9 countries)	In 2018 it was reported that on average 8.4% of patients experience an ADR at hospital admission and 2.8% of ADRs cause admission to a hospital.	Mekonnen *et al*. (2018:22).
South Africa	In 2014, 2.9% of hospital admissions were due to an ADR and 16% of patients died. Fourty-three percent of these deaths were considered preventable.	Mouton *et al*. (2014:818).
	A study on HIV patients from 2009 – 2011 indicated that 37% of patients on ARV medication experience at least one ADR.	Masenyetse *et al.* (2015:6).

4.1.3 Objective 3: Compare and criticize the current national good pharmacovigilance practices with international guidelines.

Pharmacovigilance are defined by the WHO as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems*" (WHO, 2012a:1), The WHO specified the aims of pharmacovigilance, and initiated specific requirements for a practical and effective pharmacovigilance system (WHO, 2002): To develop patient care and safety in relation to the use of medicines and all medical and paramedical interventions.

i. *"To improve public health and safety in terms of the use of medicines".*

ii. *"To contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use".*

iii. *"To promote understanding, education and clinical training in pharmacovigilance and improve effective communication to the public (WHO, 2002:8)".*

Table 4-3 shows the current national good pharmacovigilance practices in South Africa compared to international guidelines as set out by the WHO, to achieve a successful pharmacovigilance centre (WHO, 2014:5). South Africa has been involved in pharmacovigilance activities for over 40 years, as they became a member of the WHO International Drug Monitoring Programme in 1992 (Metha *et al*., 2017:125; WHO, 2002). Pharmacovigilance in South Africa developed from passive regulatory reporting to an active surveillance system. South Africa has a strong legal and regulatory framework and well-established systems and structures for pharmacovigilance.

Table 4-3: Current national pharmacovigilance practices, compared to WHO guidelines

WHO guidelines	**South African pharmacovigilance practices**
Establishment of national pharmacovigilance systems for the reporting of adverse events, including national and, if appropriate, regional pharmacovigilance centres.	The MCC established a National Adverse Drug Event Monitoring Centre (NADEMC) in 1978, together with the University of Cape Town to ensure the safety of medicines by managing, collecting and reviewing the voluntary reporting of suspected adverse events submitted by industry and health professionals in order to be able to detect ADRs (Metha *et al*., 2017).
Development of legislation/regulation for medicine monitoring.	The Medicines Control Council (MCC) (now SAPHRA since 2019), under the Medicines and Related Substances Control Act (101 of 1965), are responsible for the regulation of medicines, which includes pharmacovigilance, and ethical standards toward the advertising of medicines (Metha *et al.,* 2017:125). Standard Operating Procedures (SOPs) are in place for the reporting of ADRs and submitting patient safety reports (SAHPRA, 2019:10).
National policy development (to include costing, budgeting and financing).	No policy published, but guideline was established in 2010.
Continuing education of healthcare providers on safe and effective pharmacotherapy.	Continuous training can be undertaken by healthcare academies, universities and certain pharmaceutical companies. In-service training. Undergraduate and postgraduate education and training is discussed in 4.2.5.
Monitoring the impact of pharmacovigilance through process indicators and outcomes.	Pharmacovigilance in South Africa is categorised into regulatory pharmacovigilance and programmatic pharmacovigilance. These two categories cover the quality and efficacy of all medicines, and medicines used in public health programmes. Regulatory pharmacovigilance is divided into passive and active surveillance (Metha *et al*., 2017:130). Passive surveillance **i**ncludes

	the spontaneous reporting of ADRs to the NADEMC by health professionals and is useful to identify new signals or ADR trends. Active surveillance requires pharmaceutical manufacturers to submit risk management plans, by means of conducting post-marketing studies as part of their registration for license applications.
Provision of up-to-date information on adverse reactions to professionals and consumers.	Published studies by academia and journals.

The pharmaceutical industry's efforts to recognise safety signals and assess risks are still not enough in South Africa (SPS, 2011:106). Roux (2014:40) reported that inadequate education and knowledge to identify risks of medication, due to the lack of awareness created by pharmaceutical companies, could be a major setback in terms of reporting ADRs.

After consideration of the national pharmacovigilance system in South Africa compared to the WHO guidelines, the following recommendations can be made to improve the current system:

- to improve and publish the policy,
- SOPs needs to be improved and explained to healthcare professionals,
- internal processes need to be improved to meet the local requirements and regulations,
- a formal information sharing and tracking process among HCPs should be established,
- developing the scope of pharmacovigilance, including all other ADEs, and
- to develop a strategy to ensure compliance from HCPs toward pharmacovigilance requirements internally (i.e., self-audit) (SPS, 2011:108).

4.1.4 Objective 4: Identify possible barriers/facilitators that influenced the successful implementation of pharmacovigilance in different health sectors in South Africa.

Metha *et al*. (2013:104) stated that the voluntary reporting of ADRs is the foundation of pharmacovigilance. Various barriers have been reported by pharmacists toward the reporting of ADRs. These barriers include a lack of knowledge on how and when to report an ADR, a lack of feedback from the pharmacovigilance centres, insufficient time to report ADRs and the reporting forms and process being time-consuming (Elkalmi *et al*., 2011b:71; Joubert & Naidoo, 2016:240; Khan, 2013b; Nagaraju *et al*., 2015; Shamim *et al*., 2016). The following factors can be seen as barriers and facilitators toward ADR reporting.

4.1.4.1 Lack of feedback

The major barrier to reporting ADRs is a lack of knowledge about the reporting process (Elkalmi *et al*., 2011b:71). Pharmacists see feedback as a sign that the reporting process is not a waste of their time (Williams, 2015:42). The study in South Africa by Joubert and Naidoo (2016:240) indicated that pharmacists (61.8%) feel the MCC is remote and 55.9% felt that NADEMC is remote. A study done by Bogolubova *et al*. (2018:2) in the South African private hospital sector indicated that 13.7% of healthcare professionals do not receive any feedback once the reporting form has been sent. In this study, 52.9% (n = 218) pharmacists agreed that after reporting an ADR, no feedback is received. Once feedback is received when an ADR is reported, pharmacists will feel more motivated and confident to report ADRs.

4.1.4.2 The reporting process

Barriers in this category are with regards to the reporting system and the forms being too complicated as well as understanding the reporting process. Pharmacists are not fully aware of which entity to report the ADR to or of the pharmacovigilance unit in their country. Only 10.7% could identify the pharmacovigilance unit, NADEMC (Joubert & Naidoo, 2016:240), which is in line with this study, where only 20% (n = 66) identified NADEMC as the reporting entity. In the same study by Joubert and Naidoo (2016:241), pharmacists (27.4%) reported that the form was not user-friendly and 20.5% felt that the form was too complicated to complete. In Saudi-Arabia, a study revealed that 64% of pharmacists in hospitals were not aware of the national pharmacovigilance system (Mohamed & Basel, 2015:157). Pharmacists mentioned in this study that an online reporting system would benefit the reporting rates and encourage them to report ADRs (See Manuscript 2:Table 1).

4.1.4.3 Lack of time

Pharmacists mentioned the they experience a lack of time with each patient due to the majority of workload and administrative duties (Khan, 2013b:45). The study by Joubert and Naidoo (2016:242) reported that 50% of pharmacists felt the reporting process is too time-consuming, which is in line with this study, as 57.0% (n = 235) of pharmacists reported ADR reported as time-consuming. A cause of underreporting identified by Varallo *et al.* (2014:744) included the lack of interest in completing the ADR form and shortage of time. In this study pharmacists mentioned that an electronic reporting system would be beneficial for the reporting rates as this method of reporting is immediate and less time-consuming, which will motivate pharmacists to report ADRs (See Manuscript 2:Table 1). It is of importance to create awareness among pharmacists to report ADRs, by pharmacovigilance centres. The reporting of ADRs could become a routine responsibility among pharmacists.

4.1.5 Objective 5: Evaluate the current South African ADR report form in terms of international standards and its implementation in both the private and public healthcare sector.

An ADR reporting form is a record of relevant data explaining the use of a medicine by a patient which might have caused the adverse reaction (SAHPRA, 2018:6). Most ADR forms used contain four sections (information about patient experiencing the ADR, description of ADR experienced, medicine involved in ADR and information of the reporter) to be completed (WHO, 2002:14; MCC, 2012:17). The following information per section is prescribed by the WHO (WHO, 2002:14):

Table 4-4: Minimum required information on ADR reporting form

Section	Information
Patient information	Patient identifier. Age at stage of event or date of birth. Gender. Weight.
Adverse event or product problem	Explanation of event or problem. Date of event. Date of this report. Applicable tests/laboratory data (if available). Other related patient information/history. Consequences attributed to adverse event.
Suspected medication (s)	Name (INN and brand name). Dose, occurrence & route used. Therapy date. Diagnosis for use. Event decreased after use stopped or dose reduced. Batch number. Expiration date. Event recurred after reintroduction of the treatment. Associated medical products and therapy dates.
Reporter	Name. Address. Telephone number. Speciality and occupation.

The South African ADR form contains all the information as prescribed by the WHO, except for information regarding; whether the event reappeared after reintroduction of the treatment and the address of the reporter. (MCC, 2012:17).

The regulation and management of ADR reporting are implemented in different ways in the private and public healthcare sectors in South Africa. These methods are illustrated and discussed in Table 4-4.

Table 4-5: Implementation of ADR reporting and pharmacovigilance in academia

Sector	Entity	Objectives
Regulatoy sector	The South African Health Products Regulatory Authority (SAHPRA).	Standards according to the Medicines and Related Substances Act (101 of 1965): • Overlooks manufacturing, distribution, sales and marketing of medicine. • Assesses risks and benefits of medicine to ensure safety. • Suspected ADRs should be reported by an applicant or holder of a certificate of registration. • The steps taken to adsress the ADR should be reported to SAHPRA. • Pharmacovigilance data should be shared with SAHPRA. • All record and data of the medicine should be kept (South Africa, 1965).
Patient level		The National Policy on Quality in Healthcare, SASQC, SAQA and SAMRC provides ways in the public and private sector to improve quality care (NDoH, 2017:2; SASQ, 2016; SAQA, 2014; SAMRC, 2018).
	National Policy on Quality in Healthcare	• Reduces and prevents the cause of illness and injury. • Assisting in the appropriate use of healthcare services to reduce ADRs (NDoH, 2017).
	South African Society for Quality Control (SASQC)	• Provides training, education and guidance in the quality of health and safety of the medicine, by increasing knowledge of HCPs (SASQ, 2016)..
	South African Qualifications Authority (SAQA)	• Improves the quality of education and training to ensure development (SAQA, 2014)..
	South African Medical Research Council (SAMRC)	• Ensures that the environment is free of health and safety risks by providing resources that complies with its health and safety regulations (SAMRC, 2018).

Academia	North-West University of Potchefstroom (NWU), University of the Witwatersrand (WITS), University of the Western Cape (UWC), Rhodes University, Sefako Makgatho Health Sciences University (SMU), and University of Kwazulu-Natal (UKZN).	Various universities offer postgraduate studies in pharmacovigilance to improve HCPs' knowledge toward the national system and the reporting of ADRs. Some of these studies include: • BSc (Honours) in pharmacology with pharmacovigilance as a research focus (WITS, 2017). • MSc in Pharmacy with pharmacovigilance as a research focus (UWC, 2018). • MPharm in pharmacovigilance and pharmacoepidemiology (NWU, 2019:98). • PharmD in pharmacy practice which includes subject around the health and safety in primary healthcare (Rhodes University, 2017). • MPharm with a focus on public health management (SMU, 2018). • Masters in health science with a focus on pharmacovigilance (UKZN, 2018).

The undergraduate programme toward the BPharm degree in South African universities does not cover the reporting of ADRs extensively, although Masters degrees at various universities are offered in this field (NWU, 2019:98; WITS, 2017; UWC, 2019; University of Kwazulu-Natal, 2018). Postgraduate studies and training are also offered by the Health Science Academy (HSA), the University of Stellenbosch and the International Council for Harmonisation (ICH) endorsed by the Pharmaceutical Industry Association of South Africa (PIASA) to teach pharmacists the importance of drug safety, ADR reporting and legislation in the pharmaceutical field (HSA, 2015; University of Stellenbosch, 2018; PIASA, 2012). An important aspect of pharmacovigilance is the ongoing under- and post-graduate training of healthcare professionals (WHO, 2000:16). Education and training toward pharmacovigilance and ADR reporting should be provided by pharmaceutical companies, national pharmacovigilance centres and academia. Pharmacists should be encouraged to promote the safe and appropriate use of medicine.

4.2 Conclusions: Empirical study

4.2.1 Background information

The demographic information of the study population included 70.7% (n = 464) female pharmacists. The South African Pharmacy Council (SAPC) have a larger representation of females as pharmacists than males, with a ratio of 1.72:1 (SAPC, 2019). The most represented age group was 37 – 43 years of age (n = 143, 21.8%). Pharmacists in the age group 55 years and older (n = 63, 53.8%) are more likely to practice healthcare in a community, corporate and mail order pharmacy.

Additional training in ADR reporting was received by 64.4% (n = 421) of the pharmacists, with most of the training being in-service training (n = 191, 29.1%). Training was also received in pharmacovigilance by 191 (29.1%) pharmacists. Most pharmacists were practicing in the private healthcare sector (n = 350, 58.0%). The most aquired qualification were a Baccaleurs in Pharmacy degree (BPharm/BSc) (n = 477, 72.7%) followed by a Masters degree (MPharm/MSc) (n = 120, 18.2%). The highest average years of experience as a practicing pharmacist was more than twenty years (n = 198, 32.8%) followed by 5 – 10 years (n = 126, 20.9%).

To determine pharmacists' current and previous area of practice and the total years of experience in the sector, the following question was asked: "Indicate your current and previous area of practice, with the total years of experience in this area". The answers are indicated in Table 4-3.

Table 4-6: Pharmacists' current and previous healthcare sector of practice and years of experience in the sector

Healthcare sector	**Current*** n (%)	**Previous*** n (%)	**Years of experience** (mean±SD) (years)
Community pharmacy	132 (20.1)	296 (45.1)	8.6±9.4
Corporate community pharmacy	64 (9.7)	126 (19.2)	3.9±3.7
Private hospital pharmacy	83 (12.6)	167 (25.4)	5.5±6.0
Public hospital pharmacy	123 (18.7)	264 (40.2)	5.2±5.9
Medical aid environment	12 (1.8)	38 (5.7)	4.8±4.9
Clinical research	39 (5.9)	37 (5.6)	6.0±6.7
Academic	37 (5.6)	39 (5.9)	6.3±7.6
Mail order pharmacy	6 (0.9)	36 (5.4)	2.8±2.2
Wholesale/distribution pharmacy	30 (4.5)	64 (9.7)	4.6±6.3
Manufacturing/production environment	46 (7.0)	79 (12.0)	6.1±7.4
Medicine registration/control	60 (9.9)	34 (5.1)	7.8±7.9
Quality control	28 (4.3)	45 (6.8)	3.6±3.2
Military services	4 (0.6)	38 (5.7)	2.6±3.2
Correctional services		17 (2.6)	2.0±1.9

*Multiple responses were allowed, SD:standard deviation

There was a statistically significant association between gender- (p=0.001, Cramér's V=0.205) and age group (p=0.020, Cramér's V=0.146) of respondents with their current area of practice. Both male (n = 90, 46.9%) and female (n = 166, 35.8%) pharmacists are more likely to practice healthcare in a community, corporate and mail order pharmacy.

4.2.2 Objective 1: Determine pharmacists' past experience with the reporting of ADRs, stratified by the pharmaceutical sector and demographic information.

This objective was addressed by Manuscript 1 which forms part of Chapter 3.

Pharmacists' past experiences regarding the reporting of ADRs are indicated (See Manuscript 1: Table 3). Most pharmacists have heard about ADR reporting (n = 537, 95.7%). Although a large number of pharmacists have noticed a suspected ADR in the past 12 months (n = 342, 60.9%), only 47.2% (n = 265) have reported between one and five ADRs in their career as a practicing pharmacist, while working in the public healthcare sector (n = 106, 16.1%). Various studies globally indicate that although pharmacists agree that ADR reporting is a part of their professional responsibility, and understand the importance thereof, the reporting of ADRs still remains uncommon in their practice (Elkalmi *et al.*, 2011:71; Green *et al.,* 2001:81; Jose *et al.,* 2014:163; Suyagh *et al.,* 2015:147; Walji *et al.*, 2011:384). Ali *et al* (2018:21) reported that only 34% of healthcare providers are reporting ADRs in Saudi Arabia. Pharmacists are under the impression that they are not responsible to report ADRs, and that it's the physicians' responsibility to do so (Green *et al.*, 2001:82).

There is a statistically and practically significant association in all the aspects of pharmacists perception and experience toward which ADR and product stability problem to report (p<0.05) (See Manuscript 1: Table 4). Only 232 (35.5%) pharmacists have received additional ADR reporting training and this indicated a statistically significant association (p<0.05) between additional training as well as practice sector and the reporting of well-known ADRs, ADRs caused by OTC medication and ADRs caused by herbs and traditional medication. Pharmacists (n = 193, 40.0%) believe that well-known ADRs do not have to be reported. Williams (2015:37) reported that pharmacists believe that the underreporting of common ADRs occurs because healthcare workers are not sure if they should report those reactions.

This study highlights the importance of pharmacists as healthcare professionals in the reporting of ADRs. Pharmacists need to be made aware of their role and responsibility toward the pharmacovigilance system of South Africa.

4.2.3 Objective 2: Assess pharmacists' perceptions regarding their ability and willingness to report an ADR, stratified by pharmaceutical sector and demographic information.

This objective was addressed by Manuscript 1 which forms part of Chapter 3.

Pharmacists' perceptions regarding their ability and willingness to report adverse drug reactions are indicated (See Manuscript 1: Tables 2 and 3). Most pharmacists (n = 383, 92.9%) believe they have the ability to report ADRs. In this study the Binomial test indicated that a statistically significant larger proportion of pharmacists' belief in having the ability to report ADRs (p<0.05, δ½=0.859). A large number

of pharmacists reported that they understand the reporting system (n = 493, 72.5%), which was also of statistical significance (p<0.05, δ½=0.504). A recent study also reported that most pharmacists could describe the reporting process (Williams, 2015:34).

Pharmacists are willing to report ADRs (n = 636, 97.0%), but still reporting remains low. More than half of the pharmacists (n = 296, 52.7%) have not yet reported an ADR in their years of practice. There are various barriers pharmacists experience in their work making it difficult for them to report ADRs (refer to section 4.2.4). Most pharmacists also believe that ADR reporting should be compulsory (n = 344, 83.5%), as they realise the importance of their role in the reporting process.

These findings indicate that although pharmacists believe they are able and willing to report ADRs, the value of future training could only strengthen the current pharmacovigilance system.

4.2.4 Objective 3: Determine from the perceptions of pharmacists' possible factors that influence the successful implementation of pharmacovigilance in different pharmaceutical sectors in South Africa.

This objective was addressed by Manuscript 2 which forms part of Chapter 3.

Pharmacists indicated various factors which motivate or discourage them to report adverse drug reactions. The main barriers reported were a lack of knowledge to identify the ADR, a lack of feedback from the National Pharmacovigilance Centre and the reporting process being too time-consuming (See Manuscript 2: Table 3). These barriers have also been mentioned in various previous studies (Elkalmi *et al*., 2011b:72; Green *et al*., 2001:83; Walji *et al*., 2011:385). There was a statistically significant association between the current area of practice and the reporting of ADRs being too time-consuming (p<0.05, Cramér's V = 0.202). Pharmacists are being tasked with various administrative duties, making pharmacovigilance activities of less importance, leading to the underreporting of ADRs. On-going adequate training provided by pharmacovigilance authorities could improve these obstacles.

The lack of feedback after reporting an ADR, from the National Adverse Drug Event Monitoring Centre (NADEMC) was a common barrier to reporting ADRs. Elkalmi *et al.* (2011b:73) indicated that appropriate feedback is important to ensure on-going ADR reporting. A statistically significant association exists between additional ADR training received by pharmacists and the lack of feedback received from NADEMC (p<0.05). Feedback from NADEMC could create awareness and improve pharmacists' willingness to report ADRs more regularly. Pharmacists reported that they are uncertain about identifying an ADR correctly which leads to not reporting the ADR at all. Previous studies reported this as a barrier leading to underreporting (Jose *et al*., 2014:163; Ruud *et al*., 2010:345). There was a statistically significant association between additional training received and the lack of clinical knowledge to detect an ADR (p<0.05, Cramér's V = 0.141). Pharmacists who received additional training in ADR reporting are more

likely to “agree” that the lack of clinical knowledge to detect an ADR, is perceived as a barrier toward ADR reporting.

Pharmacists reported that they would be motivated to report ADRs if the reporting form was less complicated (n = 319, 77,4%), an electronic reporting system was installed (n = 382, 92.7%), feedback was received from NADEMC (n = 379, 91.9%) and if training was provided by the National Pharmacovigilance Centre (n = 374, 90.7%). These encouraging factors are in-line with previous studies (Elkalmi *et al*., 2011b; Green *et al*., 2001; Walji *et al*., 2011). Some pharmacists (n = 114, 27.6%) reported that comprehensive training toward ADR reporting will improve the reporting rate in pharmaceutical sectors.

The study illustrates that future training in the field of pharmacovigilance, specifically ADR reporting, is of utmost importance to reduce negative perceptions toward ADR reporting, to be able to improve pharmacists’ knowledge and understanding of ADR reporting. Pharmacists are able to play a key role to improve the current pharmacovigilance system in South Africa and be a part of the multidisciplinary decentralised pharmacovigilance team.

4.2.5 Objective 4: Identify pharmacists’ additional training needs regarding ADR reporting and pharmacovigilance.

This objective was addressed by Manuscript 2 which forms part of Chapter 3.

Pharmacists’ additional training needs in ADR reporting were identified and are indicated (See Manuscript 2: Table 4). The finding with regard to objective 3 indicated a lack of clinical knowledge to identify ADRs, as a barrier toward ADR reporting. This statement indicated the need for training in pharmacovigilance by pharmacists. Pharmacists have a need to be educated and trained about the reporting of ADRs (Suleman, 2010:57). A previous study mentioned, by Varallo *et al*. (2014:743) indicated that pharmacists are too ignorant and insecure to report ADRs, and believe that ongoing education and training could improve their attitude toward ADR reporting. The WHO (2000:18) emphasised that education and training will improve knowledge and awareness of ADRs, leading to increased reporting rates.

Pharmacists (N = 336, n = 300, 89.2%) reported that more training is needed in pharmacovigilance during their Baccaleurs in Pharmacy (BPharm) degree to be able to report ADRs efficiently. There was a statistically significant association between pharmacists who received additional training ($p<0.05$, Cramér’s $V = 0.189$) and their years of experience as a pharmacist ($p<0.05$, Cramér’s $V = 0.167$) toward the need for training during their undergraduate studies (See Manuscript 2: Table 4). Pharmacists with more experience as a practicing pharmacist and pharmacists who received additional training in ADR reporting are more likely to “agree” that training towards ADR reporting is needed during the undergraduate pharmacy programme. Pharmacists also indicated that on-going future training programmes at universities

and institutions will benefit the rate of ADR reporting. Williams (2015:63) indicated that improving pharmacists' pharmacovigilance knowledge would enable them to make better operational and clinical decisions when identifying a possible ADR.

Although most pharmacists have heard the term "pharmacovigilance", only fifteen (5.6%) pharmacists were able to define the term correctly. A statistically significant association exists between pharmacists' knowledge of the term and their current area of practice ($p<0.05$, Cramér's $V = 0.282$) as well as whether they received additional training in ADR reporting ($p<0.05$, Cramér's $V = 0.409$). Pharmacists who received additional training in ADR reporting are more likely to have knowledge regarding the term "pharmacovigilance". Pharmacists practicing in the public hospital pharmacy sector (n = 43) and in the medicine registration and control sector (n = 47) have more knowledge of the term "pharmacovigilance". In the study, pharmacists (N = 336, n = 308, 91.6%) reported that they would be willing to undergo additional training in ADR reporting to enable them to report ADRs more efficiently.

The study illustrates the need for on-going education and training for pharmacists toward pharmacovigilance and ADR reporting in South Africa. Pharmacists have the skill and ability to improve the current pharmacovigilance system of South Africa. Pharmacists need to be made aware of the important role they play in the reporting process to ensure the safe and effective use of medicine.

A South African study on the barriers of ADR reporting among healthcare professionals, indicated that HCPs had a need to understand what should be reported, as well as a shortage in skills and knowledge to identify ADRs (Ruud *et al*., 2010:5). Pharmacists in South Africa have less knowledge of the term "pharmacovigilance" than pharmacists in Saudi-Arabia and Pakistan, but South African pharmacists have an increased awareness of ADRs (Almandil, 2016:1359; Green *et al.,* 2001:81; Joubert & Naidoo, 2016:238; Khan, 2013b:45). In this study, only fifteen (5.6%) pharmacists defined pharmacovigilance correctly. Another South African study revealed that 76.2% of pharmacists have not received any pharmacovigilance training and that 54.5% of HCPs do not have the knowledge to report ADRs (Bogolubova, 2018:1). These statistics indicate that further training is needed by pharmacists in the field of pharmacovigilance and ADR reporting.

4.3 Limitations of the study

- The participation of the entire population of pharmacists in South Africa, could not be guaranteed.
- The response rate was dependent on whether the email addresses provided by the register of the SAPC were updated by the study population, which could have hampered generalisation of the results.
- The questionnaire was in English and Afrikaans, which could have affected respondents with other first languages' interpretation of the questions and participation in the study.

- The questionnaire took 30 minutes to complete, which might have been to time-consuming for participants, making them decide to withdraw from the study.

4.4 Recommendations

The following recommendations are proposed:

1. Pharmacists need to be made aware that all ADRs should be reported by sending out circulars, offering training and workshops and implementing awareness posters.

2. Training should be offered to pharmacists to improve their skills in identifying ADRs, how to report these ADRs and when to refer a patient.

3. The availability of ADR reporting forms should be assessed, making sure that all healthcare facilities and healthcare staff have access to the forms.

4. As this study only focussed on the perception and knowledge of pharmacists in South Africa, a study focussing on other HCP's perceptions and experience should be conducted.

5. The National Pharmacovigilance Centre should aid pharmacies with a basic ADR causality assessment tool, to enable pharmacists to identify a possible ADR with confidence.

4.5 Chapter summary

In this chapter, the objectives of both the empirical and literature studies were discussed and concluded. Recommendation were made based on the findings of the study. Limitations toward the study were also discussed which might aid future studies and investigations.

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ANNEXURES

ANNEXURE A: INFORMATION LEAFLET

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOM CAMPUS

PHARMACISTS' PERCEPTION TOWARDS PHARMACOVIGILANCE AND THE REPORTING OF ADVERSE DRUG REACTIONS IN SOUTH-ARICA

Thank you for giving me the opportunity to tell you more about this research project and for agreeing to participate in the study.

The general aim of this study is to evaluate the pharmacovigilance system of South Africa from the perspective of pharmacists from different pharmaceutical sectors. The study will contribute in future drug monitoring to detect adverse drug reactions, specifically in relation to counterfeit and substandard quality products. The study will improve pharmacists' awareness of the importance of adverse drug reactions monitoring to help ensure that patients obtain safe and efficacious medical products.

Please indicate your answer by marking with an **X symbol** for closed-ended questions or by giving your **opinion** for open-ended questions. Your opinion is very valuable so please be as honest as possible. The estimated completion time of the questionnaires is ± 30 minutes.

Your replies are strictly confidential and your participation is completely voluntary. If a specific question makes you to be uncomfortable, you may skip it and ask to proceed to the next question. Alternatively, you may also withdraw from the study without any penalties. The findings of the research project will be shared with the South African Pharmacovigilance Unit, National Adverse Drug Event Monitoring Centre (NADEMC) and will be presented at both relevant national conferences and published in both national and international pharmaceutical journals. It also forms part of my dissertation for the Master of Pharmacy Practice post-graduate programme at the North-West University

The questionnaire should only be completed by participants who have given their informed consent. Confidentiality will be maintained through a confidentiality agreement signed by the study mediator who is responsible for distribution of the questionnaires. Participants will not be identified from the results.

You are welcome to contact the researcher, supervisor, co-promoter or the ethics committee if you have any questions regarding the study.

Researcher:
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Ethics committee: email: healthscience-ethics@nwu.ac.za tel: 018 299 2089

Study mediator:
Mrs Celeste du Preez email: celeste.dupreez@nwu.ac.za tel 018 299 8525

Thank you for your time. Your participation is highly appreciated and will definitely benefit the outcomes of the research project.

ANNEXURE B: STRUCTURED QUESTIONNAIRE

Questionnaire number:	
Date on which the questionnaire was completed:	_dd_|_mm_|_yyyy_|

A. <u>DEMOGRAPHIC INFORMATION</u>:

For each question mark **only one** response unless otherwise indicated.

1. Gender:

Male	1	Female	0

2. Age (in years): _____

3.1 Highest pharmacy qualification obtained:

Field	**Indicate (x)**
B achelor's degree (BPharm / BSc or other applicable degree)	
Master's degree (MPharm / MSc or other applicable degree)	
Doctorate (DPharm / DSc / PhD or other applicable degree)	
Diploma in Pharmacy	
Specialist pharmacy degree	
Other	

3.2 If other, please specify: _____

4. If you have a doctorate / specialist pharmacy degree, in which area of pharmacy did you specialise?

_____

_____

5. Have you had any additional training in the reporting of adverse drug reactions?

Yes	1	No	0

6. If you answered **yes** in question 5, at which level of education did you receive training?

		Indicate (x)
6.1	University level (during your BPharm / MPharm / PhD degree)	
6.2	An additional degree	
6.3	An additional diploma	
6.4	Training received by pharmaceutical company	
6.5	In-service training	
	Other	

6.6 If other, please specify: _____

7. Did you have any additional training in any of the following fields? **(Indicate, with an X, more than one, if necessary).**

	Training	**Indicate (x)**
7.1	Pharmacovigilance	
7.2	Adverse drug reactions and drug-related problems	
7.3	Toxicology	
7.4	None	

8. Indicate in which sector you currently practice

	Sector	**Indicate (X)**
8.1	Public health sector	
8.2	Private health sector	
8.3	Not applicable	

9. Indicate your current and former work environment **(indicate, with an X, more than one, if necessary).**

	Sector	**Current**	**Former**
9.1	Community pharmacy		
9.2	Corporate[1] community pharmacy		
9.3	Private hospital pharmacy		
9.4	Public hospital pharmacy		
9.5	Medical aid environment		
9.6	Clinical research		
9.7	Academic		
9.8	Mail order pharmacy		
9.9	Wholesale / distribution facility		
9.10	Manufacturing / production		
9.11	Medicine registration / control		
9.12	Quality control		
9.13	Military services		
9.14	Correctional services		
	Other		

9.15 If other, please specify: _____

10. Indicate your total years of experience as a practising pharmacist.

	Total years	**Indicate (X)**
10.1	< 5 years	
10.2	5-10 years	
10.3	11-15 years	
10.4	16-20 years	
10.5	>20 years	

[1] Corporate – Dischem, Clicks, Medirite, Spar or Pick n Pay pharmacy groups

11. How much experience do you have in the following fields? **Indicate in years all categories applicable.**

	Sector	**Number of years**
11.1	Community pharmacy	
11.2	Corporate[2] community pharmacy	
11.3	Private hospital pharmacy	
11.4	Public hospital pharmacy	
11.5	Medical aid environment	
11.6	Clinical research	
11.7	Academic	
11.8	Mail order pharmacy	
11.9	Wholesale / distributor facility	
11.10	Manufacturing / production	
11.11	Medicine registration / control	
11.12	Quality control	
11.13	Military services	
11.14	Correctional services	
11.15	Other	

B. EXPERIENCE WITH REPORTING OF ADVERSE DRUG REACTIONS:

Indicate at each question with an (x):

1. Have you noticed any adverse drug reactions (Answer every question)

	Period	**Yes**	**No**
1.1	During the past 3 months	1	0
1.2	During the past 3 to 6 months	1	0
1.3	During the past 6 to 12 months	1	0
1.4	More than 12 months ago	1	0

[2] Corporate – Dischem®, Clicks®, Medirite®, Spar® or Pick 'n Pay® pharmacy groups

2. Have you ever heard about adverse drug reactions reporting?

Yes	1	No	0

3. Do you know where to obtain the adverse drug reactions forms?

Yes	1	No	0

4. Where would you obtain adverse drug reactions forms when needed? **More than one answer can be indicated if necessary.**

	Area	**Indicate (x)**
4.1	From the pharmacy you practise (current working environment)	
4.2	From your own personal files	
4.3	From the head office of the pharmacy group where you are currently working.	
4.4	From the website of the South African Medicines Control Council (MCC) [Name change to South African Healthcare Products Regulatory Authority (SAHPRA)	
4.5	From a hard copy of the Medicines Act available in my current work environment	
4.6	On the website of the Medical University of South Africa (MEDUNSA) (currently the Sefako Makgatho Health Science University)	
4.7	From the Bloemfontein Pharmacovigilance Centre at the University of the Free State	
4.8	I do not know	
	Other	

4.9 If other, please indicate:

_____

5. Estimate the number of adverse drug reactions you have reported in your professional career.

None	1	1-5	2	6-10	3	>10	4

6. If you have reported adverse drug reactions, where were you working during the incident? Indicate more than one if necessary.

	Sector	**Indicate (X)**
6.1	In a pharmacy in the public health sector	
6.2	In a pharmacy in the private health sector	
	Other	

6.3 If other, please specify: _____

7. If you have reported adverse drug reactions, please answer the following two questions as good as possible

7.1 Give a brief description of the most recent reported adverse drug reactions (as indicated in Question 5).

_____

_____

_____

_____

7.2 Give a brief description of the process you followed to report the most recent adverse drug reactions (as indicated in Question 5):

_____

_____

_____

_____

8. Which adverse drug reactions do you think should be reported? **Please answer all questions.**

	Drug-related problem	**Yes**	**No**
8.1	All serious reactions	1	0
8.2	Unexpected / unknown reactions	1	0
8.3	Well-known adverse drug reactions	1	0
8.4	Unexpected therapeutic effects	1	0
8.5	Reactions caused by over-the-counter medicine (unscheduled)	1	0
8.6	Reactions caused by over-the-counter medicine (schedules 1 & 2)	1	0

	Drug-related problem	Yes	No
8.7	Reactions caused by prescription medication (schedules 3 to 6)	1	0
8.8	Adverse reactions to vaccines	1	0
8.9	Reactions toward herbal and traditional medicine	1	0
8.10	Adverse reactions not indicated in the package insert	1	0
8.11	A reaction caused by an interaction between drugs	1	0
8.12	A reaction caused by a food-drug interaction	1	0
8.13	Adverse reaction caused due to medication error	1	0

9. Which product stability problems do you think should be reported?

	Drug-related problem	Yes	No
9.1	Product contamination because of uncleanness that occurred during production or packaging and storage of the product	1	0
9.2	Defective components that are harmful to the patient and could result in a defect	1	0
9.3	Possible product stability (chemical and physical appearance at the time of packaging and storage)	1	0
9.4	Poor packaging and labelling of a product	1	0
9.5	Other, please specify. _____	1	0

10. Have you observed any adverse drug reactions that caused the following?

		Yes	No
10.1	Hospitalisation	1	0
10.2	A life-threatening situation	1	0
10.3	A congenital anomaly	1	0
10.4	Death of a patient	1	0
10.5	Any skin rashes over parts of the body	1	0
10.6	Disability	1	0

11. Please answer the following two questions as good as possible

11.1 Have you received completed adverse drug reaction forms from a patient / physician?

	Yes	No	If yes, how many

Patient	1	0	
Physician	1	0	

11.2 Describe what you have done with the completed form:

_____

_____

12. Do you think adverse drug reactions can be reported on the following?

		Yes	**No**
12.1	Scheduled drugs	1	0
12.2	Over-the-counter medication	1	0
12.3	Medical devices	1	0
12.4	All three the options	1	0

13. Which healthcare professionals do you think should report adverse drug reactions?

	Healthcare professional	**Yes**	**No**
13.1	Medical practitioner	1	0
13.2	Pharmacist	1	0
13.3	Registered nurse	1	0
13.4	Dentist	1	0
13.5	Physiotherapist	1	0

14. When reporting an adverse drug reaction, to whom would you report it?

		Indicate (x)
14.1	I do not know to whom to report an adverse drug reaction.	
14.2	I would report the adverse drug reaction to the patient's physician, for them to complete the forms.	
14.3	I would report the adverse drug reaction to the involved pharmaceutical company.	
14.4	To the Medicines Control Council[3]	

[3] Name change to South African Healthcare Products Regulatory Authority (SAHPRA)

		Indicate (x)
14.5	To the pharmacovigilance unit National Adverse Drug Event Monitoring Centre (NADEMC)	
14.6	I will report adverse drug reactions during clinical trials to the Medicines Control Council[4].	
14.7	I will report adverse drug reactions on antiretroviral therapy to the Medical University of South Africa (MEDUNSA)[5]	
14.8	I will report adverse drug reactions to the Bloemfontein Pharmacovigilance Centre at the University of the Free State	
14.9	I would report adverse drug reactions during clinical trials to the involved pharmaceutical company.	
14.10	I would report the adverse drug reaction to another entity.	

14.11 If you selected question **number 14.10**, to who would you report the adverse drug reactions?

_____

_____

15. To whom do you think should patients report adverse drug reactions? **Indicate more than one answer if necessary.**

		Indicate (x)
15.1	I am uncertain to whom the patient should report	
15.2	To the physician who prescribed the involved medicine causing the adverse drug reaction.	
15.3	To the manufacturer (pharmaceutical company) of the involved medicine.	
15.4	To the South African Pharmacy Council.	
15.5	To the South African Pharmacovigilance Centre, NADEMC who serve as secretariat to the Medicines Control Council[6] (MCC).	
15.6	To the Department of Pharmacology, University of Cape Town.	
15.7	To the Medical University of South Africa (MEDUNSA)	
15.8	To the Bloemfontein Pharmacovigilance Centre at the University of the Free State	
15.9	To their pharmacist when the patient goes to the pharmacy for their repeat prescription	
	Other	

[4] Name change to South African Healthcare Products Regulatory Authority (SAHPRA)
[5] Currently the Sefako Makgatho Health Science University
[6] Name change to South African Healthcare Products Regulatory Authority (SAHPRA)

15.10 If other, please specify: _____

16. The following steps need to be followed by you as a pharmacist when an adverse drug reaction is detected. **Please indicate your level of agreement with the following statements.**

1	2	3	4	5
Completely disagree	**Disagree**	**Uncertain**	**Agree**	**Completely agree**

	Statement	**1**	**2**	**3**	**4**	**5**
16.1	Contact the patients' physician so he/she can report the adverse drug reaction.					
16.2	Send the patient back to her/his physician.					
16.3	Complete the adverse drug reaction form through information received from the patient or physician and send it to the Medicine Control Council[7].					
16.4	Give the patient an adverse drug reaction form to complete in their own time.					
16.5	Report the adverse drug reaction on the adverse drug reaction form as well as on the patient's file					
16.6	Nothing needs to be done					
16.7	Phone the doctor to change the therapy					

17. When reporting an adverse drug reaction, which information do you think is required to report an adverse drug reaction on the official adverse drug reaction form?

	Information	**Yes**	**No**
17.1	Patient's country of residence	1	0
17.2	Pharmacist's/physician's (reporter) name, address and qualification	1	0
17.3	Patient's surname, age, gender and reference number	1	0
17.4	The suspected product(s) that caused the adverse drug reaction	1	0
17.5	The suspected adverse drug reaction observed / experienced by the patient	1	0
17.6	Dosage of medication taken by the patient	1	0
17.7	Duration of treatment (prior to event)	1	0

[7] Name change to South African Healthcare Products Regulatory Authority (SAHPRA)

	Information	Yes	No
17.8	Time to onset of adverse drug reaction	1	0
17.9	Outcome of the adverse drug reaction (death, hospitalisation, disability)	1	0
17.10	Product causing the adverse drug reaction's name	1	0
17.11	Product causing the adverse drug reaction's batch number	1	0
17.12	Product causing the adverse drug reaction's expiry date	1	0
17.13	Product causing the stability problem's batch number	1	0
17.14	Product causing the stability problem's expiry date	1	0
17.15	Product causing the stability problem's name	1	0
17.16	Laboratory test results	1	0

C. <u>PERCEPTIONS ON REPORTING ADVERSE DRUG REACTIONS AND THE BARRIERS THERETO</u>:

1. Are you as a pharmacist willing to report adverse drug reactions?

	Indicate (x)
Yes	1
No	0

If **NO**, why are you not willing to report adverse drug reactions?

_____

_____

2. Do you think you have the ability to report adverse drug reactions?

	Indicate (x)
Yes	1
No	0

If **NO**, why do you think you are not able to report adverse drug reactions?

_____

_____

3. Reflect your views / perception toward adverse drug reaction reporting by pharmacists. **Please indicate your level of agreement with the following statements.**

1	2	3	4	5
Strongly disagree	**Disagree**	**Uncertain**	**Agree**	**Strongly agree**

	Statement	**1**	**2**	**3**	**4**	**5**
3.1	Pharmacists are aware of the importance of adverse drug reaction reporting in healthcare facilities.					
3.2	Pharmacists are aware of the process to follow for the reporting of adverse drug reactions in healthcare facilities.					
3.3	You have been provided with adverse drug reaction reporting forms.					
3.4	You have received enough training to be able to identify an adverse drug reaction (pharmacological and clinical knowledge).					
3.5	You have received training on how to report an adverse drug reaction.					
3.6	The pharmacy you currently practise in, have the necessary standard operating procedures to report an adverse drug reaction.					
3.7	You have previously received feedback from the National Pharmacovigilance centre regarding a reported adverse drug reaction.					

4. The following factors may encourage you to report an adverse drug reaction?

	Statement	**1**	**2**	**3**	**4**	**5**
4.1	Adverse drug reaction reporting should be compulsory for all pharmacists.					
4.2	Training from the National Pharmacovigilance Centre.					
4.3	Feedback from the National Pharmacovigilance Centre will encourage the reporting of adverse drug reactions.					
4.4	Making the reporting forms less complicated will increase motivation to report adverse drug reactions.					
4.5	Installing an electronic system for the reporting of adverse drug reactions will increase the reporting of adverse drug reactions.					
4.6	The healthcare system will benefit from a pharmacovigilance specialist working in the pharmacy environment.					

5. The following factors may discourage you from reporting an adverse drug reaction?

No.	Statement	Agree	Disagree	Not applicable*
5.1	Lack of clinical knowledge how to detect. (I do not know how to detect an adverse drug reaction).	1	0	2
5.2	Lack of confidence to know when to report an adverse drug reaction. I am not confident on when to report an adverse drug reaction.	1	0	2
5.3	I do not know where to obtain an adverse drug reaction form to enable me to report the adverse drug reaction.	1	0	2
5.4	After reporting an adverse drug reaction, I do not receive feedback from the Pharmacovigilance Unit National Adverse Drug Event Monitoring Centre (NADEMC).	1	0	2
5.5	Reporting adverse drug reactions is time consuming.	1	0	2
5.6	Adverse drug reaction forms are complicated to complete, which increases my workload.	1	0	2
5.7	Adverse drug reaction reporting is not part of my healthcare practice.	1	0	2
5.8	I believe that drugs on the market are safe to use.	1	0	2
5.9	I fear legal liability following the reported adverse drug reaction.	1	0	2
5.10	I fear that the adverse drug reaction is caused by a medication error made by me.	1	0	2
5.11	There are no adverse drug reactions reporting forms available in in your work environment.	1	0	2
5.12	I feel that adverse drug reaction reporting is not compulsory.	1	0	2
5.13	There is no incentive (e.g. financial or other recognitions) involved for the reporting of adverse drug reactions.	1	0	2
5.14	I experience other challenges than the mentioned ones.	1	0	2

* Not applicable for certain pharmacy sectors of environments

15.14.1 If you selected **agree** at question 5.14, please specify the challenge that you are experiencing:

_____

_____

6. Do you think adverse drug reaction reporting should be compulsory or voluntary?

Compulsory	1	Voluntary	2

7. Do you understand the process of reporting an adverse drug reaction?

	Indicate (x)
Yes	1
No	0

8. Do you have standard operating procedures for the reporting of adverse drug reactions in your current work environment?

	Indicate (x)
Yes	1
No	0
Not applicable	2

9. Do you have any recommendation to improve the adverse drug reaction reporting system in your current work environment (your pharmacy)?

	Indicate (x)
Yes	1
No	0

9.1 If **YES**, please give recommendations.

_____

_____

D. <u>KNOWLEDGE OF PHARMACOVIGILANCE IN SOUTH AFRICA:</u>

1. How familiar are you with the term Pharmacovigilance (PV)? Please indicate (X) your level of agreement with the following statements.

Not at all familiar	Slightly familiar	Somewhat	Moderately	Extremely familiar
1	2	3	4	5

2. Please define pharmacovigilance in your own words.

_____

_____

3. Who serves as South-Africa's pharmacovigilance unit?

_____

4. Reflect your views / perception toward pharmacovigilance in South-Africa. **Please indicate your level of agreement with the following statements.**

1	2	3	4	5
Completely disagree	**Disagree**	**Uncertain**	**Agree**	**Completely agree**

	Statement	**1**	**2**	**3**	**4**	**5**
4.1	Pharmacovigilance in SA or the identification of adverse drug reactions encourages national regulatory decision-making.					
4.2	Drug monitoring in SA is of value as a tool for detecting adverse drug reactions.					
4.3	Adverse drug reaction monitoring help to ensure that patients obtain safe and efficacious products.					
4.4	The results of adverse drug reaction monitoring have an important educational value.					
4.5	Adverse drug reaction reporting can improve drug information on labels/package inserts.					
4.6	The effectiveness of a national post-marketing surveillance programme is directly dependent on the active participation of health professionals.					
4.7	Healthcare providers (physicians, pharmacists, nurses, dentists and others) should report adverse drug reactions as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication.					
4.8	Pharmacovigilance means improving patient care and safety towards the use of medicine.					
4.9	Pharmacovigilance means improving public health and safety towards the use of medicine.					
4.10	Pharmacovigilance means promoting education in the reporting of adverse drug reactions.					
4.11	The current adverse drug reaction reporting system in South Africa is sufficient.					
4.12	If more pharmacists reported adverse drug reactions, it would make a positive difference in the current healthcare system of South-Africa.					
4.13	It will be financially beneficial for private and public hospitals if more healthcare professionals reported adverse drug reactions.					

	Statement	1	2	3	4	5
4.14	The reporting of adverse drug reactions forms part of the Scope of Practice of the Pharmacist in South Africa pharmacist					
4.15	More training in pharmacovigilance regarding specific products is needed by pharmaceutical companies.					
4.16	More training in pharmacovigilance is needed by pharmacy schools in the undergraduate programmes.					
4.17	More continuing education programmes in pharmacovigilance is needed by pharmacy schools and other training institutions.					
4.18	The reporting of adverse drug reactions is included in your task agreement in your current work environment					
4.19	You are willing to undergo additional training aimed at the reporting of adverse drug reactions					

E. SUGGESTIONS AND COMMENTS:

1. Do you have any suggestions or comments you would like to add?

_____

Vraelysnommer	
Datum waarop die vraelys voltooi is:	_dd_|_mm_|_yyyy_|

A. <u>DEMOGRAFIESE INLIGTING</u>:
Antwoord asseblief elke vraag deur 'n **kruisie (X)** in die aangeduide spasie te maak, tensy anders aangedui. By sommige vrae is meer as een antwoord aanvaarbaar.

1. Dui u geslag aan:

Manlik	1	Vroulik	0

2. Ouderdom (in jare): _____

3.1 Wat is u hoogste kwalifikasie in aptekerswese :

	Dui aan (x)
Baccalaureusgraad (BPharm / BSc(Pharm) of ander toepaslike graad)	
Meestersgraad (MPharm / MSc Pharm of ander toepaslike graad)	
Doktorsgraad (PhD / DPharm / DSc)	
Diploma in Aptekerswese	
Spesialisapteker graad	
Ander	

3.2

Indien u *ander* gekies het, gee asseblief meer besonderhede:

_____

4. Indien u 'n Doktorsgraad / spesialisapteker (By die SAAR as sodanig geregistreer) is , in watter area van Farmasie het u gespesialiseer?

_____

_____

5. Het u enige bykomende opleiding ontvang in nadelige geneesmiddel reaksie rapportering?

Ja	1	Nee	0

6. Indien u **ja** geantwoord het in vraag 5, waar het u opleiding ontvang? **Dui meer as een aan indien nodig**

		Dui aan (x)

6.1	Universiteits vlak (gedurende u BPharm / MPharm / PhD-graad)	
6.2	Bykomende graad	
6.3	Bykomende diploma	
6.4	Opleiding ontvang deur farmaseutiese maatskappy	
6.5	In-diens opleiding	
	Ander	

6.6 Indien u **ander** gekies het, gee asseblief meer besonderhede:

_____

7. Het u enige bykomende opleiding in die volgende velde? **Dui meer as een aan indien nodig.**

	Opleiding	**Dui aan (x)**
7.1	Farmako-waaksaamheid	
7.2	Nadelige geneesmiddel reaksie en geneesmiddel verwante probleme	
7.3	Toksikologie	
7.4	Geen	

8. Dui aan in watter gesondheid sektor u tans praktiseer

	Sektor	**Dui aan (X)**
8.1	In ’n apteek in die openbare gesondheid sektor	
8.2	In ’n apteek in die private gesondheid sektor	
8.3	Nie van toepassing	

9. Dui u huidige en vorige werksomgewing aan (meer as een antwoord word aanvaar).

	Sektor	**Huidige**	**Vorige**
9.1	Gemeenskap apteek		
9.2	Korporatiewe gemeenskap apteek		
9.3	Privaat hospitaal apteek		
9.4	Publieke hospitaal apteek		
9.5	Mediese fonds omgewing		
9.6	Kliniese navorsing		

	Sektor	Huidige	Vorige
9.7	Akademie		
9.8	Koerier apteek		
9.9	Groothandel apteek / verspreidingsfasiliteite		
9.10	Vervaardiging / produksie		
9.11	Medisyne registrasie / beheer		
9.12	Kwaliteitsbeheer		
9.13	Militêre dienste		
9.14	Korrektiewe dienste		
	Ander		

9.15 Indien u *ander* geselekteer het, wees asseblief spesifiek: _____

10. Dui u totale jare van ondervinding as 'n praktiserende apteker aan.

	Totale jare	Dui aan (X)
10.1	< 5 jaar	
10.2	5-10 jaar	
10.3	11-15 jaar	
10.4	16-20 jaar	
10.5	>20 jaar	

11. Hoeveel aantal jare ondervinding het u in die volgende velde? **Dui die totale aantal jare aan in die velde van toepassing.**

	Sektor	Aantal jare
11.1	Gemeenskap apteek	
11.2	Korporatiewe gemeenskap apteek	
11.3	Hospitaal – privaat	
11.4	Hospitaal – provinsiaal	
11.5	Mediese fonds omgewing	
11.6	Kliniese navorsing	

11.7	Akademie	
11.8	Koerier apteek	
11.9	Groothandel / verspreidingsfasiliteite	
11.10	Vervaardiging / produksie	
11.11	Medisyne registrasie / beheer	
11.12	Kwaliteitsbeheer	
11.13	Militêre dienste	
11.14	Korrektiewe dienste	
11.15	Ander	

B. RAPPORTERING VAN NADELIGE GENEESMIDDELREAKSIES:

Dui die antwoord van toepassing aan met 'n (x):

1. Het u enige nadelige geneesmiddel reaksies geïdentifiseer (Beantwoord al die vrae).

	Period	**Yes**	**No**
1.1	Gedurende die afgelope 3 maande	1	0
1.2	Gedurende die afgelope 3 tot 6 maande	1	0
1.3	Gedurende die afgelope 6 tot 12 maande	1	0
1.4	Meer as 12 maande gelede	1	0

2. Het u al van tevore van nadelige geneesmiddel reaksie rapportering gehoor?

Ja	1	Nee	0

3. Weet u waar om die nadelige geneesmiddel reaksie rapportering vorms te kry?

Ja	1	Nee	0

4. Waar sal u die nadelige geneesmiddelreaksievorms kry indien u dit benodig? **Meer as een antwoord is aanvaarbaar.**

	Area	**Dui aan (x)**
4.1	Die apteek / area waarin u tans praktiseer	

	Area	**Dui aan (x)**
4.2	Vanaf u eie persoonlike lêers	
4.3	Vanaf die apteek groep se hoofkantoor	
4.4	Op die Medisynebeheerraad se webwerf	
4.5	Vanaf 'n harde kopie van die Wet op die Beheer van Medisyne en Verwante Stowwe (101 van 1965) beskikbaar in my huidige werksomgewing	
4.6	Op die webblad van die Mediese Universiteit van Suid Afrika (MEDUNSA)[8]	
4.7	Vanaf die Universiteit van die Vrystaat se Farmako-waaksaamheidseenheid in Bloemfontein	
4.8	Ek weet nie waar om die vorms te kry nie	
	Ander	

4.9 Indien u **ander** gekies het, gee asseblief meer besonderhede:

_____

5. Gee 'n skatting van die hoeveelheid nadelige geneesmiddel reaksies wat u gerapporteer het in u professionele loopbaan.

Geen	1	1-5	2	6-10	3	>10	4

6. Indien u al 'n nadelige geneesmiddel reaksie in u professionele loopbaan gerapporteer het, waar het u gepraktiseer gedurende hierdie insidente? **Merk meer as een indien nodig**

	Sektor	**Dui aan (X)**
6.1	Publieke gesondheid sektor	
6.2	Private gesondheid sektor	
	Ander	

6.3 Indien u *ander* gekies het, gee asseblief meer besonderhede:

_____

7. Indien u wel 'n nadelige geneesmiddel reaksie gerapporteer het, antwoord asseblief die volgende twee vrae so goed as moontlik.

7.1 Gee 'n kort beskrywing van die mees onlangse gerapporteerde nadelige geneesmiddel reaksie.

[8] Currently the Sefako Makgatho Health Science University

_____

_____

_____

_____

7.2 Gee 'n kort beskrywing van die proses wat u gevolg het om die nadelige geneesmiddel reaksie te rapporteer:

_____

_____

_____

_____

8. Watter nadelige geneesmiddel reaksies dink u moet gerapporteer word? **Antwoord asseblief alle vrae.**

	Geneesmiddel verwante reaksie	**Ja**	**Nee**
8.1	Alle ernstige reaksies	1	0
8.2	Onverwagse / onbekende reaksies	1	0
8.3	Bekende nadelige geneesmiddel reaksies	1	0
8.4	Onverwagse terapeutiese effekte	1	0
8.5	Reaksies veroorsaak deur oor-die-toonbank medisyne (ongeskeduleerde medisyne)	1	0
8.6	Reaksies veroorsaak deur oor-die-toonbank medisyne (skedules 1 & 2)	1	0
8.7	Reaksies veroorsaak deur voorgeskrewe medisyne (skedules 3 tot 6)	1	0
8.8	Nadelige reaksies met entstowwe	1	0
8.9	Reaksies teenoor kruie en tradisionele medisyne	1	0
8.10	Nadelige reaksies wat nie in die ingeslote voubiljet aangetoon word nie.	1	0
8.11	'n Reaksie deur 'n interaksie tussen geneesmiddels veroorsaak	1	0
8.12	'n Reaksie deur 'n voedsel-geneesmiddel interaksie veroorsaak	1	0
8.13	Nadelige geneesmiddel reaksie as gevolg van 'n medikasie fout	1	0

9. Watter produkstabiliteitsprobleme dink u moet gerapporteer word?

	Geneesmiddelstabiliteitsprobleem	**Ja**	**Nee**

9.1	Produk kontaminasie as gevolg van onreinheid wat plaasgevind het gedurende produksie of verpakking en storing van die produk.	1	0
9.2	Foutiewe komponente wat skadelik is vir die pasiënt en kan lei tot 'n defek.	1	0
9.3	Moontlike produk stabiliteit (chemiese en fisiese voorkoms tydens verpakking en storing).	1	0
9.4	Swak verpakking en etikettering van die produk.	1	0

9.5 Ander, spesifiseer asseblief: _____

10. Het u al enige nadelige geneesmiddel reaksie waargeneem wat die volgende veroorsaak het?

		Ja	**Nee**
10.1	Hospitalisering	1	0
10.2	'n Lewensbedreigende situasie	1	0
10.3	'n Kongenitale abnormaliteit	1	0
10.4	Afsterwe van 'n pasiënt	1	0
10.5	Enige veluitslag oor verskeie dele van die liggaam	1	0
10.6	'n Gestremdheid	1	0

11.1 Het u al voltooide nadelige geneesmiddel reaksie vorms vanaf 'n pasiënt / dokter ontvang?

	Ja	**Nee**	**Indien ja, hoeveel het u ontvang**
Pasiënt	1	0	
Dokter	1	0	

11.2 Beskryf wat u met die voltooide vorm gedoen het?

_____

_____

_____

12. Dink u nadelige geneesmiddel reaksies kan gerapporteer word rakende die volgende:

		Ja	**Nee**
12.1	Geskeduleerde medisyne	1	0
12.2	Oor-die-toonbank medisyne	1	0
12.3	Mediese toestelle	1	0
12.4	Al drie bogenoemde opsies	1	0

13. Watter gesondheidswerkers dink u moet die nadelige geneesmiddel reaksies rapporteer?

	Gesondheidswerker	**Ja**	**Nee**
13.1	Mediese praktisyn	1	0
13.2	Aptekers	1	0
13.3	Geregistreerde verpleegster	1	0
13.4	Tandarts	1	0
13.5	Fisioterapeut	1	0

14. Indien u 'n nadelige geneesmiddel reaksie gaan rapporteer, aan wie of aan watter entiteit sal u dit rapporteer?

		Dui aan (x)
14.1	Ek weet nie aan wie om die reaksie te rapporteer nie	
14.2	Ek sal die reaksie aan die pasiënt se dokter rapporteer, sodat hulle die vorms kan voltooi.	
14.3	Ek sal die reaksie aan die betrokke farmaseutiese maatskappy rapporteer	
14.4	Ek sal die reaksie aan die Medisynebeheerraad rapporteer.	
14.5	Ek sal die reaksie aan die Farmako-waaksaamheideenheid, NADEMC	
14.6	Ek sal die nadelige geneesmiddel reaksie gedurende kliniese proewe aan die Medisynebeheerraad rapporteer	
14.7	Ek sal nadelige geneesmiddel reaksies van antiretrovirale terapie rapporteer aan die Mediese Universiteit van Suid Afrika (MEDUNSA)[9].	
14.8	Ek sal nadelige geneesmiddel reaksies rapporteer aand die Universiteit van die Vrystaat se Farmako-waaksaamheideenheid in Bloemfontein.	
14.9	Ek sal die nadelige geneesmiddel reaksie gedurende kliniese proewe aan die betrokke farmaseutiese maatskappy rapporteer.	
14.10	Ek sal die reaksie aan 'n ander entiteit rapporteer	

14.11 Indien u vraag 14.10 geselekteer het, aan wie sal u die reaksie rapporteer?

_____

_____

[9] Currently the Sefako Makgatho Health Science University.

15. Aan wie dink u moet pasiënte se nadelige geneesmiddel reaksies gerapporteer word? **Dui meer as een antwoord aan indien nodig.**

	Raporteringsinstansies	**Dui aan (x)**
15.1	Ek is onseker aan wie pasiënte moet rapporteer	
15.2	Aan die dokter wat die medikasie voorgeskryf het wat verantwoordelik is vir die nadelige reaksie rapporteer	
15.3	Aan die vervaardiger van die betrokke geneesmiddel (Farmaseutiese maatskappy) rapporteer	
15.4	Aan die Suid-Afrikaanse Aptekersraad rapporteer	
15.5	Aan Suid-Afrika se Farmako-waaksaamheideenheid, NADEMC wie dien as die sekretariaat van die Medisynebeheerraad rapporteer	
15.6	Aan die Departement van Farmakologie van die Universiteit van Kaapstad	
15.7	Aan die Mediese Universiteit van Suid Afrika (MEDUNSA)[10]	
158	Aan die Universiteit van die Vrystaat se Farmako-waaksaamheideenheid in Bloemfontein	
15.9	Aan hulle aptekers wanneer die pasiënt vir hulle herhaling van die medikasie terug gaan	
	Ander	

15.10 Indien u **ander** geselekteer het, wees asseblief spesifiek: _____

16. Die volgende stappe moet geneem word wanneer 'n nadelige geneesmiddel reaksie geïdentifiseer word. **Dui u vlak van ooreenstemming aan teenoor die volgende verklarings.**

1	**2**	**3**	**4**	**5**
Stem glad nie saam nie	**Stem nie saam nie**	**Onseker**	**Stem saam**	**Stem heeltemal saam**

	Verklaring	**1**	**2**	**3**	**4**	**5**
16.1	Kontak die pasiënt se geneesheer sodat hy/sy die nadelige geneesmiddel reaksie kan rapporteer.					
16.2	Stuur die pasiënt terug na hulle dokter.					
16.3	Voltooi die nadelige geneesmiddel reaksie vorm met die inligting ontvang vanaf die pasiënt en stuur die vorm na die Medisynebeheerraad.					

[10] Currently the Sefako Makgatho Health Science University

16.4	Gee die pasiënt die nadelige geneesmiddelreaksievorms om op hulle eie tyd te voltooi.					
16.5	Rapporteer die nadelige geneesmiddel reaksie op die vorm asook op die pasiënt se lêer.					
16.6	Niks hoef gedoen te word nie.					
16.7	Bel die dokter om die terapie te verander.					

17. Dui die inligting wat benodig word aan, om 'n nadelige geneesmiddel reaksie te rapporteer op die amptelike vorm:

	Inligting benodig	**Ja**	**Nee**
17.1	Pasiënt se land van verblyf	1	0
17.2	Die apteker/dokter (rapporterende persoon) se naam, adres en kwalifikasie.	1	0
17.3	Die pasiënt se van, ouderdom, geslag en verwysingsnommer.	1	0
17.4	Die produk wat vermoedelik die nadelige reaksie veroorsaak het.	1	0
17.5	Die vermoedelik nadelige geneesmiddel reaksie geobserveer / ervaar deur die pasiënt.	1	0
17.6	Dosering van die medisyne deur die pasiënt geneem.	1	0
17.7	Duur van die behandeling (voor die reaksie)	1	0
17.8	Tyd tot aanvang van nadelige geneesmiddel reaksie	1	0
17.9	Uitkoms van die nadelige geneesmiddel reaksie (dood, hospitalisering, gestremdheid)	1	0
17.10	Produk wat die nadelige geneesmiddel reaksie veroorsaak het se handelsnaam	1	0
17.11	Produk wat die nadelige geneesmiddel reaksie veroorsaak het se lotnommer	1	0
17.12	Produk wat die nadelige geneesmiddel reaksie veroorsaak het se vervaldatum	1	0
17.13	Produk wat die stabiliteit probleem veroorsaak het se lotnommer.	1	0
17.14	Produk wat die stabiliteit probleem veroorsaak het se vervaldatum.	1	0
17.15	Produk wat die stabiliteit probleem veroorsaak het se handelsnaam	1	0
17.16	Laboratorium toetsresultate	1	0

C. <u>PERSEPSIE TEENOOR NADELIGE GENEESMIDDELREAKSIE RAPPORTERING EN DIE HINDERNISSE DAARAAN GEKOPPEL</u>:

1. Is u as apteker gewillig om nadelige geneesmiddel reaksies te rapporteer?

	Dui aan (x)
Ja	1
Nee	0

Indien **NEE**, hoekom is u nie gewillig om nadelige geneesmiddel reaksies te rapporteer nie?

_____

_____

2. Na u mening, het u die vermoë om nadelige geneesmiddel reaksies te rapporteer?

	Dui aan (x)
Ja	1
Nee	0

Indien **NEE**, hoekom het u nie die vermoë om nadelige geneesmiddel reaksies te rapporteer nie?

_____

_____

3. Reflekteer u siening / persepsie teenoor nadelige geneesmiddel reaksie rapportering. **Dui asseblief u vlak van ooreenstemming aan teenoor die volgende stellings.**

1	**2**	**3**	**4**	**5**
Stem glad nie saam nie	**Stem nie saam nie**	**Onseker**	**Stem saam**	**Stem sterk saam**

	Verklaring	**1**	**2**	**3**	**4**	**5**
3.1	Aptekers is bewus van nadelige geneesmiddel reaksie rapportering in gesondheidsorgfasiliteite.					
3.2	Aptekers is bewus van die proses om te volg vir die rapportering van nadelige geneesmiddel reaksies in gesondheidsorgfasiliteite.					
3.3	U word voorsien van die nodige nadelige geneesmiddel reaksie rapportering vorms.					
3.4	U het genoeg opleiding gehad om nadelige geneesmiddel reaksies te kan identifiseer (farmakologiese kennis).					
3.5	U het opleiding ontvang om nadelige geneesmiddel reaksies te kan rapporteer.					

3.6	Die apteek waarin u tans praktiseer, het die nodige standaard werksprosedures om nadelige geneesmiddel reaksies te rapporteer.					
3.7	U het voorheen terugvoer vanaf die Nasionale Farmako-bewakingsentrum ontvang aangaande 'n gerapporteerde geneesmiddel reaksie.					

4. Moedig die volgende faktore u aan om nadelige geneesmiddel reaksies te rapporteer?

	Verklaring	**1**	**2**	**3**	**4**	**5**
4.1	Rapportering van nadelige geneesmiddel reaksies moet verpligtend wees vir alle aptekers.					
4.2	Opleiding vanaf die Nasionale Farmako-waaksaamheideenheid.					
4.3	Terugvoer vanaf die Nasionale Farmako-waaksaamheideenheid sal my aanmoedig om nadelige geneesmiddel reaksies te rapporteer.					
4.4	Aptekers sal meer gemotiveerd voel om nadelige geneesmiddel reaksies te rapporteer indien die rapportering vorms minder ingewikkeld was.					
4.5	Installering van 'n elektroniese sisteem vir die rapportering van nadelige geneesmiddel reaksies sal rapportering vermeerder.					
4.6	Die gesondheidsorgkoste sal voordeel trek uit 'n Farmako-waaksaamheidpesialiste in die farmaseutiese sektor.					

5. Die volgende faktore kan u ontmoedig om nadelige geneesmiddel reaksies te rapporteer?

No.	**Verklaring**	**Stem saam**	**Stem nie saam nie**	**Nie van toepassing***
5.1	Gebrek aan kennis om die nadelige geneesmiddel reaksies te rapporteer te identifiseer / U weet nie hoe om die nadelige reaksie te identifiseer nie.	1	0	2
5.2	Gebrek aan vertroue in verband met wanneer 'n nadelige reaksie gerapporteer moet word.	1	0	2
5.3	Ek weet nie waar om 'n nadelige geneesmiddelreaksievorm te kry nie, wat veroorsaak dat ek nie in staat is om die reaksie te rapporteer nie.	1	0	2
5.4	Nadat die reaksie gerapporteer is, ontvang ek geen terugvoer vanaf die Farmako-bewakingseenheid af nie.	1	0	2
5.5	Die rapportering van nadelige geneesmiddel reaksies is tydrowend.	1	0	2
5.6	Nadelige geneesmiddelreaksievorms is te ingewikkeld om te voltooi, wat 'n toename in my werkslading veroorsaak.	1	0	2
5.7	Nadelige geneesmiddel reaksie rapportering is nie deel van my gesondheidsorg praktyk nie.	1	0	2

No.	Verklaring	Stem saam	Stem nie saam nie	Nie van toepassing*
5.8	Ek glo dat geneesmiddels op die mark veilig is om te gebruik.	1	0	2
5.9	Ek vrees wetlike aanspreeklikheid indien die nadelige geneesmiddel reaksie gerapporteer word.	1	0	2
5.10	Ek vrees dat die nadelige geneesmiddel reaksie veroorsaak was deur 'n medikasie fout wat deur my gemaak is.	1	0	2
5.11	Daar is geen nadelige geneesmiddelreaksievorms beskikbaar in my werksomgewing nie.	1	0	2
5.12	Ek is van mening dat die rapportering van nadelige geneesmiddel reaksie nie verpligtend is nie.	1	0	2
5.13	Daar is geen aansporing (finansieel of ander erkenning) betrokke vir die rapportering van die reaksies nie.	1	0	2
5.14	Ek ervaar ander uitdagings as die bogenoemde.	1	0	2

5.14.1 Indien u by vraag 5.14 "**saam stem**", wees asseblief spesifiek oor die uitdaging wat u ervaar:

_____

_____

6. Dink u die rapportering van nadelige geneesmiddel reaksies moet verpligtend of vrywillig wees?

Verpligtend	1	Vrywillig	0

7. Verstaan u die prosedure vir die rapportering van nadelige geneesmiddel reaksies?

Ja	1
Nee	0

8. Het u standaard werksprosedures beskikbaar aangaande die rapportering van nadelige geneesmiddel reaksies in u werksomgewing?

Ja	1
Nee	0
Nie van toepassing	2

9. Het u enige voorstelle om die Suid-Afrikaanse rapportering sisteem van nadelige geneesmiddel reaksies te verbeter in die farmaseutiese sektor waar u werksaam is?

Ja	1
Nee	0

_____

_____

D. KENNIS VAN FARMAKO-BEWAKING IN SUID-AFRIKA:

1. Hoe vertroud is u met die term Farmako-waaksaamheid (Pharmacovigilance in Engels)? Dui asseblief u vlak van ooreenstemming aan teenoor die volgende verklarings

Glad nie vertroud nie	Min vertroud	Gedeeltelik vertroud	Vertroud	Baie vertroud
1	2	3	4	5

2. Definieer Farmako-waaksaamheid in u eie woorde.

_____

_____

3. Wie tree op as Suid-Afrika se Farmako-waaksaamheid?

_____

4. Reflekteer u siening / persepsie teenoor Farmako-waaksaamheid in Suid-Afrika. **Dui asseblief u vlak van ooreenstemming aan teenoor die volgende verklarings.**

1	2	3	4	5
Stem glad nie saam nie	**Stem nie saam nie**	**Onseker**	**Stem saam**	**Stem heeltemal saam**

	Verklaring	1	2	3	4	5
4.1	Farmako-waaksaamheid in Suid-Afrika of die identifisering van nadelige geneesmiddel reaksie moedig nasionale regulatoriese besluite aan.					
4.2	Geneesmiddel monitering in SA is van geweldige waarde vir die opsporing van nadelige geneesmiddel reaksies.					
4.3	Nadelige geneesmiddelreaksiemonitering help met die versekering van veilige en effektiewe produkte aan pasiënte.					

	Verklaring	1	2	3	4	5
4.4	Die resultate van nadelige geneesmiddelreaksiemonitering is van opvoedkundige waarde.					
4.5	Nadelige geneesmiddel reaksie rapportering is van belang vir die verbetering van inligting t.o.v. etikettering/ingeslote voubiljette.					
4.6	Die effektiwiteit van 'n nasionale bemarking toesigprogram is direk afhanklik van die aktiewe deelname van gesondheidswerkers.					
4.7	Gesondheidswerkers (dokters, aptekers, verpleegsters, tandartse en ander) moet nadelige geneesmiddel reaksies rapporteer as deel van hulle professionele verantwoordelikheid, selfs as hul twyfel oor die presiese verhouding met die betrokke geneesmiddel.					
4.8	Farmako-waaksaamheid is belangrik vir die verbetering van pasiënt versorging en veiligheid teenoor die gebruik van medisyne.					
4.9	Farmako-waaksaamheid verbeter openbare gesondheidsorg en veiligheid rakende die gebruik van medisyne.					
4.10	Farmako-waaksaamheid bevorder opleiding in die rapportering van nadelige geneesmiddel reaksies.					
4.11	Die huidige nadelige geneesmiddel reaksie rapportering sisteem in SA is voldoende.					
4.12	Indien meer aptekers nadelige geneesmiddelreaksies dokumenteer sal dit 'n positiewe verskil in die huidige gesondheidsorgsisteem van Suid-Afrika maak.					
4.13	Dit sal finansieel voordelig wees vir beide privaat en publieke hospitale indien meer gesondheidswerkers nadelige geneesmiddel reaksies rapporteer.					
4.14	Die rapportering van nadelige geneesmiddel reaksies vorm deel van die Apteker se Omvang van Praktyk					
4.15	Meer opleiding is nodig in die veld aangaande spesifieke produkte deur farmaseutiese maatskappye.					
4.16	Meer opleiding in farmako-waaksaamheid is nodig by farmasieskole in die voorgraadse programme.					
4.17	Meer voortdurende opvoedkundige programme in farmako-waaksaamheid is nodig by farmasieskole en ander opleidinginstansies.					
4.18	Die rapportering van nadelige geneesmiddel reaksies is ingesluit in u taakooreenkoms in u huidige werksomgewing.					
4.19	U is gewillig om bykomende opleiding te ontvang in die rapportering van nadelige geneesmiddel reaksies.					

5. **E. VOORSTELLE EN KOMMENTAAR:**

1. Het u enige voorstelle of kommentaar wat u graag sal wil byvoeg?

_____

ANNEXURE C: ADVERSE DRUG REACTION REPORTING FORM

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

ADVERSE DRUG REACTION (ADR)/ PRODUCT QUALITY PROBLEM REPORT FORM (PUBLIC AND PRIVATE SECTOR)
(Including Herbal Products)

MCC MEDICINES CONTROL COUNCIL

Reports will be shared with the Pharmacovigilance Centre for Public Health Programmes (PCPHP) - 0123959506

Reporting Health Care Facility/Practice					
Tel: 012 395 8197 (MCC) 021 447 1618 (NADEMC) **Fax:** 086 620 7253 **E-mail:** adr@health.gov.za	Facility/Practice				
	District		Tel		
	Province		Fax		

Patient Details									
Patient Initials		File/Reference Number		Date of Birth/Age					
Sex	☐ M ☐ F ☐ Unk	Race		Weight (kg)		Height (cm)		Pregnant?	☐ N ☐ Y
Allergies		Estimated Gestational Age at time of reaction							

Suspect Medicine(s) [Medicines suspected to have caused the ADR]

Trade Name [Generic Name if Trade Name is unknown]	Route	Dose (mg) and Interval	Date Started/Given	Date Stopped	Reason for use	Batch Number	Expiry Date

All other Medicines Patient was taking at time of reaction [Including over-the-counter and herbal products]

Trade Name [Generic Name if Trade Name is unknown]	Route	Dose (mg) and Interval	Date Started/Given	Date Stopped	Reason for use	Batch Number	Expiry Date

Adverse Drug Reaction/Product Quality Problem

Date and time of onset of reaction		Date reaction resolved/duration	

Please describe Adverse Reaction/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention(tick all that apply)	**Patient Outcomes (tick all that apply)**
☐ No intervention	☐ ADR recovered/resolved☐ recovering/resolving
☐ Intervention unknown	☐ not recovered/not resolved
☐ Patient Counselled/non-medical treatment	☐ Patient Died: Date of death:_____
☐ Discontinued Suspect Drug; **Replaced with:**_____	☐ Impairment/Disability ☐ Congenital Anomaly
☐ Decreased Suspect Drug Dosage; **New Dose:**_____	☐ Patient Hospitalised or Hospitalisation prolonged
☐ Treated ADR - with:_____	☐ Life Threatening ☐ Other:_____
☐ Referred to Hospital: **Hospital Name**_____	☐ ADR reappeared after restarting suspect drug/similar drug (rechallenge)?: ☐ N ☐ Y ☐ Not done ☐ Unknown
☐ Other Intervention (e.g. dialysis): _____	

Laboratory Results			**Additional Laboratory Results**		
Lab Test	**Test Result**	**Test Date**	**Lab Test**	**Test Result**	**Test Date**

Co-morbidities/Other Medical Condition(s)

Reported by			
Name		E-mail	
Designation	☐ Nurse ☐ Pharmacist ☐ Doctor ☐ Other:	Telephone	
Date reported:		Signature	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR **v4.0 07/16**

Adverse drug reactions *ARF 1*

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:
- medications (drugs, vaccines and biologicals)
- medical devices (including *in-vitro* diagnostics)
- complementary / alternative medicines (including traditional, herbal remedies, etc)

Please report especially:
- adverse drug reactions to newly marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report Product Quality Problems such as:
- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Report even if:
- you're not certain the product caused the event
- you don't have all the details

Important numbers:

Investigational Products and Product Quality Problems:
- fax: (012) 395-9201
- phone: (012) 395-8010
- email: Wondo.Mlungisi@health.gov.za

Adverse Events Following Immunisation:
- fax: (012) 395 8486
- phone: (012) 395 8914/8273
- email: Makgomo.Mphaka@health.gov.za

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

PLEASE USE ADDRESS PROVIDED BELOW - JUST FOLD IN THIRDS, TAPE and MAIL

Postage will be paid by the Addressee
Posgeld sal deur die geadresseerde betaal word

No Postage stamp necessary if posted in the Republic of South Africa
Geen posseël nodig nie indien in die Republiek van Suid-Afrika gepos

BUSINESS REPLY SERVICE
BESIGHEIDSANTWOORDDIENS
Free Mail Number: **BNT 178**
Vryposnommer:

DEPARTMENT OF HEALTH
DEPARTEMENT VAN GESONDHEID

REGISTRAR OF MEDICINES
REGISTRATEUR VAN MEDISYNE

PRIVATE BAG / *PRIVAATSAK* X828
PRETORIA
0001

ANNEXURE D: SAPC APPROVAL

South African Pharmacy Council

Registered Office
SAPC Building
591 Belvedere Street
Arcadia, Pretoria, 0083

Postal Address
Private Bag X40040
Arcadia, 0007

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Website
www.sapc.za.org

Prof M Lubbe
Leader: Medicine Usage in SA
Faculty of Health Sciences
School of Pharmacy

martielubbe@nwu.ac.za

Our ref	Date
TA Masango	29 November 2017

Dear Prof Lubbe

PERMISSION TO USE INFORMATION FROM THE REGISTER OF PHARMACISTS AND PHARMACIES

Receipt of your electronic mail dated 21 November 2017 is herewith acknowledged.

We confirm that the information you are requesting may be used for the purpose for which you have detailed in your email. However, in using the said information, it must be noted that this is personal information and must be treated and used within the confines of the law relating to research and protection of personal information.

The South African Pharmacy Council (SAPC) will not accept any liability for inappropriate use of the information. In addition it should be noted that where possible, information must be protected from unauthorised access and distribution and be used for the sole purpose of the said research.

Kindly note that the SAPC would like to receive details of the research once same has been completed.

Yours faithfully

TA MASANGO
REGISTRAR/CEO
/ag

ANNEXURE E: ETHICAL APPROVAL

Private Bag X6001, Potchefstroom,
South Africa, 2520

Tel: (018) 299-4900
Faks: (018) 299-4910
Web: http://www.nwu.ac.za

Research Ethics Regulatory Committee
Tel: +27 18 299 4849

Email : Ethics@nwu.ac.za

ETHICS APPROVAL CERTIFICATE OF STUDY

Based on approval by **Health Research Ethics Committee (HREC)** on **04/12/2017**, the North-West University Research Ethics Regulatory Committee (NWU-RERC) hereby **approves** your study as indicated below. This implies that the NWU-RERC grants its permission that provided the special conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Pharmacists' perception towards pharmacovigilance and the reporting of adverse drug reactions in South-Africa
Study Leader/Supervisor: Prof MS Lubbe
Student: PH Jordaan-22821889
Ethics number:

N	W	U	-	0	0	1	3	7	-	1	7	-	A	1
Institution				Study Number						Year			Status	

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Single study
Commencement date: 14/11/2017 **Risk:** **Minimal**
Approval of the study is initially provided for a year, after which continuation of the study is dependent on receipt of the annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The study leader (principle investigator) must report in the prescribed format to the NWU-RERC via HREC:*
  - *annually (or as otherwise requested) on the monitoring of the study, and upon completion of the study*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *Annually a number of studies may be randomly selected for an external audit.*
- *The approval applies strictly to the proposal as stipulated in the application form. Should any changes to the proposal be deemed necessary during the course of the study, the study leader must apply for approval of these amendments at the HREC, prior to implementation. Should there be any deviations from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility the NWU-RERC and HREC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the study;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the study are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the HREC or that information has been false or misrepresented,*
    - *the required amendments, annual (or otherwise stipulated) report and reporting of adverse events or incidents was not done in a timely manner and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*
- *HREC can be contacted for further information or any report templates via Ethics-HRECApply@nwu.ac.za or 018 299 1206.*

The RERC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the RERC or HREC for any further enquiries or requests for assistance.

Yours sincerely

Prof. Refilwe Phaswana-Mafuya
Chair NWU Research Ethics Regulatory Committee (RERC)

ANNEXURE F: AUTHOR GUIDELINES: JOURNAL OF RESEARCH IN PHARMACY PRACTICE

Instructions to the Authors

About the Journal

Journal of Research in Pharmacy Practice (JRPP) is an international peer-reviewed quarterly research journal published by Wolters Kluwer Health | Medknow. This journal provides a forum for exchange of knowledge and ideas between pharmacists in all fields and sub specialties of Health-System Pharmacy Practice (including: Clinical, Hospital and Community Practice) and other healthcare professionals.

Scope of the Journal

JRPP invites submissions on all aspects of drug-related human (non-animal and non-laboratory work) studies. The main focus of the journal will be on evidence-based medication-related medical researches (with clinical pharmacists' intervention or documentation), particularly in the Eastern Mediterranean region. However, a wide range of closely related issues will be also covered. These will include clinical studies in the field of pharmaceutical care, reporting adverse drug reactions and pharmaco-epidemiology, social aspects of pharmacy practice, pharmacy education and economic evaluations of treatment protocols (e.g. cost-effectiveness studies). Local reports of medication utilization studies at hospital or pharmacy levels will only be considered for peer-review process only if they have a new and useful message for the international pharmacy practice professionals and readers.

Copyright Statement

The Editorial Process

A manuscript will be reviewed for possible publication with the understanding that it is being submitted to JRPP alone at that point in time and has not been published anywhere, simultaneously submitted, or already accepted for publication elsewhere. The journal expects that authors would authorize one of them to correspond with the Journal for all matters related to the manuscript. All manuscripts received are duly acknowledged. On submission, editors review all submitted manuscripts initially for suitability for formal review. Manuscripts that are found suitable for publication in JRPP are sent to two or more expert reviewers. During submission, the contributor is requested to provide names of two or three qualified reviewers who have had experience in the subject of the submitted manuscript. The reviewers should not be affiliated with the same institutes as the contributor/s. However, the selection of these reviewers is at the sole discretion of the editor. All articles undergo an external peer-review process which normally lasts at least between 4-6 months. The journal follows a double-blind review process, wherein the reviewers and authors are unaware of each other's identity. Every manuscript is also assigned to a member of the editorial team, who based on the comments from the reviewers takes a final decision on the manuscript. The comments and suggestions (acceptance/rejection/ amendments in manuscript) received from reviewers are conveyed to the corresponding author. If required, the author is requested to provide a point by point response to reviewers' comments and submit a revised version of the manuscript. This process is repeated till reviewers and editors are satisfied with the manuscript.

The pre-accepted manuscripts will be treated on a first-come, first served basis for the issue assignment. The uniform requirements and specific requirement of JRPP only accept the manuscripts written in American English. Manuscripts accepted for publication are copy edited for grammar, punctuation, print style, and format. Page proofs are sent to the corresponding author. The corresponding author is expected to return the corrected proofs within three days. It may not be possible to incorporate corrections received after that period. The whole process of submission of the manuscript to final decision and sending and receiving proofs is completed online. To achieve faster and greater dissemination of knowledge and information, the journal publishes articles online as Ahead of Print immediately on acceptance.

Publication Fee

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Ethics Considerations

The Journal will adhere to the principles and recommendations of the Committee on Publication Ethics (COPE), the World Association of Medical Editors (WAME) and the European Association of Science Editors (EASE). It will also follow research reporting statements of the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network. Submissions should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, developed by the International Committee of Medical Journal Editors (ICMJE).

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Identifying information should not be published in written descriptions, photographs, sonograms, CT scans, etc., and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian, wherever applicable) gives informed consent for publication. Authors should remove patients' names from figures unless they have obtained informed consent from the patients. The journal abides by ICMJE guidelines:

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2) If the manuscript contains patient images that preclude anonymity, or a description that has obvious indication to the identity of the patient, a statement about obtaining informed patient consent should be indicated in the manuscript.

Clinical Trial Registry

JRPP favors registration of clinical trials and is a signatory to the Statement on publishing clinical trials in the International biomedical journals. From January 2013 issue, JRPP would publish clinical trials that have been registered with a clinical trial registry that allows free online access to public. Registration in the following trial registries is acceptable: http://www.trialregister.nl/trialreg/index.asp; http://isrctn.org/; http://www.irct.ir/; http://www.clinicaltrials.gov/; and http://www.umin.ac.jp/ctr/. Please note that providing a valid registration number and ethical clearance for the RCTs are a must for the submission and peer review process.

Authorship Criteria

Authorship credit should only be based on substantial contributions to each of the following three components:

1. Concept and design of study or acquisition of data or analysis and interpretation of data;

2. Drafting the article or revising it critically for important intellectual content; and
3. Final approval of the version to be published.

Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient for authorship. Each contributor should have participated sufficiently in the work to take public responsibility for appropriate portions of the content of the manuscript. The order of naming the contributors should be based on the relative contribution of the contributor towards the study and writing the manuscript. Once submitted, the order cannot be changed without written consent of all the contributors. The journal prescribes a maximum number of authors for manuscripts depending upon the type of manuscript, its scope and number of institutions involved (vide infra). The authors should provide a justification, if the number of authors exceeds these limits.

Contribution Details

Contributors should provide a description of contributions made by each of them towards the manuscript. Description should be divided in following categories, as applicable: concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. Authors' contributions will be printed along with the article. One or more author(s) should take responsibility for the integrity of the work as a whole from inception to the published article and should be designated as 'Guarantor'.

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The submitted manuscripts that are not as per the “Instructions to Authors” would be returned to the authors for “Technical Modification”, before they undergo editorial/peer-review. Generally, the manuscript should be submitted in the form of two separate files:

[1] **Title Page / First Page / Covering Letter**

This file should provide:

1. The type of manuscript (review article, original article, brief communication, case report, letter to the editor, etc.), title of the manuscript, running title, names of all authors / contributors (with their highest academic degrees, designation and affiliations) and name(s) of department(s) and/or institution(s) to which the work should be credited (without the name of schools/ faculties and postal details like buildings, etc.). All information which can reveal your identity should be here. Use text / doc files. Do not zip the files;
2. Source(s) of support in the form of grants, equipment, drugs, or all of these;
3. Acknowledgment(s), if any. One or more statements should specify 1) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chair; 2) acknowledgments of technical help; and 3) acknowledgments of financial and material support, which should specify the nature of the support. This should be included in the title page of the manuscript and not in the main article file;
4. A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically, and referenced in the new paper. Copies of such material should be included with the submitted paper, to help the editor decide how to handle the matter;
5. Registration number in case of a clinical trial and where it is registered (name of the registry and its URL);
6. “Conflicts of Interest” of each author / contributor. A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form;
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The main text of the article, beginning from “Abstract” till “References” (including tables) should be in this file. The file must not contain any mention of the authors' names or initials or the institution at which the study was done or acknowledgments. Use doc files. Do not zip the files. **Limit the file size to 1 MB**. To reduce the size of the file (if file size is large), graphs can be submitted as images separately without incorporating them in the article file. The pages should be numbered consecutively, beginning with the first page of the blinded article file.

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Submit good quality color images of size 4” × 6” and not more than 400KB size. Images should be uploaded in JPEG, TIFF, BMP, or GIF format. JPEG is most preferred format. Size of the image can be reduced by decreasing the actual height and width of the images. Do not zip the files. Legends for the figures / images should be included at the end of the article file.

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This form has to be submitted in original with the signatures of all the contributors at the time of submission from the authors’ area on http://www.journalonweb.com/jrpp, as a scanned image.

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The revised version of the manuscript should be submitted online in a manner similar to that used for submission of the manuscript for the first time. However, there is no need to submit the “First Page” or “Covering Letter” file while submitting a revised version. When submitting a revised manuscript, contributors are requested to include the referees’ remarks along with point to point clarification. In addition, they are expected to mark the changes as underlined or colored text in the article.

Type of Manuscripts

Type of Manuscript *	Review article	Original article	Brief communication	Case report †	Letter to the Editor ‡
Including …	-	Randomized controlled trials, intervention studies, pharmacy practice, outcome studies, case-control series, medication utilization studies, cost-effectiveness studies, and surveys with high response rate	Like as "Original articles"	New, interesting and really rare cases with a clear rational of its report	These should be short and including decisive observations
Scope	-	All aspects of drug-related human (non-animal and non-laboratory work) studies	Like as "Original articles"	Drug-related human reports	Preferably be related to articles previously published in the Journal or views expressed in the journal
Word count limitation (including Abstract, and References)	5000	3000 - 3500	2000	1500	500
Headings	Abstract (un-structured), Keywords, Introduction, Methods, Results, Conclusion, References, Table and Figure legends	Abstract, Keywords, Introduction, Methods, Results, Discussion, References, Table and Figure legends (Do not divide the Introduction, Methods, Results and Discussion into various sub-headings)	Like as "Original articles"	Abstract (un-structured), Keywords, Introduction, Case report, Discussion, Reference, Tables and Legends	To the Editor
Abstract	Up to 250 words; un-structured	Up to 250 words; structured as: Objective, Methods, Findings, Conclusion	Up to 200 words; structured as: Objective, Methods, Findings, Conclusion	Up to 200 words; un-structured	-
References	Unlimited	Up to 30	Up to 12	Up to 10	Up to 5
Tables and Figures	Unlimited	Up to 4	Up to 2	Up to 3	-
Authors §	Up to 6	Up to 8	Up to 5	Up to 4	Up to 2

* Editorial, Guest Editorial, and Commentary are solicited by the editorial board.
† JRPP rarely publishes case reports but new, interesting and really rare cases with a clear rational of its report may be taken to consideration. They should be unique, describing a great diagnostic or therapeutic challenge and providing a learning point for the readers. Cases with clinical significance or implications will be given priority.
‡ Letters must not duplicate other material published or submitted for publication. Letters considered for publication undergo external peer review.
§ Other persons who have contributed to the study may be indicated in an "Acknowledgment", with their permission, including their academic degrees, affiliation, contribution to the study, and an indication if compensation was received for their role.

Introduction: State the purpose and summarize the rationale for the study or observation. Please provide a clear research question at the end of Introduction section.

Methods: This part should not be structured or have any sub-headings. In the "Methods" section, please start with the type of study, time period and place which it is carried out. It should include and describe the following aspects (without sub-headings):

Ethics: When reporting studies on human beings, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013 (available at: http://jamanetwork.com/journals/jama/fullarticle/1760318). For prospective studies involving human participants, authors are expected to mention about approval of (regional / national / institutional or independent Ethics Committee or Review Board, obtaining informed consent from adult research participants and obtaining parent(s)' assent for children aged over 7 years participating in the trial. The age beyond which assent would be required could vary as per regional and/or national guidelines. Ensure confidentiality of subjects by desisting from mentioning participants' names, initials or hospital numbers, especially in illustrative material.

Evidence for approval by a local Ethics Committee (for both human studies) must be supplied by the authors on demand. The ethical standards of experiments must be in accordance with the guidelines provided by the "World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects" (http://jamanetwork.com/journals/jama/fullarticle/1760318) for studies involving human beings. The journal will not consider any paper which is ethically unacceptable. A statement on ethics committee permission and ethical practices must be included in all research articles under the "Methods" section.

Selection and Description of Participants: Describe your selection of the observational or experimental participants (patients, and controls) clearly, including eligibility and exclusion criteria and a description of the source population. Reports of randomized clinical trials should present information on all major study elements, including the protocol, assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding), based on the CONSORT Statement (http://www.consort-statement.org).

Reporting Guidelines for Specific Study Designs:

Initiative	Type of Study	Source
CONSORT	Randomised trials	http://www.equator-network.org/reporting-guid
STROBE	Observational studies	http://www.equator-network.org/reporting-guid
PRISMA	Systematic reviews and meta-analyses	http://www.equator-network.org/reporting-guid
CARE	Case reports	http://www.equator-network.org/reporting-guid

Statistics: Whenever possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Exact methods should be used as extensively as possible in the analysis of categorical data. For analysis of measurements, non-parametric methods should be used to compare groups when the distribution of the dependent variable is not normal. Results should be presented with only as much precision as is of scientific value. For example, measures of association, such as odds ratios, should ordinarily be reported to two significant digits. Measures of uncertainty, such as confidence intervals, should be used consistently, including in figures that present aggregated results. Except when one-sided tests are required by study design, such as in non-inferiority trials, all reported P values should be two-sided. In general, P values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as $P < 0.001$. Notable exceptions to this policy include P values arising in the application of stopping rules to the analysis of clinical trials and genetic-screening studies. Authors should report losses to observation (such as dropouts from a clinical trial). When data are summarized in the "Results" section, specify the statistical methods used to analyze them. Avoid non-technical uses of technical terms in statistics, such as 'random' (which implies a randomizing device), 'normal', 'significant', 'correlations', and 'sample'. Define statistical terms, abbreviations, and most symbols. Specify the computer software and each analytical tests used.

Results: This part should not be structured or have any sub-headings. Results should start with baseline parameters and comparison of groups. Present your results in a logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra- or supplementary

materials and technical detail can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

When data are summarized in the "Results" section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Where scientifically appropriate, analysis of data by variables such as age and sex should be included.

Discussion: This part must include summary of:

Key Findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis);

Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation);

Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to? if not, could one be reasonably done here and now?; what this study adds to the available evidence; effects on patient care and health policy; possible mechanisms);

Controversies raised by this study; and *Future research directions* (for this particular research collaboration, underlying mechanisms, clinical research).

Do not repeat in detail data or other material given in the "Introduction" or the "Results" section. In particular, contributors should avoid making statements on economic benefits and costs unless their manuscript includes economic data and analysis. Avoid claiming priority and alluding to work that has not been completed. New hypotheses may be stated if needed, however they should be clearly labeled as such. About 40 references can be included. These articles generally should not have more than **six** authors.

References: References should be numbered consecutively in the order in which they are first mentioned in the text (not in alphabetic order). Identify references in text, tables, and legends by Arabic numerals in superscript with square bracket after the punctuation marks. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text at the point where the table or figure is first mentioned. Use the style of the examples below, which are based on the formats used by the National Library of Medicine (NLM) in Index Medicus. The titles of journals should be abbreviated according to the style used in Index Medicus. Use complete name of the journal for non-indexed journals. Avoid using abstracts as references. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source. Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text.

For presenting different types of references, please refer to ICMJE Guidelines: http://www.icmje.org, or http://www.nlm.nih.gov/bsd/uniform_requirements.html.

Tables:

- Tables should be self-explanatory and should not duplicate textual material.
- Tables with more than 10 columns and 25 rows are not acceptable.
- Number tables, in Arabic numerals, consecutively in the order of their first citation in the text and supply a brief title for each.
- Place explanatory matter in footnotes, not in the heading.
- Explain in footnotes all abbreviations that are used in each table.
- Obtain permission for all fully borrowed, adapted, and modified tables and provide a credit line in the footnote.
- For footnotes, use the following symbols, in this sequence: *, †, ‡, §, ||,¶ , **, ††, ‡‡

- Tables with their legends should be provided at the end of the text after the references. The tables along with their number should be cited at the relevant place in the text.

Illustrations (Figures):

- Figures should be numbered consecutively according to the order in which they have been first cited in the text.
- Labels, numbers, and symbols should be clear and of uniform size. The lettering for figures should be large enough to be legible after reduction to fit the width of a printed column.
- The photographs and figures should be trimmed to remove all the unwanted areas.
- If photographs of individuals are used, their pictures must be accompanied by written permission to use the photograph.
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- The Journal reserves the right to crop, rotate, reduce, or enlarge the photographs to an acceptable size.

Checklist

It is strongly recommended to consider the following checklist while preparing the manuscript.

√	Items
Covering Letter	
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	Previous publication / presentations mentioned
	Source of funding mentioned
	Conflicts of interest disclosed
Authors/Names	
	Author for correspondence, with academic e-mail address provided
	Number of contributors restricted as per the instructions
	Identity not revealed in paper except title page (e.g. name of the institute in “Methods”, citing previous study as 'our study', names on figure labels, name of institute in photographs, etc.)
Presentation and Format	
	Title page contains all the desired information
	Running title provided (not more than 50 characters)
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	Abstract provided (with the maximum allowed number of words)
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	Send the article file without ‘Track Changes’
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	Write the full term for each abbreviation at its first use in the abstract, keywords and text separately, unless it is a standard unit of measure. Numerals from 1 to 10 spelt out
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	If a brand name is cited, supply the manufacturer's name and address (city and state/country).
	Species names should be in italics
Tables and Figures	
	No repetition of data in tables and graphs and in text
	Actual numbers from which graphs drawn, provided
	Figures necessary and of good quality (colour)
	Table and figure numbers in Arabic letters (not Roman)

	Figure legends provided (not more than 40 words)
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	Credit note for borrowed figures / tables provided
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Our helpful **guide** to make your paper more discoverable with Search Engine Optimization.

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Manuscript Preparation

General guidelines

- All contributing authors of a manuscript should include their full name, affiliation, postal address, telephone and email address on the title page of the manuscript. A brief description of contributions should also be listed per author. Anyone who has contributed to the manuscript but does not qualify as an author should appear as an acknowledgement on the title page. One author should be identified as the corresponding author.
- For all manuscripts non-discriminatory (inclusive) language should be used.
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- The word count (excluding references and the word count of the abstract) should be included on the title page of the manuscript.

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- Authors should supply a conflict of interest statement with their submitted manuscript, detailing any financial or personal relationships that may bias their work, or a declaration that they have no conflicts of interest to disclose.

- Original research studies involving animals or human volunteers must include details of ethical approval. This should include:

  (a) the name of the Institutional Review Board or Ethics Committee that approved the study and all protocols
  (b) the date of this approval and
  (c) the number of the certification or document which verified approval of the study.

  If you have not needed to seek ethical approval for the work, we also require the reason for this. Papers that do not comply with internationally accepted ethical criteria will not be accepted for publication.
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Further information can be found in our **Ethical Guidelines document**.

This journal is a member of, and subscribes to the principles of, the **Committee on Publication Ethics (COPE).**

Authors will be asked during online submission to confirm that the submitted work is not published, in press or currently being considered for publication elsewhere.

The Journal carefully scrutinizes all papers for evidence of plagiarism and falsified data using CrossCheck software. This encompasses the following:

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- changes to authorship after publication due to discovery of guest or ghost authors
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Manuscripts are accepted only in English (British English). Authors whose first language is not English are recommended to ask a native speaker to proofread their manuscript before submission. Alternatively, a **pre-acceptance Editing Service (comprising English language editing, translation services, manuscript formatting and figure preparation) is available** and can provide you with expert help to ensure your manuscript is ready for submission. All services are paid for and arranged by the Author, and use of one of these services does not guarantee acceptance or preference for publication.

Original research papers

Original research papers should not exceed 3000 words. Manuscripts should be written in the passive voice.

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- Structured abstracts are required for all papers and should include objectives, methods, key findings and conclusions.
- Approximate length: 250 words

Keywords

No more than 5 keywords should be supplied for all papers.

Introduction

- An introduction should provide a background to the study (appropriate for an international audience) and should clearly state the specific aims of the study. Please ensure that any abbreviations and all symbols used in equations are fully defined.
- Approximate length: 500-1000 words

Methods

- This section should describe the materials and methods used in sufficient detail to allow the study to be replicated. Please include details of ethical approval in this section.
- Approximate length: 500 - 1000 words

Results

- This section should provide detailed response rates. It is essential to include statistical analyses or other indicators to enable assessment of the variance of replicates of the experiments. Data should not be repeated in figures and tables.
- Approximate length: 700 - 1000 words

Discussion

- The discussion should start with a short sharp paragraph summarising the main findings of the study.
- Followed by a critique of the strengths and limitations of the research.
- The full results should then be discussed in the context of international published literature and the contribution made to the field.
- Any policy, practice and research implications (if any) should be included.
- Approximate length: 700 - 1000 words

Conclusions

- A brief conclusions section should summarise the salient findings of the study. Authors are strongly advised to emphasise the contribution made to the field by their study in this section.

- Approximate length: 150 - 250 words

Tables

- Please keep the number of tables to a minimum.
- Tables should be numbered consecutively (Table 1, Table 2 etc) and each table must start on a separate page at the end of the manuscript.
- Each table must have a title. Each table legend, in paragraph form, should briefly describe the content and define any abbreviations used. If values are cited in a table, the unit of measurement must be stated.
- Tables should not be ruled.

Figures

- Please keep the number of figures to a minimum.
- Each figure must have a title. Each figure legend, in paragraph form, should briefly describe the content and define any abbreviations used. If values are cited in a figure, the unit of measurement must be stated. Graphs must have clearly labelled axes. A key may be included if appropriate.
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