

Evaluation of the pharmacovigilance system in the Dr Kenneth Kaunda District in the North West Province

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Dissertation submitted in partial fulfilment of the requirements for the degree Magister Pharmaciae in Pharmacy Practice at the Potchefstroom Campus of the North West University

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November 2015

PREFACE

This research dissertation was written in article format according to the standards provided by the North-West University. The results of the study are presented in Chapter 3 as research manuscripts. The two manuscripts have been submitted for peer review and possible publishing in the following journals:

- Health Policy and Planning
- Drug Safety

The reference list contains all the references used in the manuscripts and in the dissertation according to the Harvard referencing style as required by the North-West University. The reference list in each manuscript was done according to the author guidelines for each journal. The author guidelines for these journals are included as annexures to the dissertation.

The layout of the dissertation is as follows:

- Chapter 1: Description of the orientation to the study and the method used to conduct the study
- Chapter 2: The fundamentals of pharmacovigilance
- Chapter 3: Results and discussion as presented in two manuscripts
- Chapter 4: Conclusion, recommendations and limitations
- The annexures and the reference list follow after Chapter 4

The study supervisor and the co-supervisors of the study were also co-authors on the articles and gave consent that these articles may be used in the submission of the dissertation.

AUTHORS CONTRIBUTIONS

The contributions of the authors were as follows for manuscript 1 and manuscript 2:

Article	Author and co-author contributions
<p>Manuscript 1 Healthcare professionals' awareness of, experiences with and perceptions of the pharmacovigilance system in the public health sector in South Africa.</p>	<p>L Goosen was involved in the study design, the implementation of the study, the data collection, data interpretation and drafting of the manuscript.</p> <p>MS Lubbe was involved in the study design, the implementation and data analysis of the study and drafting of the manuscript.</p> <p>HE Bekker contributed to the study design, assisted the researcher with data collection activities and made recommendations regarding the content of the manuscript.</p> <p>DM Rakumakoe contributed to the study design and the language and content review of the manuscript.</p> <p>M Malik and M Cockeran were responsible for the data analysis and the language and content review of the manuscript.</p> <p>R van Reenen is mentioned in the acknowledgements for her correspondence between the research team and the healthcare facilities.</p> <p>All authors read and approved the final manuscript.</p>
<p>Manuscript 2 Evaluation of the completeness of adverse drug reaction forms in public health facilities in South Africa</p>	<p>L Goosen was involved in the study design, the implementation of the study, the data collection and drafting of the manuscript.</p> <p>MS Lubbe was involved in the study design, the implementation and data analysis of the study and drafting of the manuscript.</p> <p>HE Bekker contributed to the study design, assistant the researcher with data collection activities and made recommendations regarding the content of the manuscript.</p> <p>DM Rakumakoe contributed to the study design and the language and content review of the manuscript.</p> <p>M Malik and M Cockeran were responsible for the data analysis and the language and content review of the manuscript.</p> <p>R. van Reenen is mentioned in the acknowledgements for her correspondence between the research team and the healthcare facilities.</p> <p>All authors read and approved the final manuscript.</p>

Authors' declaration of their contribution to the study:

I declare that the above-mentioned contributions to the study are correct. I hereby provide consent that it may be published as part of the MPharm dissertation of L Goosen.

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HE Bekker

DM Rakumakoe

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ACKNOWLEDGEMENTS

- My Heavenly Father. Without you as my Lord, none of this would be possible. Thank you God for guiding me and for your promise in Proverbs 3:5-6: Trust in the Lord with all your heart and lean not on your own understanding; in all your ways submit to Him, and He will make your paths straight.
- I want to acknowledge the North-West University and National Research Foundation for financial support during the course of my study.
- A special word of appreciation to my supervisor, Professor MS Lubbe, for all the hard work as leader of the MUSA entity and your contribution to the success of the study. Mrs HE Bekker, thank you for your support during the data collection process and all your contribution and words of motivation during the course of the study. Dr DS Rakumakoe, thanks for all your time and your contribution throughout the study.
- I want to acknowledge Fadeela Motara, Sonja Uys and Dr Carien Leon-Cachet for their contribution throughout the study.
- Madeeha Malik and Marike Cockeran, thank you for your insight into the content of the manuscripts, the literature review and your assistance with the data analysis, the ethics application. Your time spent on improving the dissertation is greatly appreciated.
- Engela Oosthuizen, I cannot express sufficient appreciation for you and your work. Thank you for all the appointments and plans you made to accommodate and help us every day. Thank you for the heart you have for students and the love and support during these two years.
- Danel Husselmann, living with you was a privilege during these two years. Thank you for your words of encouragement and always being ready to provide a helping hand in difficult times.
- A special word of appreciation to my parents, Gert and Esther Goosen, for your support during these years and for making a post-graduate degree possible for me. My two brothers, Dreyer and Johan Goosen, and sister in-law, Aletia Goosen, thank you for your support and love during difficult times.
- Pieter Meuwesen, thank you for just being you. Your patience, your motivation and your love for me have carried me through every day. I am privileged to share this accomplishment with you.

ABSTRACT

The use of drugs is not without the risk of possible adverse drug reactions (ADRs). Information about ADRs is limited due to the short time frame and limited population groups in clinical trials. Pharmacovigilance is the only system that monitors the safety of any drugs on the market. The pharmacovigilance system depends on healthcare professionals to report ADRs on an ADR report form. The information from the ADR reports is used to expand the limited drug safety information. The under-reporting of ADRs by healthcare professionals and the lack of quality ADR reports have been identified as barriers in the pharmacovigilance system. To determine the standard of the pharmacovigilance system in the Dr Kenneth Kaunda District (DKKD), this study evaluated pharmacovigilance practice in the DKKD in the North West Province.

This cross-sectional study was conducted in two steps. The healthcare professionals' awareness, experience and perception of pharmacovigilance and factors that contribute to the success of pharmacovigilance in the Tlokwe Local Municipality were determined in Step 1. Step 2 evaluated the completeness of the content of the completed ADR forms available in the DKKD and compared these forms with the minimum requirements for an ADR report form according to the World Health Organization (WHO).

In Step 1 a structured questionnaire was provided to medical practitioners (n=52), pharmacists (n=15), and professional nurses (n=53) in the Tlokwe Local Municipality. The questionnaire was developed according to the WHO and South African ADR reporting guidelines and a literature review of similar studies. The response rate for Step 1 was 40.8% (n=49). In Step 2, two checklists were designed to evaluate the completeness of the contents of 1 454 Medicines Control Council (MCC) ADR and 92 antiretroviral (ART) ADR report forms. The checklists for the MCC and the ART ADR report forms were based on the different sections that have to be completed on the respective ADR report forms.

The majority of healthcare professionals indicated a good awareness of what should be reported, what to do when an ADR occurs, and who is responsible for reporting ADRs. The awareness concerning the reporting of well-known ADRs and ADRs caused by a medication error can be strengthened. The majority of healthcare professionals (64.6%) had reported an ADR in the past, but the training history to identify and report ADRs varied between the healthcare professional groups. Healthcare professionals do not receive feedback from the national pharmacovigilance centre (77.1%) and no reimbursements are provided when an ADR is reported (71.4%). These were identified as professional factors that discourage ADR reporting among healthcare professionals, in addition to the time it takes to complete the ADR

report (56.3%) and the increased workload (54.2%). The majority of healthcare professionals agreed that pharmacovigilance can be improved if ADR reporting is mandatory (95.5%).

The completeness of all sections on the MCC and ART ADR report forms was low. Sections about ADR outcomes were completed at 57.9% for the MCC and only 13.0% for the ART ADR report forms. The most incomplete section on the MCC ADR report form was the section that describes the ADR (0.1%). This same section was fully completed on 46.7% of ART ADR report forms. The most incomplete section on the ART ADR report form was patient information (1.1%). Product quality problems were reported on 17 MCC ADR report forms, but not one report was fully completed.

The study determined that the awareness of and attitude towards reporting ADRs among healthcare professionals was good, but the completeness of the ADR report forms was poor. Recommendations for possible improvement of identified problems in Step 1 and Step 2 were made, including recommendations for future studies.

Key words: healthcare professionals, adverse drug reaction report, perception, pharmacovigilance, completeness, public health sector, South Africa.

OPSOMMING

Die gebruik van enige geneesmiddels dra die risiko van moontlike ongunstige geneesmiddelreaksies. Die tydsduur van kliniese studies is kort en die geneesmiddel word slegs aan 'n beperkte populasie blootgestel. Gevolglik is die inligting rakende ongunstige geneesmiddelreaksies beperk. Geneesmiddelbewaking is die enigste sisteem wat na kliniese proewe die veiligheid van geneesmiddels monitor. Hierdie sisteem maak staat op gesondheidswerkers om ongunstige geneesmiddelreaksies te rapporteer deur van die ongunstige geneesmiddelreaksieverlag gebruik te maak. Die inligting in hierdie verslag vermeerder die beperkte inligting oor die veiligheid van geneesmiddels. Om die standaard van die geneesmiddelbewakingsisteem te bepaal, evalueer hierdie studie die geneesmiddelbewakingspraktyke in die Dr Kenneth Kaunda Distrik (DKKD) in Noord-Wes.

Hierdie deursneestudie is in twee stappe uitgevoer. Gesondheidswerkers se begrip, ervaring en persepsie oor die geneesmiddelbewakingsisteem en faktore wat bydra tot die sukses van geneesmiddelbewaking in die Tlokwe plaaslike munisipaliteit is in stap 1 bepaal. In stap 2 is die volledigheid van die beskikbare ongunstige geneesmiddelreaksieverlae in die DKKD bepaal. Hierdie verslae is ook met die Wêreld Gesondheidsorganisasie (WGO) se minimum vereistes vir 'n ongunstige geneesmiddelreaksieverlag vergelyk.

In stap 1 is 'n gestruktureerde vraelys aan geneesherre (n=52), aptekers (n=15), en professionele verpleegkundiges (n=53) verskaf. Die ontwikkeling van die vraelys is op die Suid-Afrikaanse en WGO-riglyne vir die rapportering van ongunstige geneesmiddelreaksies en 'n literatuurstudie van soortgelyke studies gebaseer. Die persentasie terugvoer vir stap 1 was 40.8% (n=49). Twee kontrolelyste is vir Stap 2 ontwerp. Die ontwerp van die kontrolelyste is op die verskillende afdelings van die ongunstige geneesmiddelreaksieverlag van die Suid-Afrikaanse Medisynebeerraad (MBR) en die antiretrovirale (ART) ongunstige geneesmiddelreaksieverlag gebaseer.

Die meeste gesondheidswerkers het 'n goeie begrip van watter geneesmiddelreaksies gerapporteer moet word, wat gedoen moet word as 'n ongunstige geneesmiddelreaksie voorkom en wie verantwoordelik is om ongunstige geneesmiddelreaksies te rapporteer. Gesondheidswerkers se begrip oor die rapportering van bekende ongunstige geneesmiddelreaksies, asook reaksies wat deur medikasiefoute veroorsaak word, kan verbeter word. Die meeste gesondheidswerkers (64.6%) het in die verlede 'n ongunstige geneesmiddelreaksie gerapporteer, maar opleiding oor hoe om 'n ongunstige geneesmiddelreaksie te identifiseer en te rapporteer, verskil by geneesherre, aptekers en professionele verpleegkundiges. Gesondheidswerkers ontvang nie erkenning (71.4%) of

terugvoer van die Nasionale Geneesmiddelbewakingsentrum nie (77.1%). Hierdie faktore is geïdentifiseer as professionele faktore wat die rapportering van ongunstige geneesmiddelreaksies beïnvloed, en sluit die tydsduur in om 'n ongunstige geneesmiddelreaksie vorm in te vul (56.3%), en die moontlike verhoogde werkslading (54.2%). Die meeste gesondheidswerkers het saamgestem dat geneesmiddelbewaking in die toekoms verbeter kan word as die rapportering van ongunstige geneesmiddelreaksies verpligtend word (95.5%).

Die volledigheid van al die verskillende afdelings op die MRB en ART ongunstige geneesmiddelreaksieverlag was laag. Die afdeling oor die uitkoms van die ongunstige geneesmiddelreaksie was in 57.9% vir die MBR en in 13.0% vir die ART ongunstige geneesmiddelreaksie verslae volledig voltooi. Die onvolledigste afdeling op die MBR vorm was die beskrywing van die ongunstige geneesmiddelreaksie (0.1%). Dieselfde afdeling is volledig voltooi op 46.7% van die ART se ongunstige geneesmiddelreaksieverlae. Die onvolledigste afdeling op die ART se ongunstige geneesmiddelreaksieverlae was pasiëntinligting (1.1%). Produktkwaliteitsprobleme is gerapporteer op 17 MBR ongunstige geneesmiddelreaksieverlae, maar nie een van hierdie verslae was volledig nie.

Die studie het bevind dat gesondheidswerkers 'n goeie begrip en gesindheid het rakende die rapportering van ongunstige geneesmiddelreaksies, maar die ongunstige geneesmiddelreaksieverlae was onvolledig. Die studie het aanbevelings gemaak vir moontlike oplossings van die probleme wat in stap 1 en stap 2 geïdentifiseer is asook aanbevelings vir moontlike toekomstige studies.

Sleuteltermes: gesondheidswerkers, ongunstige geneesmiddelreaksieverlag, persepsie, geneesmiddelbewaking, volledigheid, openbare gesondheidssektor, Suid-Afrika.

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LIST OF DEFINITIONS

Adverse drug reactions (ADRs)

Adverse drug reactions are appreciably harmful or unpleasant reactions resulting from an intervention relating to the use of a medicinal product, and which predict hazard from future administration and warrant prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product (Edwards & Aronson, 2000:1255).

Adverse drug reaction report (ADR report)

An adverse drug reaction report is a detailed record of all relevant data associated with the use of a medicine in a subject or patient (MCC, 2014:6). It is a “notification relating to a patient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine” (WHO, 2000:7).

Adverse drug event (ADE)

Any untoward occurrence that may present during treatment with a pharmaceutical product, but that does not necessarily have a causal relation to the treatment (Edwards & Aronson, 2000:1256).

Clinic

A suitable permanent equipped facility that provides a range of PHC services. Services are provided at least eight hours a day, at least four days a week (Department of Health, 2006:8).

Community day centre (CDC)

A facility that is not open 24 hours a day, seven days a week, but still provides a range of PHC services. It provides assistance with accidents and emergencies, but not midwifery services or surgery under general anaesthesia (Department of Health, 2006:8).

Community health centre (CHC)

A facility that provides a range of PHC services, 24 hours a day, seven days a week. This facility offers accident, emergency and midwifery services, but not surgery under general anaesthesia (Department of Health, 2006:8).

Community service pharmacist

A person registered as a community service pharmacist in terms of the Pharmacy Act (53 of 1974) may perform the services or acts specifically pertaining to the scope of practice of a pharmacist in a public health facility without the personal supervision of a pharmacist.

Drug interactions

Drug interaction is the “modification of the effect of the drug when administered with another drug. The effect of the drug may increase or decrease the action of either drugs or it may be an adverse effect that is not normally associated with either drug” (Mosby’s Medical Dictionary, 2009c)

Evaluation

Evaluation is the systematic acquisition and assessment of information to provide useful feedback about some object (Trochim, 2008).

Healthcare facility

An institution (hospital, clinic, primary care centre and other service delivery point) involved in direct patient care on site (WHO, 2004b:28).

Healthcare professional

A person, who by education, training, certification or licensure, is qualified to provide and is engaged in providing healthcare (Mosby’s Medical dictionary, 2009a). In the event of reporting adverse drug reactions, the Medicines and Related Substances Control Act (Act No. 101 of 1965) refers to healthcare professionals as any medical practitioner, pathologist, dentist, pharmacist, nurse, veterinarian and para-veterinary professional, including a veterinary nurse and animal health technician (MCC, 2014:7).

Medication error

Medication error is 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 (FDA, 2013).

Mobile clinic

A mobile clinic is a temporary service that makes use of a mobile unit/bus/car as a resource to provide a variety of primary healthcare (PHC) services. A number of sites on a fixed route are visited on a consistent basis (Department of Health, 2006:8).

Perception

The constellation of mental processes by which a person recognises, organises and interprets intellectual, sensory and emotional data in a logical or meaningful fashion (Segen's Medical Dictionary, 2012).

Pharmacist

"A person prepared to formulate, dispense and provide clinical information on drugs or medications to health professionals and patients, through completion of a university program in pharmacy of at least 4 years' duration and passing state and federal licensure exams" (Mosby's Medical Dictionary, 2009b)

Pharmacoepidemiology

Pharmacoepidemiology "[is] the study of the nature and the extent of drug taking behaviors and drug use problems" (Waning & Montagne, 2001:1).

Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug-related problem (WHO, 2012:1). It involves the processes and science of monitoring the safety of medicines and taking action to reduce risk and increase benefit (Isah *et al.*, 2012:45).

Primary healthcare

Primary healthcare involves approved services provided by a professional nurse, technician, mid-level worker, counsellor, community health worker, midwife and emergency medical practitioner. All services performed are within the skills base of the healthcare professionals concerned (Department of Health, 2006:6).

Professional nurse

A person, also known as a registered nurse, who has successfully completed a four-year curriculum at a university or a nursing college and is educated and capable of practising the scope of nursing and midwifery (HST, 2015). In the context of this study, this person will be referred to as professional nurse.

Risk management

Risk management is the systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating, and reviewing risk (FDA, 2006:10).

Satellite clinic

A facility that is a fixed building where one or more rooms are permanently equipped and from which a range of PHC services are provided. Services are provided for up to eight hours per day, less than four days per week (Department of Health, 2006:8).

Spontaneous reporting

Spontaneous reporting is a system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national health pharmacovigilance centre (WHO, 2006:22).

Substandard medicines

Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and that are consequently ineffective and often dangerous to the patient (WHO, 2003).

Therapeutic risk management

Therapeutic risk management is defined as “an ongoing cycle of risk detection, risk assessment, risk characterisation, risk minimisation, effectiveness evaluation and improvement” (Mayall & Banerjee, 2014:9). Therapeutic risk management “aims to assure safe medication use in a population, show a positive benefit/risk balance and reduce the risk of exposure in populations that show a negative benefit/risk balance” (Hartzema *et al.*, 2008:205).

LIST OF ABBREVIATIONS

ADE	Adverse drug event
ADR	Adverse drug reaction
ART	Antiretroviral therapy
CDC	Community day centre
CHC	Community health centre
DKKD	Dr Kenneth Kaunda District
DOH	Department of Health
FDA	Food and Drug Administration, United States of America
GPvP	Good pharmacovigilance practice
HCP	Healthcare professional
HREC	Health Research Ethics Committee
ICSR	Individual case safety report
MCC	Medicines Control Council
ME	Medication errors
NADEMC	National Adverse Drug Event Monitoring Centre
PHC	Primary healthcare
PMS	Post-marketing surveillance
RM	Risk management
SOP	Standard operating procedure
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SPS	Strengthening Pharmaceutical Services
TRM	Therapeutic risk management

UMC Uppsala Monitoring Centre

WHO World Health Organization

CHAPTER 1 ORIENTATION OF THE STUDY

“The world needs a global health guardian, a custodian of values, a protector and defender of health, including the right to health” (WHO, 2012:4).

In this chapter, pharmacovigilance is introduced as an area of interest, with specific emphasis on the pharmacovigilance system in the Dr Kenneth Kaunda District (DKKD) in the North West Province. This chapter describes how the researcher evaluated the existing pharmacovigilance system. The research design and the study population are identified. The study was divided into two steps, with two different data collection tools and an appropriate data analysis plan for each step. The reliability, validity and ethical implications were taken into consideration to conduct a successful study.

1.1 Background

According to the World Health Organization (WHO, 2002a:5), pharmacovigilance became part of healthcare practice after the thalidomide disaster in 1961. Thalidomide was thought to be a safe drug for morning sickness and nausea (WHO, 2004a:2). This “harmless” drug resulted in large numbers of congenitally deformed infants being born after exposure in the womb. These terrifying events led to the international awareness of the adverse effects of drugs, with the subsequent merging of the practice and science of pharmacovigilance (WHO, 2004a:2). Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem” (WHO, 2012:1).

Therapeutic risk management is an interactive process of assessing products’ benefit-risk balance (Hartzema, 2008:2). This entails the development of a tool that can be used to minimise identifiable risks. The therapeutic risk-management tool must be tested for its effectiveness to ensure a desired benefit-risk balance and this evaluation will indicate any adjustments needed to promote benefit-risk balance (Hartzema, 2008:2). Pharmacovigilance is part of the risk-management plan (FDA, 2005:3).

Experience with new medicines has shown that new adverse drug effects, interactions and risk factors can be detected only during a period of time after the release of a new product (WHO, 2004a:1). When the drug is released on the market and used by a larger population than the clinical trial, unidentified effects of the drug may be detected, thus demanding the monitoring of the patient and reporting of any negative reactions that were not identified in the trial (Egualé *et al.*, 2008:1005).

Adverse drug reactions (ADRs) are the leading cause of mortality rates in hospitals (Bandekar *et al.*, 2010:1181). In 2010 the Australian database indicated a total of 233 300 reports of ADRs (Department of Health and Ageing, 2011:4). According to Wu *et al.* (2010:239), England reported 557 978 hospital admissions between 1999 and 2009 that were caused by ADRs. The repercussions of ADRs impel healthcare systems to employ a reliable working documentation system to report ADRs. This emphasises the need for the implementation of proper guidelines to reduce probable harm and relieve symptoms as a result of ADRs (WHO, 2012:10).

The existence of ADRs varies between countries, because of differences between diseases and prescribing practices, genetics, diets, culture, drug development and distribution, and the use of traditional medicines. Data obtained from each country has added a different value to that specific country, which may not be relevant to any other country. This is why the detection of ADRs is significant for the safety of patients and to ensure the success of the product (WHO, 2002a:9).

There is a national pharmacovigilance programme or centre in most countries that is responsible for the monitoring of ADRs. These centres collect ADR reports and submit them to a supervisory authority. These authorities send the reports to the WHO's ADR monitoring centre in Uppsala, Sweden (Bandekar *et al.*, 2010:1182).

According to Bandekar *et al.* (2010:1182), most countries have their own ADR reporting form. South Africa was the first country in Africa to become part of the WHO in 1992 (Mehta *et al.*, 2014:104). Although the WHO sets guidelines for the development of report forms, the WHO Pharmaceutical Newsletter demonstrated the need for a universal form to report ADRs, because different countries have different reporting forms according to each country's national requirements (Olsson, 2007:7). Bandekar *et al.* (2010:1182) identified 18 characteristics that are vital to producing a quality ADR reporting form. The results of this study showed that the different forms from 10 countries had all asked for complete patient information. According to Bandekar *et al.* (2010:1182), the United Kingdom (UK), Kenya and Pakistan did not require information about the patient's allergy status. Information regarding pregnancy was found only on the forms of Pakistan and Kenya. Malaysia obtained the highest score with 16 out of 18 points with their report form. Pakistan has the lowest score with 6 out of 18, and South Africa, Australia and the UK scored 12 out of 18 (Bandekar *et al.*, 2010:1184). Different reporting forms result in different reporting styles, which may result in a loss of information (Bandekar *et al.*, 2010:1182; WHO, 2012:5).

The South African Medicines Control Council (MCC) is responsible for quality, safe and efficient medicine use in South Africa and manages the National Pharmacovigilance Programme (Department of Health, 2012:389). The safety of all registered medicine in South Africa is

monitored by the National Adverse Drug Event Monitoring Centre (NADEMC) in Cape Town (Malangu, 2014:211). The pharmacovigilance programme requires all healthcare workers, doctors, dentists, pharmacists and nurses to report ADRs.

The Department of Health (DOH) of South Africa developed an ADR report form according to the standards provided by the WHO, and these forms must be completed with as many specifications as possible (Department of Health, 2012:392; WHO, 2007:7). The national ADR database is used to manage all ADR reports. These reports are evaluated to detect the significance of the reaction and the medicines. If the forms are completed according to the standards set by the DOH, these events can be investigated and may result in informative proposals to develop the safe use of medicine, or they could lead to changes on the package insert and changes in the scheduling or manufacturing to reduce adverse drug effects in the future. The risk relating to the medicine is reduced and patient care improves with ADR reports (Department of Health, 2012:389).

1.2 Problem statement

The World Health Organisation is concerned about the global state of pharmacovigilance because the majority of government authorities do not support this system (WHO, 2006:31). It has been stated that pharmacovigilance can be afforded only by developed nations, because developing countries do not have the resources to train and invest in the development of a quality pharmacovigilance system (WHO, 2006:32). Public health programme managers do not perceive the detection of ADRs to be a priority (WHO, 2006:32). The perception arises among healthcare professionals (HCP) that medicine that has been used for a long time or is available on the market can be assumed to be safe to use. Healthcare professionals in public health programmes in developing countries do not have the knowledge to detect adverse reactions (WHO, 2006:32).

ADRs are identified as a global problem in healthcare systems (Metha, 2011:247). This problem can be resolved if the reporting of ADRs is as complete as possible, with a successfully implemented information system, to assist decision-makers with regard to the probable harmful effects of medicines (Ndosimao, 2013:1). It is a constant battle to see pharmacovigilance as part of public health, because the concept of pharmacovigilance is misunderstood by health care workers, patients and society (WHO, 2006:24). The facilities receiving, organising and evaluating the ADR reports are not up to standard and the lack of reporting as a part of everyday healthcare influence the success of the pharmacovigilance system (WHO, 2006:32).

South Africa was the first African country that became part of the Pharmacovigilance International Network in 1992. A national pharmacovigilance plan was designed at a meeting

with regard to the pharmacovigilance workshop that was held in August 2012 (Mehta *et al.*, 2014:104). Mehta *et al.* (2014:104) identified three pharmacovigilance systems in South Africa namely Immunisation, HIV/AIDS and TB and specific clinical specialities.

Pharmacovigilance is still considered to be poor in Africa, even though the rest of the countries in Africa included pharmacovigilance in their health systems in 2006 (Isah *et al.*, 2012:25). According to Lopez-Gonzalez *et al.* (2009:19), one of the main reasons for the failure of pharmacovigilance systems is under-reporting, and this has a direct effect on the universal pharmacovigilance system. Professional and personal barriers were identified as a cause of the under-reporting of adverse effects (Lopez-Gonzalez *et al.*, 2009:19).

The question arises as to whether these barriers can be drawn to South Africa or if there are other factors that influence the standard reporting on ADRs in South Africa. The successful implementation of an ADR documentation system will strengthen the management of health systems and services at district level. The Medicines and Related Substances Control Act (Act No. 101 of 1965) indicates that it is compulsory for pharmaceutical companies to report ADRs, but HCPs are not obligated to abide by this law. This leads to a low rate of spontaneous reporting in South Africa (Misra, 2010). A previous study regarding pharmacovigilance in South Africa indicated that healthcare professionals do not have the required skills and knowledge to identify ADRs (Ruud *et al.*, 2010:351).

The problem with pharmacovigilance gave rise to the following questions, which were investigated in the DKKD:

- What is the difference between ADEs, the inappropriate usage of medicines and ADRs?
- What is the current prevalence of ADRs and drug-related problems globally and in South Africa?
- What is the national and international standard regarding good pharmacovigilance practice?
- Where are the possible challenges for the successful implementation of the pharmacovigilance programme?
- Does the attitude of healthcare professionals influence the implementation of pharmacovigilance in the public health care sector?
- What are the perceptions of healthcare professionals (general practitioners, hospital pharmacists and professional nurses) with prescribing rights in the Tlokwe Local Municipality regarding the reporting of ADRs?

- What is the current standard of completeness of already completed ADR forms available in the DKKD, with special reference to the Tlokwe Local Municipality?

1.3 Research aims and objectives

The research aims and objectives for phases 1 and 2 of this study explain what the researcher did and how the researcher accomplished the intended aim. The aim of a research study is a clear indication of what is being researched (Parahoo, 2006:167). Research objectives are a detailed indication of the goal that the researcher intends to achieve at the end of the study (Kumar, 2014:381).

1.3.1 Research aim

The aim of this study was to evaluate the public health pharmacovigilance system in the Dr Kenneth Kaunda District in the North West Province, with specific reference to the Tlokwe Local Municipality.

1.3.2 Specific research objectives

The research project consisted of two phases, namely Phase 1, a literature review, and Phase 2, the empirical investigation:

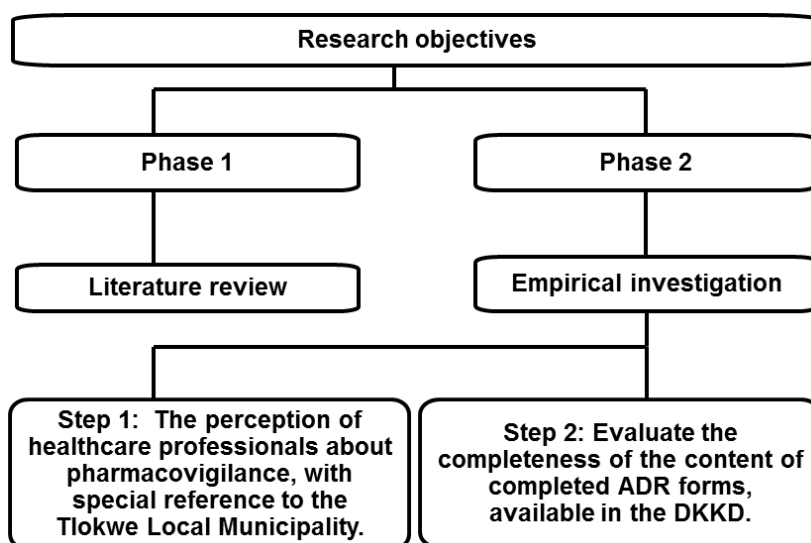


Figure 1.1: Research objectives

1.3.2.1 Phase 1: Literature review

The specific research objectives of the literature review included the following:

- Conceptualisation and comparison of good pharmacovigilance practice with international and national guidelines

- Evaluation of the current South African ADR report form according to international guidelines
- Description of the relationship between inappropriate drug use, medication errors, ADEs (preventative and non-preventative) and ADRs through an extensive literature review
- Identification of the current prevalence of ADRs globally and in South Africa
- Identification of the possible challenges for the successful implementation of pharmacovigilance specifically, in the public healthcare sector of South Africa

1.3.2.2 Phase 2: Empirical investigation

The specific research objectives of the empirical investigation are grouped according to the following two steps and include the following:

Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

- Evaluate current pharmacovigilance practices from the perception of healthcare professionals (general practitioners, hospital pharmacists and professional nurses) in the Tlokwe Local Municipality against national and international guidelines.
- Determine from the perception of healthcare professionals possible factors that can contribute to the successful implementation of pharmacovigilance in the Tlokwe Local Municipality.

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

- Evaluate the completeness of the content of completed ADR forms available in the DKKD and compare these forms with the minimum requirements for an ADR report form according to the WHO.
- Make recommendations for the training of healthcare professionals and improvement of the pharmacovigilance system in the DKKD with reference to the Tlokwe Local Municipality.

Table 1.1: Specific research objectives according to the presented manuscripts

Objective	Manuscript (refer to chapter 3)
Evaluate current pharmacovigilance practices from the perceptions of healthcare professionals (general practitioners, hospital / community/sub-district pharmacists and professional nurses) in the Tlokwe Local Municipality against national and international guidelines.	Manuscript 1 Healthcare professionals' awareness, experience and perceptions with the pharmacovigilance system in the public health sector in South Africa. This manuscript is submitted for peer review and possible publishing to the <i>Health Policy and Planning</i> .
Determine from the perception of healthcare professionals possible factors that can contribute to the successful implementation of pharmacovigilance in the Tlokwe Local Municipality.	
Evaluate the completeness of the content of completed ADR forms available in the DKKD and compare these forms with the minimum requirements for an ADR report form according to the WHO	Manuscript 2 Evaluation of the completeness of adverse drug reaction forms in public health facilities in South Africa. This manuscript is submitted for peer-review and possible publishing to the <i>Drug Safety</i> journal.
Make recommendations for the training of healthcare professionals and improvement of the pharmacovigilance system in the DKKD with reference to the Tlokwe Local Municipality.	Chapter 4, Section 4.2.3

1.4 Research methodology

The research methodology focuses on how the study was conducted to answer the research questions. This section includes the research design, target and study population, sample method, data collection tools and data analysis for this study.

1.4.1 Phases of the research project

The study consisted of two phases, namely Phase 1 (a literature review) and Phase 2 (the empirical investigation).

1.4.1.1 Phase 1: Literature review

A literature review involves the search for existing literature that relates to the current research problem, and is used to integrate the results of this study. The new research is placed into perspective with the findings of the other problems already investigated (Kumar, 2014:374). The literature review explains the difference between MEs, ADEs and ADRs and conceptualises the current and global prevalence of ADRs. Good pharmacovigilance practices (GPvP), nationally

and internationally, were identified and the current MCC national ADR report form was compared to international guidelines.

1.4.1.2 Phase 2: Empirical study

The empirical study describes the research design, setting, target and study population. The empirical study comprised the following steps:

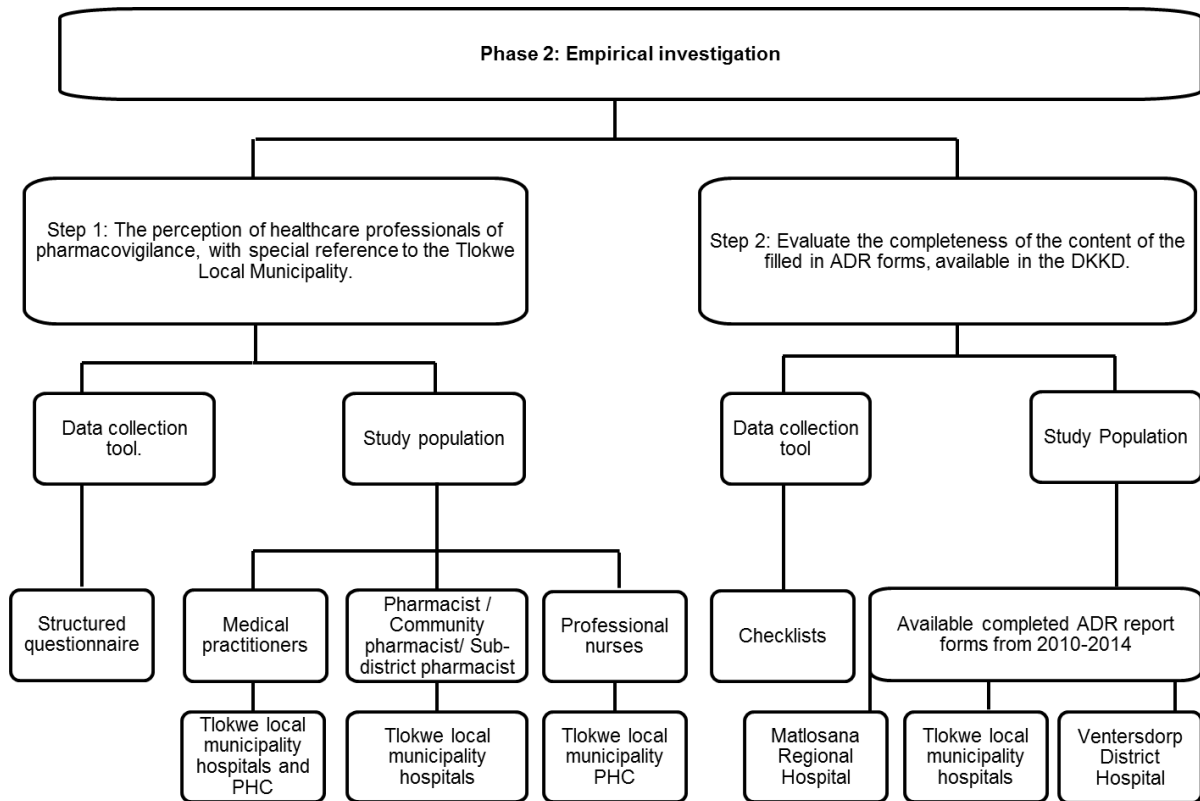


Figure 1.2: Empirical investigation

Step 1: The perceptions of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

A structured questionnaire was used to evaluate the perceptions of healthcare professionals regarding the pharmacovigilance system.

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

The MCC and Essential Drugs Programme of the Department of Health are dedicated to improving the safety of drugs through ADR monitoring (Department of Health, 2012:389). An ADR report is a “detailed record of all relevant data associated with the use of a medicine in a

subject or patient” (MCC, 2014:6). Two standard ADR report forms (Annexure E and G) with information regarding the ADR presented should be completed to report ADRs on a daily basis (Department of Health, 2012:389). Two checklists, developed specifically for this investigation, were used to determine the completeness of available ADR forms in the DKKD (Annexure D and F). These ADR report forms were also compared to the WHO minimum requirements for an ADR report form (WHO, 2002c:16).

1.4.2 Research design

There are two different types of research approaches, i.e. quantitative and qualitative. The most suitable research approach to address this research problem was a descriptive, cross-sectional, quantitative approach.

A quantitative study can be defined as the process that uses numerical data from a carefully selected group in the population in a systematic and objective way to correlate the findings universally (Maree & Pietersen, 2007a:145). A quantitative study design is divided into two groups, namely experimental and non-experimental research. In an experimental design, the variables in the study can be controlled by the researcher. In a non-experimental study, the researcher cannot manipulate the independent variable (Brink *et al.*, 2012:9). A cross-sectional study is conducted at one point in time (Edmonds & Kennedy, 2013:108). Cross-sectional research can be exploratory, descriptive or explanatory, but a descriptive design is the most reliable (Neuman, 2014:44). A descriptive design, a class of non-experimental study, is used in an observation study to explain and record aspects of the state of affairs as they occur (Beck & Polit, 2012:226).

Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

A quantitative, non-experimental, cross-sectional research design is the most suitable for Step 1. According to Brink *et al.* (2012:10), “a descriptive design can be used to identify problems with current practice: to justify current practice, make judgements or determine what other professionals in similar situations are doing: or to develop theories”. A structured questionnaire was used to evaluate health professionals’ awareness, experience and perception regarding the pharmacovigilance system and to determine possible factors that contribute to the success of pharmacovigilance in the Tlokwe Local Municipality (Annexure A).

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

A quantitative, non-experimental, cross-sectional research design was used to conduct Step 2 of the study. This is the method of choice for the evaluation of information systems (Stoop & Berg, 2003:6). There are two ADR report forms available in the DKKD, namely the MCC ADR report form and the regional antiretroviral therapy (ART) ADR report form. Two checklists (Annexure D and F) were designed to evaluate the completeness of the available ADR reports in the DKKD. These ADR report forms were also compared to the WHO minimum requirements for an ADR report form (WHO, 2002c:16).

1.4.3 Study setting

Step 1 and Step 2 of the study were conducted in the North West Province in South Africa. South Africa consists of nine provinces with a total population of 51 770 560 (StatsSA, 2011). The North West Province, with a population of 3 253 390, in South Africa consists of four districts (National Heritage Council, 2014):

- Dr Kenneth Kaunda
- Ngaka Modiri Molema
- Dr Ruth S Mompati
- Bojanala Region

The Dr Kenneth Kaunda District, with a population of 807 252 (Department of Health, 2013a:3), has four local municipalities (The Local Government Handbook, 2012):

- Tlokwe Local Municipality
- Ventersdorp Local Municipality
- Matlosana Local Municipality
- Maquassi Hills Local Municipality

Public health services in the DKKD are delivered by six clinics, two community health centres (CHC), one district hospital, one health post, 15 mobile services, four regional hospitals, six satellite clinics and one specialised psychiatric hospital (Department of Health, 2013a:6).

Step 1: The perceptions of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

Step 1 was conducted in the Tlokwe Local Municipality in the DKKD. Public health services in the Tlokwe Local Municipality are delivered in 13 facilities (Department of Health, 2013a:6):

- Potchefstroom District Hospital
- Witrand Specialised Hospital
- Mohadin Clinic
- Lesego Clinic
- Boskop Clinic
- Top City Clinic
- Potchefstroom Clinic
- Steve Tshwete Clinic
- Gateway Clinic
- Promosa CHC
- Boiki Thlapi CHC
- Mobile Clinic 1
- Mobile Clinic 2

The North-West University (NWU), Potchefstroom Campus, is situated in the Tlokwe Local Municipality. The researcher was required to travel to the health facilities included in the study; therefore the Tlokwe Local Municipality was more cost-effective. This area is still significant, because the study included three different HCP groups, namely pharmacists, medical practitioners and professional nurses. No previous studies have been conducted to evaluate the pharmacovigilance system and it was indicated as a priority specifically for pharmaceutical services in the DKKD.

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

Step 2 of the study included the following facilities in the DKKD:

- Matlosana Regional Hospital
- Tlokwe District Hospital
- Ventersdorp District Hospital

The DKKD was chosen for Step 2 of this study. The DKKD is an area of interest to the Department of Health because it is a pilot area for the National Health Insurance and it was indicated as a priority specifically for the delivery of pharmaceutical services in the DKKD (Matsoso & Fryatt, 2012:29).

1.4.4 Target and study population

The population for a study needs to be identified by the researcher to present a well-structured proposal (Bowling, 2009:157). When the researcher conducts a quantitative study, the people participating in the study are referred to as subjects/study participants (Beck & Polit, 2012:48).

1.4.4.1 Target population

Step 1: The perceptions of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

According to an audit on community healthcare professionals in the North West Province in 2011, Tlokwe Local Municipality has a total of 164 healthcare professionals (Ogunmefun *et al.*, 2011:30). The target population included the following healthcare professionals involved in prescribing and dispensing medicines in the Tlokwe Local Municipality:

- All medical practitioners employed in the North West Department of Health in the Tlokwe Local Municipality who are involved in prescribing drugs independently of a healthcare institution (e.g. hospital or PHC facility).
- All pharmacists (including community service pharmacists and pharmacists responsible for the PHC facilities in the sub-district) currently employed by the North West Department of Health in the Tlokwe Local Municipality involved in dispensing drugs independently of a healthcare institution.

- All professional nurses (including the nursing manager) employed by the North West Department of Health who may diagnose and prescribe medicines in primary healthcare (PHC) facilities (CHC, mobile clinics, clinics) in the Tlokwe Local Municipality.

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

The target population included all the completed MCC and ART ADR forms independent of pharmacological category or drug use from 2010 to 2014 that were available at the hospitals and clinics in DKKD. The completed forms of the PHC facilities are normally sent to the sub-district hospitals.

1.4.4.2 Study population

“The study population is the population which meets the criteria for inclusion stipulated by the researcher” (Parahoo, 2006:474).

Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

The study population included all healthcare professionals employed (permanently/temporarily) in the Tlokwe Local Municipality who complied with the following inclusion criteria and consented to participate.

Inclusion criteria for Step 1:

- All healthcare professionals (medical practitioners, pharmacists, professional nurses) in the Tlokwe Local Municipality currently employed/working in the public health sector on a permanent or temporary contract.
- All healthcare professionals (medical practitioners, pharmacists, professional nurses) in the Tlokwe Local Municipality involved in prescribing and/or dispensing drugs.
- All healthcare professionals (medical practitioners, pharmacists, and professional nurses) in the Tlokwe Local Municipality who signed the informed consent form.
- Only healthcare professionals (medical practitioners, pharmacist and professional nurses) in the Tlokwe Local Municipality directly involved with the identification and confirmation of ADRs.

Exclusion criteria for Step 1:

- All healthcare professionals (medical practitioners, pharmacists, professional nurses) in the Tlokwe Local Municipality currently employed in a management or administrative occupation in the health sector.

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

The study population regarding the evaluation of the completeness of ADR reports included all the available MCC and ART ADR forms completed in the Matlosana Regional Hospital, Tlokwe District Hospital and Ventersdorp District Hospital in the DKKD from 2010 until 2014. These ADR report forms included the ADR report forms received from the primary healthcare clinics in each sub-district in the DKKD.

Inclusion criteria:

- All ADR forms available in the DKKD hospitals independent of pharmacological category or drug use.

Exclusion criteria:

- Report forms that were not provided to the researcher were not used in the study.
- Permission to conduct the study in the Tlowke Specialised Psychiatric Hospital was denied due to the vulnerability of the patients.

1.4.5 Sampling

“Sampling involves selecting a portion of the population to represent the population” (Beck & Polit, 2012:177).

1.4.5.1 Sampling type

Two basic types of samples are used in research, i.e. probability and non-probability sampling. The probability sample is randomly selected from the target population and the non-probability sample contains groups whose chance of selection is unknown (Parahoo, 2006:259). Researchers can use probability sampling to their advantage to determine the extent of the sampling error. Sampling errors indicate the difference between population values and sample values (Beck & Polit, 2012:177).

Step 1: The perceptions of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

No sampling technique was required for Step 1. In this step the study population was the same as the target population. All healthcare professionals in the Tlokwe Local Municipality who complied with the inclusion criteria were selected to participate in the study. The following types and numbers of healthcare professionals were invited to participate in the study:

Pharmacists (15)

- Potchefstroom District Hospital (9)
- Witrand Specialised Hospital (6)

Medical practitioners (52)

- Primary healthcare clinics (8)
- Potchefstroom District Hospital (35)
- Witrand Specialised Hospital (9)

Professional nurses in PHC clinics (53)

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

No sampling technique was required for Step 2. All available MCC and ART ADR forms completed at the the Matlosana Regional Hospital, Tlokwe District Hospital and Ventersdorp District Hospital in DKKD from 2010 until 2014 provided to the researcher were evaluated. These ADR report forms included the ADR report forms received from the primary healthcare clinics in each sub-district in the DKKD.

1.4.6 Data collection tool

This study made use of two different data collection tools for the two different steps. A research instrument (data collection tool) must be used to gather data (Brink *et al.*, 2012:147). One tool was required to determine the perceptions of healthcare professionals about the pharmacovigilance system in the Tlokwe Local Municipality (Step 1), and another tool was required to evaluate the standard of completion of available ADR report forms in the DKKD (Step 2).

Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

1.4.6.1 Questionnaire development

The data collection tool in Annexure A, a self-completed questionnaire, was used to determine the perception of healthcare professionals of pharmacovigilance.

A questionnaire is a data collection method for a survey design (Maree & Pietersen, 2007b:157). The development of the questionnaire included the revision during the literature review of similar studies conducted to determine the perception of healthcare professionals (Bateman *et al.*, 1992:423; Cosentino *et al.*, 1997:87; Gupta & Udupa, 2011:1066; Reddy *et al.*, 2014:36; Rajesh *et al.*, 2011:680; Ramesh & Parthasarathi, 2009:11). The questions regarding the standard operating procedures of pharmacovigilance were based on guidelines provided by the WHO, the Department of Health of South Africa and the MCC (Department of Health, 2012:395; MCC, 2014; WHO, 2002a). The questionnaire was designed according to good question-writing principles. The first principle is to prevent confusion in the questionnaire, and confusion risks are excluded by means of simple word use and the explanation of possibly confusing terms. The respondent's views of the questions are considered as the second principle and therefore the questions are brief, with an easy response category (Neuman, 2014:321).

The following guidelines were used to develop the structured questionnaire (Kumar, 2014:181; Neuman, 2014:326):

- The researcher did not use slang language or abbreviations.
- The questions were clear, separated and set in categories to prevent vagueness.
- Leading questions were avoided to prevent the respondent from providing an answer that the researcher might want instead of providing an own opinion.
- All the questions were related to the study population capabilities. The terms used in the questionnaire were relevant to study population scope of practice. All questions were relevant to the current state of affairs and no hypothetical circumstances were set.
- No double negative questions were asked.

1.4.6.2 Question construction

According to Bowling (2009:304) a structured questionnaire can include open and close-ended questions. Close-ended questions are structured and provide a fixed response and open-ended questions are unstructured and a free response may be provided by the respondent (Neuman, 2014:331). The Likert scale was used for a response of five categories for structured questions, i.e. strongly agree, agree, uncertain, disagree or strongly disagree (Maree & Pietersen, 2007b:167). The researcher made use of both close- and open-ended questions in the questionnaire.

(a) Close-ended questions

Close-ended questions have the following advantages (Kumar, 2014:181; Neuman, 2014:333):

- They are easy and not time consuming to answer.
- It is easy to compare answers from different respondents.
- These answers are easy to code and analyse statistically.
- They are more cost-effective.
- They ensure greater anonymity.

Close-ended questions have the following disadvantages (Kumar, 2014:181; Neuman, 2014:333):

- It is possible for respondents with no knowledge to answer the questions.
- It is difficult to detect misinterpretation of the questions.
- It is possible for the respondents to mark the wrong response.
- There could be a low response rate.

(b) Open-ended questions

Open-ended questions are unstructured (Neuman, 2014:331) and can be used to gain information that is unknown to the researcher (Bowling, 2009:305). This provides an opportunity for the participant to state an honest opinion and themes for recommendations can be identified in these answers (Maree & Pietersen, 2007b:161). The researcher assigned different codes to the answers of open-ended questions to form discrete categories. This is regarded as nominal data, which can be analysed quantitatively (Mathers *et al.*, 2009:21-22).

Section F of the questionnaire contained open-ended questions, with sufficient space for the participant to respond to the questions. Examples of open-ended questions from the questionnaire include: Is pharmacovigilance training needed and give recommendations regarding the future of pharmacovigilance. Open-ended questions have the following advantages (Bowling, 2009:305; Neuman, 2014:333):

- The respondent can provide detailed answers.
- Unexpected themes can be identified.
- They provide an opportunity for self-expression.

Open-ended questions have the following disadvantages (Bowling, 2009:305; Neuman, 2014:333):

- Different detailed answers can be expected.
- They can take more time than expected to complete.
- It is difficult to code and analyse all the answers.

(c) Advantages/disadvantages of the Likert-type scale

The Likert-type scale, used in close-ended structured questions, is classified as an attitudinal scale and is used to evaluate respondents' thoughts about a matter with regard to which thoughts can be measured (Gerrish & Lacey, 2010:376; Kumar, 2014:202).

Advantages of Likert-type scales:

- Easy to construct.
- Produce a reliable scale.
- Easy to complete for the participant.

Disadvantages of Likert-type scales:

- Acquiescence bias may occur if the respondent has agreed with statements in order to favour the researcher.
- Social desirability bias may occur if the respondents agree/disagree with a statement that represents the view of society, instead of being honest.

(d) Questionnaire divisions

The questionnaire was divided into the following sections:

- **Demographic information**

This category included general information about the participant, i.e. gender, age, qualification, current working environment and experience in practice.

- **ADR system and structure**

This category focused on the guidelines for reporting ADRs.

- **Healthcare professionals' perceptions regarding ADR reporting**

In this category, the health professional provided their views on ADR reporting and included statements to generate possible improvements for ADR reporting.

- **ADR reporting in practice**

This category focused on the healthcare professionals' experience regarding ADR reporting.

- **Factors that may influence ADR reporting**

This category focused on factors that may lead to the discouragement of ADR reporting.

- **Challenges of ADR reporting**

This section focused on instructions and guidelines regarding the completion of an ADR report form and provided space for recommendations from participants for future improvement.

Step 2: Evaluate the completeness of the content of completed ADR forms available in the DKKD

A checklist was used as the data collection tool. According to Robson (2011:330), "a checklist is seen as providing a long series of items which can be recorded as present or absent". A checklist was used by the researcher to indicate whether the required features were available or not (Leedy & Ormrod, 2014:198). This was ideal to evaluate the completeness of available MCC and ART ADR reports in the DKKD. The criteria used in the checklists were based on the sections that should be completed on the two ADR report forms. These checklists consisted only of close-ended questions (Brink *et al.*, 2012:155). These ADR report forms were also compared to the WHO minimum requirements for an ADR report form (WHO, 2002c:16).

(a) Criteria for evaluation

According to Robson (2011:182), the following criteria should be adhered to in order to improve the evaluation process:

- Utility is important, because an evaluation is only useful to the healthcare system in the DKKD if the healthcare professionals can use the results.
- Feasibility: an evaluation should only be done if it is practical and cost-effective.
- Propriety: the evaluation must be done fairly and according to the standard code of ethical conduct.
- Technical adequacy: highlight the function, viability and suitable behaviour that indicate that the evaluation will be done with the necessary skills.

The evaluation was done in the hospitals to ensure the safety of the information on the forms and to ensure cost-effectiveness, as the researcher visited the sites only once. The information from the evaluation can contribute to the ADR reporting in the DKKD.

(b) Different categories on the checklist to evaluate the MCC ADR report forms.

- **Patient information**

The researcher evaluated only whether this information had been completed. No personal information from the form was used.

- **Medicines/vaccines/devices**

This c section described the current medicine used by the patient, including the dosage, duration of use and reason for use.

- **Adverse reaction outcome**

The form provided categories to describe the type of adverse reaction, with information regarding the treatment of the reaction.

- **Product quality problem**

This section was used to describe possible product quality problems and included the trade name, batch number, registration number, dosage form and strength, expiry date and the type of container.

- **Reporting doctor/pharmacist/nurse**

The reporter was obliged to complete this part: name, qualification, address, contact number, date of reporting and a signature.

(c) Different categories on checklist to evaluate the ART ADR report forms.

The ART ADR report form had eight different sections. This form also included patient information, medicines/vaccines/devices, adverse reaction outcome and reporting doctor/pharmacist/nurse. A section to report product quality problems is not available on the ART ADR report form. The following three sections were also available on the ART ADR report:

- **Laboratory results**

This section described possible laboratory test done by the healthcare professionals on the patient to evaluate ADRs.

- **Relevant clinical history**

This section described the patient's history regarding HIV diagnosis and the initial anti-retroviral (ARV) regime used by the patient.

- **Early warning drug resistance**

This section described the patient's compliance regarding the use of the ARV's.

(d) Minimum requirements for an ADR report from according to the WHO (WHO, 2002c:16)

- **Patient information.**

This section includes information to identify the patient, the date of birth or the age of the patient including the patient's gender and weight.

- **Adverse event/product quality problem**

This section includes the description of the ADR, the date of the ADR and the date of the ADR report. Reporters are also required to include relevant test done or laboratory date and patient history.

- **Outcome of the event**

This section includes the indication of the suspected drug that led to the ADR, the name of all other drugs used by the patients, including the batch number and expiration date of all drugs administered by the patient. The reporter should indicate the diagnosis for the use of all drugs, and include the start date of the therapy, the dosage, frequency of use and route of administration of all drugs used by the patient. A description of events that followed after the use of the suspected drug are stopped should be included as well as a description of events if the suspected drug are administered to the patient again. All concomitant medical products and therapy dates should be indicated on the ADR report form.

- **Reporter details**

The WHO requires ADR healthcare professionals to indicate their name, facility address, contact number, occupation and speciality.

1.4.6.3 Validity and reliability of the data collection tools

The validity and reliability of the research measurements influence the probability of the study significance during the data analysis. This influences the conclusion based on the results. Validity and reliability are concerned with how specific the measurements or indicators for the study are developed (Leedy & Ormrod, 2014:91; Neuman, 2014: 31).

1.4.6.3.1 Validity

Measurement validity “is the degree of fit between a construct and indicators of it” (Neuman, 2014:215). It is used to measure the amount of systematic or built-in error in the questionnaire (Van Tilburg Norland, 1990). Validity is used to determine whether the indicator used describes the meaning of the theory that the researcher is testing (Bowling, 2009:162; Neuman, 2014:212). There are four different types of validity:

- Face validity
- Content validity
- Construct validity
- Criterion validity

Face validity and content validity were used in this study. Face validity “is a judgement by the scientific community that the indicator really measures the construct” (Neuman, 2014:216). It is a technical explanation of the judgement that the content is significant and appropriate and is

used to determine whether, on the face of it, the questionnaire is testing the desired outcome (WHO, 1994:11). The face validity of the data collection tools was ensured by a statistician.

Content validity identifies whether the questionnaire is representative of all the questions that could have been asked to make the assumptions from the data valid (WHO, 1994:12). The content validity addresses the question: is the full content of a definition represented in a measure (Neuman, 2014:216)? When a questionnaire is used to collect data, the literature reviews identify concepts that must be included in the questionnaire (Brink *et al.*, 2012:166). The following procedures were used to ensure the content validity of the questionnaire:

(a) Protocol evaluation: structured questionnaire and checklist

The questionnaire for Step 1 was sent to three different groups to test whether the participants understood the questions correctly (Maree & Pietersen, 2007b:155).

General practitioners

- One employed by the DOH, who is not directly involved in the prescribing and dispensing of drugs, Dr C van Deventer (Head of District Clinical Specialist in the DKKD).

Pharmacist

- Voluntary personnel from the School of Pharmacy at the NWU (Potchefstroom Campus).

Nurses

- Mrs J Claassen and Dr P Bester, employed at the NWU (Potchefstroom Campus) in the School of Nursing.

The checklists for Step 2 were sent to voluntary personnel from the School of Pharmacy and the School of Nursing at the NWU (Potchefstroom Campus) to test the content validity of these checklists.

The feedback from these groups was used to improve the questionnaire's structure and the evaluation form and to ensure content validity.

(b) Criteria used to determine the content validity

- The conceptualisation of questions is the key to ensuring content validity (WHO, 1994:13).
- The experts need to evaluate the suitability of the data collection instrument for this study (Brink *et al.*, 2012:166).

(c) Areas used as a checklist for face and content validity of the questionnaire (refer to Annexure C) (Maree & Pietersen, 2007b:159)

- Is the appearance of the questionnaire up to standard for healthcare professionals?
- Does the questionnaire have clear instructions regarding the completion of the forms?
- A good time for completing a standard questionnaire is 30 minutes.
- Is the question sequence in the correct order?
- Do the questions result in any confusion?
- Is the wording of the questions understandable to ensure the correct response from the pharmacists, medical practitioners and nurses?
- Are the response categories easy to understand and to complete? Will these response categories provide the researcher with sufficient data?

(d) Steps used to ensure content validity of the checklist

- The checklists were assessed according to the standard MCC and ART ADR form.

1.4.6.3.2 Reliability

Reliability “deals with an indicator’s dependability” (Neuman, 2014:215) and indicates the random error in the measurement and the precision of the measuring instrument (Van Tilburg Norland, 1990). Reliability is used to determine on what level the instrument can be depended on to provide consistent results if the study is repeated (Brink *et al.*, 2012:168).

There are three types of reliability (Brink *et al.*, 2012:169):

- Stability
- Internal consistency
- Equivalence reliability

The procedures to be followed to improve the reliability of the questionnaire are:

- A pilot test with experts who are not included in the sample (Radhakrishna, 2007).

- The reliability method of test/re-test. The same group of experts must complete the questionnaire twice and a correlation between the scores must result in a coefficient of stability (Van Tilburg Norland, 1990).

The total population of HCPs that complied with the inclusion criteria participated in the final study, and therefore no pilot study was done. This also eliminated the test-retest method. However, the data collection method was evaluated as described in section 1.4.6.3.1, with specific reference to the structured questionnaire and the checklist.

1.4.7 Data collection process

The data collection process highlights information regarding where and when the data will be collected with the methods that will be followed to record the data (Beck & Polit, 2012:59). Approval from the following sectors was obtained before the data collection process started:

- (i) North West DOH: Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) directorate (Annexure H)
- (ii) Health director of DKKD
- (iii) PHC Tlokwe Local Municipality manager
- (iv) CEO/clinical head/hospital manager of the various hospitals (Matlosana Regional Hospital, Tlokwe District Hospital, Tlokwe Specialised Psychiatric Hospital, Ventersdorp District Hospital)
- (v) The head of pharmaceutical services in the North West Province (specifically for Step 2)

1.4.7.1 Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to Tlokwe Local Municipality

The questionnaire used in this study was a self-administered questionnaire. These types of questionnaires are the least expensive and have the least investigator participation. Although there is an increased risk for non-response, the self-administered questionnaire reduces information bias. A self-reporting technique is used to determine what people think or know and can also be used to collect truthful information from the participants (Brink *et al.*, 2012:153).

According to Punch (2005:100), the quality of the data can be influenced during data collection. The researcher needs to approach the participants professionally and explain all the details demanded on the basis of ethical considerations. Professionalism can motivate healthcare professionals to cooperate, which will improve the quality of the data. The cooperation of the

healthcare professionals is important, because a low response rate will influence the data quality.

For Step 1 of the study mediators were included for each facility. The mediators were well informed about the purpose and the process of the study so that they could address questions from participants at each facility in the absence of the research team. The contact numbers of the research team were provided to the mediators. The different healthcare professionals in the study each required different methods for the announcement and implementation for the study.

(a) Pharmacists in Tlokwe Local Municipality hospitals

Study site:

Tlokwe District Hospital

Tlokwe Specialised Psychiatric Hospital

Study announcement:

The research team, together with the regional pharmacist, introduced the project at a monthly meeting with all the pharmacists in charge of all the hospital pharmacies in the Tlokwe Local Municipality . The pharmacists in charge of the different hospital pharmacies were asked to act as mediators in the study. The announcement of the study included the aim of the project and an overview of the data collection plan (refer to the agenda in Annexure J). The research team also made an appointment with the pharmacists in charge of the two pharmacies in the two Tlokwe Local Municipality hospitals at that meeting.

Recruitment of participants:

The following activities were conducted during the meeting with pharmacists in charge of the pharmacies in the Tlokwe Local Municipality hospitals:

- The researcher explained the implementation of the study in their specific pharmacy and also explained the informed consent form to the pharmacist in charge. Emphasis was placed on the anonymity of the research process, the free and voluntary choice to participate, as well as the right of participants to withdraw from the study at any given time.
- The informed consent forms and the questionnaires with two sealed boxes (one for the consent form and one for the completed questionnaires in envelopes) were provided to the pharmacist in charge.

Distribution of questionnaire:

The following activities were conducted to distribute the questionnaire:

- The pharmacist in charge introduced the study according to the same agenda points (refer to Annexure J) to the pharmacists in the two hospitals.
- The informed consent form and the questionnaires were provided to the respondents by the pharmacist in charge. The respondents also received a copy of the informed consent form for personal reference.
- The sealed box for the purpose of collecting signed informed consent forms was provided to the pharmacist in charge. The box was positioned in the tea room in the pharmacy, where it was accessible to participants without compromising their anonymity.
- Participants were required to sign the informed consent forms and place them in the sealed box before the questionnaires could be completed.
- Each questionnaire included an envelope, and all completed questionnaires had to be sealed in the envelope provided.
- A second sealed box provided exclusively for the questionnaires was also stored in the tea room to ensure the privacy and anonymity of the participants.
- The researcher collected the sealed boxes five days after the questionnaires had been distributed.
- This sealed box exclusively for the informed consent forms was only opened in the privacy of the researcher's office.
- The researcher first counted the informed consent forms and then took the same number of completed questionnaires from the other box.

(b) Medical practitioners in Tlokwe Local Municipality hospitals

Study site:

Tlokwe District Hospital

Tlokwe Specialised Psychiatric Hospital

Study announcement:

The researcher conducted a pre-meeting with the clinical heads at the Tlokwe Local Municipality hospitals to announce the aim of the study and provided an overview of the implementation plan of the study according to the agenda points (refer to Annexure J). The clinical head announced the study to the medical practitioners during a monthly meeting. The pharmacist in charge at each of the respective hospitals acted as mediator for the study.

Recruitment of participants:

The following activities were conducted during the meeting with all the medical practitioners and specialists at the Tlokwe Local Municipality hospitals:

- The pharmacist in charge introduced the study, explained the informed consent forms and described the data gathering process that would be followed in the hospital. Emphasis was placed on the anonymity of the research process, the free and voluntary choice to participate, as well as the right of participants to withdraw from the study at any given time.
- The informed consent forms and the questionnaires with two sealed boxes (one for the consent form and one for the completed questionnaires in envelopes) were provided to the pharmacist in charge.

Distribution of questionnaires:

The following activities were conducted to distribute the questionnaire:

- The pharmacist in charge introduced the study according to the same agenda points (refer to Annexure J) to the medical practitioners in the two hospitals.
- The informed consent form and the questionnaire were provided to the respondents by the pharmacist in charge. The respondents also received a copy of the informed consent form for personal reference.
- The sealed box for the signed informed consent forms was positioned in the tea room in the pharmacy, where it was accessible to participants without compromising their anonymity.
- Participants were required to sign the informed consent forms and place them in the sealed box before the questionnaires could be completed.
- Each questionnaire included an envelope, and all completed questionnaires had to be sealed in the envelope provided.

- A second sealed box provided exclusively for the completed questionnaires was also stored in the tea room to ensure the privacy and anonymity of the completed questionnaires.
- The researcher collected the sealed boxes five days after the questionnaires had been distributed.
- This sealed box exclusively for the informed consent was opened in the privacy of the researcher's office.
- The researcher first counted the completed informed consent forms and then took the same number of completed questionnaires from the other box.

(c) Medical practitioners in Tlokwe Local Municipality PHC

Study site:

Tlokwe Clinics

Tlokwe CHC

Study announcement:

The researcher conducted a pre-meeting with the medical practitioner in charge of all the medical practitioners in the Tlokwe Local Municipality, Dr Karin Leon-Cachet, to announce the aim of the study and to provide an overview of the implementation plan of the study according to the agenda points (refer to Annexure J). The medical practitioner in charge of all the general practitioners in the Tlokwe Local Municipality, Dr Karin Leon-Cachet, acted as mediator for the study in this section of the study population.

Recruitment of participants:

The following activities were conducted during the meeting with medical practitioners at Tlokwe Local Municipality PHC facilities:

- Dr Karin Leon-Cachet introduced the study to the medical practitioners during a monthly meeting at the office of the sub-district at Dassierand. Emphasis was placed on the anonymity of the research process, the free and voluntary choice to participate, as well as the right of participants to withdraw from the study at any given time.
- The informed consent forms and the questionnaires with two sealed boxes (one for the consent form and one for the completed questionnaires in envelopes) were provided to Dr Karin Leon-Cachet.

Distribution of questionnaires:

The following activities were conducted to distribute the questionnaire:

- The medical practitioners visited the office of the sub-district at Dassierand for meetings with Dr Karin Leon-Cachet.
- The distribution of the questionnaire was done by the mediator after the introduction to the study according to the agenda points (refer to Annexure J).
- The informed consent form and the questionnaire were provided to the respondents by Dr Karin Leon-Cachet to sign. The respondents also received a copy of the informed consent form for personal reference.
- The sealed box for the informed consent forms was positioned in the office of the receptionist of the sub-district at Dassierand. The box was positioned so that it was accessible to participants without compromising their anonymity.
- Participants were required to sign the informed consent forms and place them in the sealed box before the questionnaires could be completed.
- Each questionnaire included an envelope, and all completed questionnaires had to be sealed in the envelope provided.
- A second sealed box provided exclusively for the completed questionnaires was stored in the office of the receptionist of the sub-district at Dassierand to ensure the privacy and anonymity of the completed questionnaires.
- The researcher collected the sealed box five days after the questionnaires had been distributed.
- This sealed box exclusively for the informed consent form was only opened in the privacy of the researcher's office.
- The researcher first counted the informed consent forms and then took the same number of completed questionnaires from the other box.

(d) Professional nurses in Tlokwe Local Municipality PHC

Study site:

Tlokwe clinics

Tlokwe CHC

Tlokwe mobile services

Study announcement:

The researcher conducted a pre-meeting according to the agenda points (refer to Annexure J) with the PHC manager and acting directors of PHC facilities to announce the aim of the study and to provide an overview of the implementation plan of the study. The operational manager from each facility acted as mediator for this study.

Recruitment of participants:

The clinical head announced the study to the professional nurses during their monthly meeting. This announcement included the purpose of the study, the informed consent form as well as the implementation process. Emphasis was placed on the anonymity of the research process, the free and voluntary choice to participate, as well as the right of participants to withdraw from the study at any given time.

The researcher provided the operational manager with a poster for each facility (refer to Annexure L). The researcher made an appointment with each operational manager to visit the site. The operational managers were asked to announce the study to the nurses at each facility before the pre-arranged date of the visit. They were also asked to put the poster on the notice board at least two days before the pre-arranged date. The researcher visited the site on the pre-arranged date to provide information according to the agenda points (refer to Annexure J) regarding the purpose of the study and explained the informed consent forms to all healthcare professionals or nurses working in the different PHC clinics.

Two sealed boxes were provided to the operational managers to be left at the office of the receptionist of the PHC facility – one for the signed informed consent forms and one for the completed questionnaires.

Distribution of questionnaires:

The following activities were carried out to distribute the questionnaire:

- The distribution of the questionnaire and two informed consent forms was done by the operational manager.
- The informed consent form and the questionnaire were provided to the respondents by the mediator to sign. The respondents also received a copy of the informed consent form for personal reference.
- The sealed box for the informed consent form was positioned in the office of the receptionist at the PHC facility. The box was positioned so that it was accessible to participants without compromising their anonymity.
- Participants had to sign the informed consent forms and place them in the sealed box before the questionnaires could be completed.
- Each questionnaire included an envelope, and all completed questionnaires had to be sealed in the envelope provided.
- A second sealed box exclusively provided for the questionnaires was also stored in the office of the receptionist at the PHC facility to ensure the privacy and anonymity of the completed questionnaires.
- The researcher collected the sealed box five days after the questionnaires had been distributed.
- This sealed box exclusively for the informed consent forms was opened in the privacy of the researcher's office.
- The researcher first counted the informed consent forms and then took the same number of completed questionnaires from the other box.

(e) Data validation and capturing

The researcher stayed in control of the data and handled all the administration of the data. The returned questionnaires were signed as soon as the researcher had received the completed questionnaires.

In order to analyse quantitative data, the raw data had to be systematically organised to provide statistics using software on a computer (Neuman, 2014:393). A coding procedure with guidelines was used by the researcher to classify the data into categories. A certain number was assigned to each questionnaire and the variables measured were indicated on a data coding sheet. During the coding procedure, non-numerical data were converted into numerical

data (Neuman, 2014:394). The data were uploaded onto the data coding sheet, which had been designed as a Microsoft Excel template and was stored on the researcher's computer. The researcher was responsible for data capturing to avoid the double capturing of data. To avoid data errors such as duplicated results or the omission of results, the researcher checked the data after each facility's data had been loaded on the data sheet. The list that accompanied the sealed box to each facility was compared with the data and coding numbers of the returned questionnaires. This was used to determine whether all the questionnaires received had been evaluated.

(f) Data storage

During the study, all electronic data and hard copies (structured questionnaires and survey form) were protected from unauthorised persons by means of a password-protected computer, and the survey forms were kept safe in a locked cupboard in the locked office of the researcher. Only the researcher, study leaders and statistician had access to the data.

After completion of the study, all hard copies of the data were kept safe and secure by locking them up in cupboards in the office of the research entity's (MUSA) and all electronic data were stored on an external drive, also locked in a cupboard in the office of the research entity. The data will be stored for five years, after which it will be permanently removed from the external drive under the direct supervision of Mrs A Bekker, the research assistant of MUSA. Furthermore, all hard copies of the data will be shredded under the direct supervision of the leader of MUSA, Prof MS Lubbe.

1.4.7.2 Step 2: Evaluate the completeness of the content of the completed ADR forms available in the DKKD

Study site:

Step 2 of the study included all the following facilities in the DKKD:

Matlosana Regional Hospital
Tlokwe District Hospital
Ventersdorp District Hospital

Study announcement:

The researchers conducted a meeting with the Head of Pharmaceutical Services in the North West Province, Mr T Mphaka, and the regional pharmacist, Mrs Ronel van Reenen, to announce the study according to the agenda point (refer to Annexure J) and obtained

preliminary permission to use the completed ADR forms from 2010 to 2014 at the three stated hospitals.

Permission and ethical clearance had been obtained from the Health Research Ethics Committee (HREC) (NWU-00003-15-S1) at the North-West University (Annexure H) and North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) (Annexure I), the researcher contacted the pharmacist in charge of the pharmacies at the three study sites to make an appointment to explain the research project. The researcher arranged a specific date and time (maybe more than one day) for a visit to the specific hospital to evaluate the completeness of the ADR forms. The researcher evaluated the completed ADR forms on site.

Administration of the checklist:

A coding scheme was designed as an important feature of this evaluation. The coding scheme for the evaluation form is to determine whether the information required on the ADR form is indicated or not (Robson, 2011:328).

The completed checklist did not contain any personal information of patients or healthcare professionals. The evaluation of the ADR forms was done by the researcher at the hospital. The data was captured on a Microsoft Excel template and only the researcher had access to the checklists. The hospital name was not used for the evaluation of the ADR forms to increase the anonymity of the each facility and no documents were removed from the premises of the different hospitals pharmacies. The checklist was completed on a hard copy and the researcher stored the checklist in a file according to numbers allocated for each checklist.

Data validation and capturing:

The researcher stayed in control of the data and handled all the administration of the data.

The data were uploaded onto the data coding sheet that had been designed as a Microsoft Excel template and was stored on the researcher's computer. The researcher alone was responsible for the entering of the data on the template. To avoid data errors such as duplicated results or the omission of results, the researcher did data checking after each facility's data was loaded onto the data sheet.

Data storage:

For the duration of the study, data from the questionnaire and the checklist was stored electronically and in the form of hard copies. No unauthorised person had access to the data, as all electronic data was secured on a password-protected computer and completed

questionnaires and evaluation forms were secured in a locked cupboard in the locked office of the researcher. Only the researcher, study leaders and statistician had access to the data.

After completion of the study, the data will be protected and secured on an external drive and will be stored with the hardcopies in a cupboard in the Research Entity's (MUSA's) office.

The data (hard copies and electronic copies) will be stored for five years and will be destroyed after that time. The electronic data on the external drive will be destroyed under direct supervision of Mrs A Bekker, the research assistant of MUSA, and the hard copies of the data will be shredded under direct supervision of Prof MS Lubbe, leader of MUSA.

1.4.8 Study variables

The characteristics that are measured in a study are the variables (Joubert, 2012:127). Quantitative data uses a scale of measurement to classify the study variables (Bowling, 2009:158). Dependent variables are variables that result in the outcome of another variable and independent variables have an effect on other variables and are responsible for a change in the state of affairs (Kumar, 2014:85; Neuman, 2014:181).

In a quantitative study, all the concepts are redefined as variables (Neuman, 2014:180). In Step 1 of the study, variables were measured on a categorical or numerical scale (Aldous *et al.*, 2013:47). Levels of measurements indicate the scale that can be used for data analysis (Neuman, 2014:222). A numerical scale can be discrete or continuous variables, and categorical values can be binary, nominal or ordinal (Aldous *et al.*, 2013:48).

A nominal scale is a set of categories used in the classification of data and do not have any natural ordering (Gerrish & Lacey, 2010:438; Robson, 2011:420). Binary data is a subcategory of nominal data and is used when there are two values for a category, for example male/female (Gerrish & Lacey, 2010:438). This can be used for the analysis of the demographic information (Robson, 2011:420). The demographic information of each participant was categorised according to gender (male or female), age, profession, working environment and years of experience.

An ordinal scale is used when variables can be categorised, and there is a natural order in the values (Brink *et al.*, 2012:148; Gerrish & Lacey, 2010:438). This level of measurement was used to analyse the questions that were coded according to the Likert scale and the open-ended questions that were coded into categories (Neuman, 2014:223). In Step 2 of this study, a categorical scale of present/absent was used (Brink *et al.*, 2012:181).

Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

Table 1.2: Independent and dependent variables for Step 1

Independent variables	Dependent variables
Type of healthcare professionals: general practitioners, hospital pharmacists and professional nurses	ADR system and structure Healthcare professionals' perception of ADR reporting
Current working environment: hospital pharmacies, district clinics and outpatient department	Healthcare professionals' experience regarding ADR reporting
Age of respondents	Factors that may influence ADR reporting
Gender of respondents	The possible challenges of ADRs
Years of experience of the respondents	The future of pharmacovigilance
Qualification of the respondents	

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Table 1.3: Independent and dependent variables for Step 2

Independent variables for evaluation checklist	Dependent variables for evaluation checklist
Yes/no	The prevalence of the incompleteness of each of the aspects that should be completed on the ADR form
Recommendations made by the researcher	Medicines/vaccines/devices
	ADR outcome
	Product-quality problem
	Reporting doctor/pharmacist

1.5 Data analysis plan

According to Brink *et al.* (2012:179), "the most powerful tool available to the researcher in analysing data is statistics". The variables identified for this study indicate which data analysis plan had to be followed.

1.5.1 Descriptive statistics

“Descriptive statistics are a set of techniques that organize, summarize and provide a general overview of the data” (Ruane, 2005:179). Descriptive statistics indicate a number of statistical approaches that present data in a valuable way, in a graphical way or a numerical way (Maree & Pietersen, 2007b:183). These statistics can be categorised by the number of variables implicated: univariate, bivariate and multivariate statistics. Univariate statistics are used to measure one variable. Bivariate analysis is more valuable statistically as it is used to measure the relationship between two variables. Covariation and statistical independence indicate the relationship between two variables (Neuman, 2014:403).

A set of data can be explained according to three characteristics, i.e. the distribution of values in a spread, central tendency and variability (Beck & Polit, 2012:382; Parahoo, 2006:384). Frequency distribution can be used to organise and explain descriptive statistics (Brink et al., 2012:180; Neuman, 2014:396). The analysis of each variable can be done according to the level of measurements. The four levels of measurements are nominal, ordinal, interval and ratio (Beck & Polit, 2012:379; Brink *et al.*, 2012:169; Neuman, 2014:223).

Nominal data can be analysed with frequency distributions, proportions, mode and cross-tabulation. Interval and ratio data can be analysed with frequency distributions, analysing proportions and means, and by analysing standard deviation (Ruane, 2005:179). Ordinal data includes the analysis of frequency distributions, proportions and median. The questionnaire in Step 1 was on an ordinal scale and ordinal data had to be transformed to numerical values (Pfeeger & Kitchenham, 2003:26). The checklist with a present/absent scale will present binary data, as the data is classified as categorical data (Aldous *et al.*, 2013:48).

Frequency distribution

The most basic method used to analyse quantitative data is to count the occurrence of a value represented in the data. Frequency statistics can be reported in percentages and in absolute numbers. The percentages can be converted to proportions if it is too difficult to compare the absolute numbers (Parahoo, 2006:380). Frequency distribution is used if the variable is categorical (Aldous *et al.*, 2013:52).

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Frequencies and percentages were used to analyse all the questions on the questionnaire. All the age groups were sorted into respective range years. Healthcare professionals' years of experience in practice were also sorted into respective range years independently of different

healthcare facilities. In Section C of the questionnaire, strongly agree and agree and strongly disagree and disagree categories on the 5 point Lickert scales were grouped together. The results were represented in three categories: namely agree; uncertain and disagree.

Step 2: Evaluate the completeness of the content of the completed ADR forms available in the DKKD

Frequency and percentages were used to analyse all the elements on the ART and the MCC checklists.

1.5.2 Inferential statistics

Inferential statistics make use of simple data to suggest that a particular characteristic in the study sample can be present in a larger population (Brink *et al.*, 2012:180). “Inferential statistics describe correlation or casual links between variables” (Parahoo, 2006:468). No inferential statistics were performed in this study, because of a low response with a small number of respondents in the various healthcare professional groups in Step 1 and no inferential statistics were required for Step 2.

1.6 Ethical considerations

According to Beck and Polit (2012:151), if the researcher includes humans as subjects in the study population, their rights must be protected at all times. “A human subject is a living individual about whom an investigator conducting research obtains: data through intervention or interaction with the individual; or identifiable private information” (UW, 2014). Beneficence, respect for human dignity and justice are the three principles on which the researcher must base their standard of ethical conduct. Beneficence is the responsibility of the researcher in order to minimise the risk of the study and to maximise the benefit of the study to ensure that no subject will be harmed. Respect for human dignity is required to reassure the subject that participation is voluntary, with no penalty if the subject does not want to participate. The researcher must explain all the relevant information. Justice involves the duty of the researcher to ensure that every subject has the right to fair treatment and the right to privacy (Beck & Polit, 2012:151).

1.6.1 Permission

Permission to conduct the study were provided by HREC (NWU-00003-15-S1) (Annexure H) at the North-West University, North West Department of Health: PPRM&E directorate (Mmabatho) (Annexure I), and the Dr Kenneth Kaunda District health director. The PHC manager of Tlokwe Local Municipality, chief executive officers of hospitals/clinical head/hospital manager of the

various hospitals (Matlosana Regional Hospital, Tlokwe District Hospital, Tlokwe Specialised Psychiatric Hospital, Ventersdorp District Hospital) were included in the process of ethical clearance to use the information from the healthcare professionals in the DKKD (NWU, 2010:48; Thomas, 2013:42). Permission was also obtained from the head of Pharmaceutical Services in the NW Province to conduct Step 2.

1.6.1.1 Permission and informed consent from the participants

The participants were provided with an informed consent form with all the necessary information (refer to Annexure B). The consent form was in a language that the participants understood (Brink *et al.*, 2012:40). Written consent was obtained from the following interest groups:

- All healthcare professionals in the public health sector on a permanent or temporary contract.
- All healthcare professionals involved in the administration of a public health institution.

1.6.2 Anonymity

According to the justice principle of ethical conduct, participants have the right to privacy (Beck & Polit, 2012:162). Anonymity means that the identity of the participants is secret, even from the researcher. Anonymity was ensured with the self-administered questionnaire, because no personal information that can be used to identify a specific respondent was required in the questionnaire, and the data was analysed and categorised according to a code/number assigned to each survey. The researcher assigned a number to each questionnaire to ensure that the opinion of one participant was not analysed more than once. The number on the questionnaire was compared with a list of numbers to prevent bias (Thomas, 2013:47). The anonymity for Step 2 was also important. The checklist did not require the identification of any patient, healthcare professional or hospital.

For the duration of the study, data from the questionnaire and the checklist was stored electronically and in the form of hard copies. No unauthorised person had access to the data, as all electronic data was secured on a password-protected computer. Only the researcher, study leaders and statistician handled the data. Completed questionnaires and evaluation forms were secured in the locked cupboard in the researcher's locked office. The researcher alone had access to the cabinet and the office. After completion of the study, the data will be protected and secured on an external drive and the hard copies will be placed in a cupboard in the office of the research entity (MUSA). The data will be stored for five years and will be destroyed after that time. The electronic data on the external drive will be destroyed under direct supervision of

Mrs A Bekker, the research assistant of MUSA, and the hard copies of the data will be shredded under direct supervision of Prof MS Lubbe, leader of MUSA.

1.6.3 Confidentiality

Confidentiality is “the ethical protection for those who are studied by holding the research data in confidence or keeping them a secret from the public, not releasing information in a way that permits linking specific individuals to specific responses” (Neuman, 2014:155).

1.6.3.1 Confidentiality regarding the participants

It is unethical for the researcher to share information regarding participants with others (Kumar, 2014:286). It is important not to compromise the confidentiality of the information obtained from the participants (Thomas, 2013:49). The study population was given the choice to participate in the study and they had the choice to withdraw from the study at any given time without the fear of being penalised in order to ensure respect for human dignity (Beck & Polit, 2012:162; Brink *et al.*, 2012:35; Thomas, 2013:49). To ensure that the confidentiality of the questionnaire was not breached, the participants returned the questionnaire to a sealed box in central facilities and these boxes were collected by the researcher. Each questionnaire had an envelope enclosed. The questionnaire did not contain any personal information on any participant (Parahoo, 2006:311). Only the researcher, study leaders and statistician handled the data.

The ADR forms in Step 2 were not removed from the hospital, because the researcher evaluated the ADR forms at the hospital. This ensured the confidentiality of the personal information on the ADR forms that were evaluated (Kumar, 2014:286).

1.6.3.2 Confidentiality regarding the data collected

The data will not be used for any other purpose than initially intended. It is important to keep the data for an appropriate time and to keep the data secure. The codes assigned to each questionnaire were used to identify all the questionnaires received. The researcher evaluated each questionnaire and provided codes for each section. The open-ended questions were assigned to categories according to themes recognised. The data was uploaded on the data coding template in Microsoft Excel. The data was saved with an encrypted document password to keep it secure (Thomas, 2013:48). Once the data had been loaded, it was filed and stored in an office at the NWU to ensure that only the researcher had access to the data.

1.6.4 Justification

Pharmacovigilance has become an important scope of practice to improve therapeutic risk management (Mehta *et al.*, 2014:104). The WHO delegates the responsibility regarding the

improvement of pharmacovigilance to healthcare professionals. These healthcare professionals were included in the study in the DKKD. The inclusion criteria were based on the necessary qualification in one of the three professions or the qualification to prescribe medicine. All the participants were selected fairly and the researcher did not select the participants according to age, gender, race or years in practice.

The results of the study will benefit the daily practice of healthcare professionals and the indication of the healthcare professionals' knowledge and the attitude regarding pharmacovigilance can promote the education of the participants.

1.6.5 Respect for participants and study committees

Feedback regarding the outcome of the study was provided to the DKKD Research Committee with an oral presentation. The managers of the different public hospitals, chief executive officers of hospitals and clinic managers in the DKKD were taken into consideration, because the researcher demanded time from them as well as the use of their facilities. This study will also be used as a source for future studies regarding pharmacovigilance in the North West Province.

1.6.6 Benefit-risk-ratio

It is the responsibility of the researcher to ensure that the benefits of the study are greater than the risk of the study. The risk of the study was the probability that participants may be harmed during the study, and the benefits identify the positive principles from the study (Brink *et al.*, 2012:42-43).

1.6.6.1 Anticipated benefits

Before the researcher starts to conduct the study, the benefit of the research problem must be identified. The study must benefit the participants and the researcher (Creswell, 2014:97). Direct benefits are when the participants are the majority beneficiaries of this study. Indirect benefits of the study are the increased knowledge for society regarding the problem identified. The following benefits were identified for this study and were included in the consent form:

1.6.6.1.1 Direct benefits

The questionnaire from Step 1 provided the healthcare professionals with the opportunity to identify challenges that they experience with the reporting of ADRs.

1.6.6.1.2 Indirect benefits

According to Mehta *et al.* (2014:104), the current status of pharmacovigilance in South Africa indicates the need for a national plan to strengthen the pharmacovigilance system. The

improvement of pharmacovigilance in the DKKD will benefit the national pharmacovigilance plan to improve patient care and contribute to treatment policy decision-making.

The successful implementation of an ADR documentation system will improve patient care with regard to the safe use of medicines in the Tlokwe sub-district. If the patient care is improved, it could boost the self-esteem of the healthcare professionals.

In Step 2, the DOH in DKKD will indirectly benefit from the evaluation of the completeness of the ADR forms. The researcher will provide them with recommendations regarding the completion of the ADR forms in the future. The recommendations will act as guidelines for future training regarding the completion of ADR forms.

The development of standard operating procedures from the results from Steps 1 and 2 will increase and improve the quality of ADR reporting in the DKKD, which can be applied or used in other health districts in the North West Province. This will benefit the patients, HCPs, hospitals or other healthcare institutions and the province.

The researcher will benefit from the study as the results are used for her dissertation for partial fulfilment of the requirements for a master's degree in Pharmacy and the possibility of publication.

1.6.6.2 Anticipated risk and precautions

The research participants and the researcher are known as the stakeholders in research (Kumar, 2014:283). When human participants with the ability to think, feel and experience physical or psychological distress are involved in the study, the potential risk of harm to the participants must be taken into consideration (Leedy & Ormrod, 2014:106). The risk of the study for the researcher will have an influence on the risk for participants (Brink *et al.*, 2012:46).

The potential risk of a study can be classified as harm, discomfort or inconvenience. The following guidelines were used to assess the level of ethical risk for this study (University of Tasmania, 2014; Beck & Polit, 2012:157,168):

- Harm to the participants: physical, psychological, social and legal harm
- Discomfort: participant anxiety
- Inconvenience: completing a form

The study design must be valid to conduct a study. The methods used for this study are fully explained, with reasons why those designs were most suitable for Step 1 and Step 2 of this research.

1.6.6.2.1 Risk to the participant and precautions

The identification and methods for preventing possible risk in the study minimised these risks.

Table 1.4: Potential risk to the participant and precautions

Risk to the participant	Precaution to reduce risk
The healthcare professionals may be resistant to answering threatening questions about their knowledge regarding pharmacovigilance, or if they are under the impression that they will be penalised for their answers (Neuman, 2014:127).	There were no threatening questions regarding pharmacovigilance in the questionnaire in order to reduce the risk of insulting the participants. No personal questions were included in the questionnaire and no individual participant could be traced after completing the questionnaire.
The publication of personal information from the questionnaires and the ADR forms are a risk for the participants (Kumar, 2014:312).	No personal information was published. No names or personal details from the patients were recorded on the ADR report form as only the completeness of the completed forms were evaluated according to the standard checklist (refer to Annexure D and E).
The questionnaire will demand time from the healthcare professional's already busy days.	The questionnaire did not take more than 20 minutes to complete.
The participant might have anxiety if the questionnaire is not understandable or if the participants have the impression that they are forced to participate.	The researcher provided all participants with an informed consent form. The consent form and information regarding the study were a precaution for participant anxiety. This form also emphasised voluntary participation in the study and withdrawal from the study without any repercussions.
Incentives to participants.	No incentives were given to the participants in an attempt to avoid false premises.

The researcher provided stationery to the participants to complete the forms. All participants were treated with respect. The researcher acted in professional manner and appreciation was shown to all voluntary participants. The researcher thanked the participants for their time and contribution in completing the questionnaire.

1.6.6.2.2 Risk to the researcher and precautions

According to the US Department of Health and Human Services (2011), “research misconduct is the fabrication, falsification or plagiarism in proposing, performing or reviewing research, or reporting research results”. Researchers collecting data must adhere to the code of conduct to avoid research bias that will result in unethical actions. The following risks were identified for the researcher to take into consideration during the study:

- **The necessity of avoiding bias**

It is the responsibility of the researcher to avoid bias, because researcher bias is unethical (Kumar, 2014:286). Bias refers to the factors other than those investigated that may influence the findings of a study (Parahoo, 2006:645). Research bias appears when a researcher intentionally attempts to hide/highlight results (Kumar, 2014:287). This includes fabrication, manipulation of designs and methods, manipulation of data, plagiarism and irresponsible collaboration (Brink *et al.*, 2012:43). Non-responder bias occurs when an HCP participates in the study without providing the researcher with a signed consent form, and if a participant responds in the same way to all the questions it results in acquiescent response bias (Gerrish & Lacey, 2010:373).

- **The prevention of harm to the participants**

A formal risk assessment must be done to minimise harm to the patient. It is the researcher’s responsibility to ensure non-maleficence, which means the researcher should not cause any harm to participants (Parahoo, 2006:112). The identification of the risk to the participant can be used to reduce bias (Gerrish & Lacey, 2010:296). The researcher needs to ensure that all the participants will benefit from the study and they are not allowed to deceive the participant. The participant must have all the relevant information before participating in the study (Creswell, 2014:98). It is unethical of the researcher to provide incentives to participants as a benefit of the study. If no incentives are given, it should be stated on the consent form (Kumar, 2014:285).

- **Incorrect reporting and use of data**

Incorrect reporting to manipulate the data to reflect your own conclusion of the study is unethical. The researcher is also not allowed to use the data for any other purpose than that stated in the consent form (Kumar, 2014:287-288).

Table 1.5: Potential risks to the researcher and precautions

Potential risks	Precautions to reduce risks
<p>The necessity to avoid bias Research bias Non-responder bias</p>	<p>No results were fabricated and all data was used. Study methods were conducted as described in the protocol. No manipulation of data occurred. Signed informed consent was obtained from the participants. The questionnaires were entrusted only to the identified participants and they were requested to return the questionnaire to the central facility. This minimised the risk that a patient or other unidentified HCP participated in the study. Non-responder bias was also assessed when the researcher compared the codes from the completed questionnaires with the codes from the signed consent forms.</p>
<p>The prevention of harm to the participants</p>	<p>A formal risk assessment was done to minimise the harm to the patient. The participant was not deceived by the researcher and all relevant information was explained in the informed consent form. No incentives were provided to participants as a benefit to the study.</p>
<p>Incorrect reporting and use of data</p>	<p>The data was not manipulated to reflect the researcher's own point of view. The researcher used the data only for the purpose stated in the informed consent forms.</p>

1.6.7 Levels of ethical risk

An assessment of the benefits and risk of the study provided relevant information to the researcher, the review committee and the participants. The researcher used this assessment to ensure that the research design was relevant and correct for this specific study. The review committee used the assessment of risk and benefits to decide whether the risks identified in the study were acceptable or not. The risk/benefit assessment assisted the participant with the decision to participate in the study (Department of Health, 1979:90).

1.6.7.1 Risk assessment for this research project

Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

Step 1 in this research was identified as a low level of risk. The only risks predicted that could not be excluded from the study were the discomfort or anxiety and the inconvenience of completing the form. Guidelines such as the announcement of the study, with time in the agenda for questions from participants (refer to Annexure J) and the short time it took to complete the questionnaire, were used to ensure that the inconvenience was as little as possible.

Step 2: Evaluation of the completion of available ADR forms in the DKKD

Step 2 of the research project was classified as a low level of risk, because the only significant risk was the time taken to evaluate all the completed ADR forms.

1.6.8 Publication of results

The researcher provided an oral presentation as feedback to the DKKD Research Committee and the Pharmaceutical and Therapeutic Committee of the North West Province. The results were presented in a dissertation, research articles and as conference presentations nationally and internationally. The pharmacist in charge at the hospitals and the PHC managers provided the participants with the results and recommendations concluded from the study.

1.6.9 Professional competence

The research team had the necessary professional and research competence to conduct this study successfully. The supervisor for this study was Prof MS Lubbe, the leader of the niche area: Medicine Usage in South Africa (MUSA). The researcher, L Goosen, was registered for the MPharm (Pharmacy Practice) programme. The researcher had also attended a course on survey design, research methodology and biostatistics. The regional pharmacist, Ms R van Reenen, was included in the study, because she provided information regarding the facilities that needed evaluation and she assisted with contributions to the questionnaire. Dr DM Rakumakoe and Mrs HE Bekker (a former regional pharmacist in the North West Province) and upcoming secondary researchers were the co-supervisors for this study. There was no conflict of interest regarding the results of the study.

1.7 Chapter summary

This chapter explained the motivation for this research study. The background and problem statement clarified the relevance and the need for the study. The aim and objectives were identified and an appropriate data collection instrument was assigned for Steps 1 and 2 in this study. The research method indicated the steps that were followed to collect the desired data. The researcher highlighted the data analysis plan and how reliability and validity were ensured. In this study, ethical clearance was compulsory and ethical guidelines were provided to minimise risk and prevent any harm to the participants or the researcher

CHAPTER 2 PHARMACOVIGILANCE

2.1 Introduction

“The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions” (WHO, 2006:22).

Chapter 2 focuses on pharmacovigilance as part of therapeutic risk management. Good pharmacovigilance practices, including the benefits of the system, the responsibilities of all the stakeholders in the system and the process of ADR reports, are identified. The ADR report form is analysed and the different sections on the report form as well as the different terms used on the ADR report form are explained. An overview of current South African pharmacovigilance practices is provided and the current MCC national ADR report form and the ART report are compared to international guidelines. This chapter also includes the prevalence of ADRs, global problems that influence the pharmacovigilance system and possible factors that may encourage ADR reporting to improve the pharmacovigilance system.

2.2 Therapeutic risk management

Therapeutic risk management (TRM) “aims to assure safe medication use in populations, show a positive benefit/risk balance and reduce the risk of exposure in populations that show a negative benefit/risk balance” (Hartzema *et al.*, 2008:205). The management of medication risk is progressing to contribute to patient care in the development of new medicine (Andrews & Dombeck, 2004:599). TRM provides a structure to manage health outcome. This structure integrates pharmacoepidemiology, medicine and public health (Epstein, 2008:201). Risk management (RM) expanded its horizon as an independent discipline to apply its principles to the evaluation and controlling of risk and preventing harmful events (Huang, 2008:185; Hyslop *et al.*, 2002:417).

According to the Food and Drug Administration (FDA) (2006:10) risk management “is the systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating, and reviewing risk.” There is a possibility of risk with every medicinal product and the purpose of RM is to control these risks to ensure the safe use of these products and to guarantee the benefits of drugs prevailing over the risk of a drug to improve patient care (Andrews & Dombeck, 2004:599; Hirst *et al.*, 2006:839; MHRA, 2012:85). Risk assessment and risk minimisation are activities of TRM (Hartzema *et al.*, 2008:205).

Although new drugs are important for the benefit of healthcare and patients, the disadvantage of a new drug cannot be ignored (Prieto *et al.*, 2012:896; Sauer *et al.*, 2008:1; WHO, 2004a:9).

The major apprehension about a drug is the effectiveness and safety of a drug (Gupta & Udupa, 2011:1064). The safe use of medicine, even with the correct use, is not flawless (Hyslop *et al.*, 2002:417). The benefit-risk evaluation of drugs includes post-marketing safety monitoring (WHO, 2002b:17). Data regarding medicine safety is gathered from pre-marketing trials, post-approval studies and spontaneous reporting of ADRs (De Ponti, 2013).

2.2.1 Factors affecting drug effectiveness and safety

The safety of medicine can be influenced by more than one factor. The pathogenesis of ADRs includes pharmacological, immunological, genetic and environmental factors (Alomar, 2014:85; Dal Pan, 2014:1).

(a) Use of traditional and complementary medicines

Africa, Asia, the Caribbean and Latin America make use of traditional medicines in primary healthcare (Abdel-Lafit & Abdel-Wahab, 2015:155; Department of Health, 2013b:21; WHO, 2002c:9). Pharmaceutical and cosmetic industries recognise the importance of medicinal materials. Medicinal plants are perceived as safe to use against a low cost (Kamsu-Foguem & Foguem, 2014:126). However, the efficacy of these drugs is unknown and fatal ADRs have been noticed (Abdel-Latif & Abdel-Wahab, 2015:155; Department of Health, 2013b:21; WHO, 2002c:9).

(b) Lack of training of prescribers

Prescribers require sufficient knowledge regarding the efficacy and safety of medicinal products to reduce the risk of harm to a patient (Star & Edwards, 2014:91). Although different countries have different prescribing approaches, regular training opportunities for new drug use or drug warnings for healthcare professionals are required around the globe (Abdel-Latif & Abdel-Wahab, 2015:159; Bouvy *et al.*, 2015; Department of Health, 2013b:21; WHO, 2002c:9).

(c) Diet and genetics

The race or genetic makeup of a patient influences the effect of drugs. Diet and food influence the uptake and metabolism of different drugs (Abdel-Latif & Abdel-Wahab, 2015:159). The variation among the ethnic groups between clinical trials and patients around the globe can lead to an ADR (Alomar, 2014:85). Age, gender, weight and creatinine clearance are regarded as risk factors in the safe use of drugs (Alomar, 2014:85). This supports the requirement for this information on the ADR report form.

(d) Disease patterns

The presence of more than one disease and drug-disease interactions influence the safety and efficacy of a drug (Alomar, 2012:83). Diseases associated with liver and kidney impairments and malabsorption may have a negative effect on the drug (Abdel-Latif & Abdel-Wahab, 2015:159). According to Kurnik *et al.* (2004:107), the drug-disease interaction between the use of amiodarone for a heart-related disease and the presence of subtle thyroid abnormality results in chronic hypothyroidism. Patients suffering from human immunodeficiency virus (HIV) are exposed to an increased risk of drug-disease interactions due to the influence of the disease (Kurnik *et al.*, 2004:110).

(e) Drug manufacturing, distribution and storage

Good manufacturing practices are required to ensure the safety and efficacy of drugs (WHO, 2003). Poor manufacturing practices, inappropriate packaging, storage and distribution of drugs may result in substandard medicine (WHO, 2006:15). Substandard medicines “are products whose composition and ingredients do not meet the correct scientific specifications and are consequently ineffective and often dangerous to the patient” (WHO, 2003).

2.3 Pharmacoepidemiology

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the prevention and control of health problems (Bonita *et al.*, 2006:2). Pharmacoepidemiology is “the study of the nature and the extent of drug taking behaviors and drug use problems” (Waning & Montagne, 2012:1). Pharmacoepidemiology is an example of applied epidemiology. Pharmacoepidemiology studies the utilisation and beneficial or adverse effect of drugs in different populations to provide an overview of the effect of a drug in real-life situations (Hilmer *et al.*, 2012:181,182).

The goal of guidelines for pharmacoepidemiological practices is to use pharmacoepidemiology studies for risk management, as pharmacoepidemiology is identified as the foundation of therapeutic risk management (Hirst *et al.*, 2006:200). The high prevalence of ADRs validates the epidemiological importance of ADRs (Adhikary *et al.*, 2013:1027).

The central function of pharmacoepidemiology is post-marketing surveillance (Waning & Montagne, 2001:17). Whenever a drug is used, a system is required to monitor and report unwanted and unexpected ADRs (WHO, 2006:22). Drug safety monitoring has a desperate need for surveillance due to increased competition among pharmaceutical companies. New drugs are released at the same time and this increases the number of undetected ADRs (Reddy *et al.*, 2014:34).

Pharmacoepidemiological studies include both clinical and health outcomes and are used to evaluate healthcare systems (Hirst *et al.*, 2006:200). The aim of the public health system is to improve health and reduce the risk of disease/harm/death in a population. This programme is implemented according to each country's epidemiology and environment influenced by the socioeconomic status, lifestyle, nutrition and behaviour patterns of the population (WHO, 2006:12).

The clinical development of new drugs is divided into four phases. Phase 1 includes healthy volunteers to gather preliminary data for the trial, Phase 2 includes varied patient groups to determine short-term safety and efficacy, and Phase 3 includes subjects with the disease to determine the safety and dosage recommendations. These three phases conclude the development of the new drug before registration (Bagheri *et al.*, 2006:629; FDA, 2005:23; WHO, 2004a:1). Phase 4 in the clinical development of a new drug is the post-approval studies of the drug to establish specific safety concerns of the drug after registration (WHO, 2004a:1).

The phases in clinical trials are limited. The drugs are tested on animals pre-clinically but this is not sufficient to predict drug safety in humans. The sample size is small due to inclusion and exclusion criteria, supporting the statement that these trials are limited to different populations (Department of Health, 2013b:23). A minimum of 30 000 people is required to be treated with a new drug in a clinical trial to provide an ADR incidence of 1 in 10 000 exposed participants. Fewer than 5 000 participants have been exposed to the new drug by the end of Phase 3 of a clinical trial, before the registration, which highlights the importance of Phase 4, post-marketing surveillance (Fine, 2013; WHO; 2002c:8; WHO, 2004a:1).

2.4 Post-marketing surveillance (PMS)

The report of ADRs is identified as a basic component of PMS (Suyagh *et al.*, 2015:148). PMS is used to identify and collect information about medicine after it has been approved by the FDA (Waning & Montagne, 2012:131). PMS entails the monitoring of medicine in realistic everyday life. This includes the drug's exposure to a bigger population, different population groups such as children that were not included in the clinical trial, and different cultural groups (Bagheri *et al.*, 2006:629; Waning & Montagne, 2012:131). Risk-management plans should be incorporated to improve post-marketing surveillance (Härmark & Van Grootheest, 2008:749). Controlled clinical trials are not strong enough to identify and report harmful effects caused by a new drug, and that leads to the perception that there are no risks associated with the use of drugs (Fine, 2013; Zorzela *et al.*, 2014:348).

PMS can include randomised clinical trials, drug-drug interaction studies, special population studies and observational pharmacoepidemiology studies (Hilmer *et al.*, 2012:1810). This

provides the opportunity to identify low-frequency reactions, high-risk groups not included in clinical trials, long-term effects of the new drug, increased severity/incidence of reactions identified during the clinical trial of the drug.

There is more than one method to collect data regarding the safety of medicine (WHO, 2006:23). Different studies can be applied to monitor ADRs (Fine, 2013; Hilmer *et al.*, 2012:182; WHO, 2006:40):

- **Cohort event monitoring**

Cohort event monitoring “is a prospective, observational, cohort study of adverse events associated with one or more medicines” (Pal *et al.*, 2013:76; WHO, 2006:40). This reporting system is applied earlier in Phase 4 of the clinical development of a new drug. This reporting system is effective as it requires the report of all the ADRs during the development of a drug (WHO, 2006:40). Cohort event monitoring requires data of all patients to whom a specific drug has been administered. This monitoring activity demands 10 000 patients for statistical power, but a larger number will provide a more accurate indication of unrecognised or unsuspected events. Although this system has the advantage of providing a full profile of adverse drug events, spontaneous reporting is the supreme approach to reporting ADRs and is regarded as the most effective surveillance system (Abubakar *et al.*, 2014:118; Khan, 2013:45; Upadhyaya *et al.*, 2012:307; WHO, 2006:41).

- **Spontaneous reporting and case series**

Spontaneous reporting is a system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national health pharmacovigilance centre (WHO, 2006:22). This method has the potential of detecting early signals of unrecognised safety problems (Pal *et al.*, 2013:75; Waller & Evans, 2003:19). Spontaneous reporting of ADRs is also implemented in the pharmaceutical industry to ensure the safe and effective use of a drug from Phase 1 until Phase 4 during the clinical development of a new drug (Härmark & Van Grootheest, 2008:743).

Spontaneous reporting of ADR is still not a flawless system, as it applies to newly released products, with a high rate of under-reporting (Härmark & Van Grootheest, 2008:743; Khan, 2013:46; Pal *et al.*, 2013:75). There are systems that rely on spontaneous reporting only for primary drug surveillance (Molokhia *et al.*, 2009:76; Pal *et al.*, 2013:75). This low-cost method of reporting ADRs is the most common reporting system in developed and developing countries (Pal *et al.*, 2013:75; WHO, 2006:23). The advantage of spontaneous reporting of ADRs is that it includes a large number of patients and opposes the idea that monitoring of ADRs is expensive

(Hazell & Shakir, 2006:386). Spontaneous reporting of ADRs is the basis of pharmacovigilance (Pal *et al.*, 2015:1).

Pharmacovigilance is a worldwide master key and an evaluation process to improve the safety of drugs released on the market (Jeetu & Anusha, 2010:315; Waller & Evans, 2003:17). Pharmacovigilance should be a priority to maintain and achieve the safe use of drugs (Suyagh *et al.*, 2015:148).

2.5 Pharmacovigilance

The term pharmacovigilance can be divided into Pharmakon, meaning drug, and Vigilance, meaning to keep alert, to monitor the safety and effectiveness of a drug (Dogra *et al.*, 2013:71; WHO, 2006:10). 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, but it has been expanded to the management of the benefits and risks of medicines on the market” (WHO, 2012:1). The science of pharmacovigilance includes the monitoring of medication error, lack of efficacy, substandard medicine and the use of medicine for other diseases than those originally indicated (WHO, 2006:21).

Risk management is at the top of the pharmacovigilance pyramid, as pharmacovigilance activities and interventions are designed to identify, characterise, prevent or minimise risk relating to medicinal products, including assessment of the effectiveness of the interventions (Bannoo 2013; Gagnon *et al.*, 2012:157). No other system has been developed to identify and reduce the risk of ADRs after the marketing of a drug (Bagheri *et al.*, 2006:630). Pharmacovigilance should be applied as the foundation of the development of a new drug (Gagnon *et al.*, 2012:142).

Pharmacovigilance expanded its discipline to include herbal, traditional and complementary products and blood products, medical devices and vaccines (WHO, 2006:21). Pharmacovigilance is now a division of patient care and originated to reduce harm to patients with the aim of improving public health (Businaro, 2013; WHO, 2007:7). The thalidomide disaster, identified by Australian physician WG McBride, in 1961 forced healthcare professionals to make the safety of a drug a priority field in everyday practice (Santosh & Tragulpiankit, 2011:2). Pharmacovigilance today is even more important. West African countries are using trial drugs for the Ebola virus, and post-marketing surveillance is inevitable. This trial is not controlled and without the correct monitoring of the safety and the effectiveness of this drug, it could result in a disaster (Abubakar *et al.*, 2014:2231; Sahu *et al.*, 2014:369).

Pharmacovigilance, an essential part of public health programmes to ensure drug safety, is strengthened by more than one scientific discipline (Dogra *et al.*, 2013:71; Waller & Evans,

2003:27; WHO, 2006:9). These scientific disciplines include basic science, clinical science, population science and information science (Biffignandi, 2009:4; Waller & Evans, 2003:27). The harmonisation of these disciplines will fortify public healthcare (WHO, 2006:31). The objective of pharmacovigilance is to reduce the risk of drug-related harm to patients, but can only be successful if this system is managed in the correct way to achieve the objective (Arun *et al.*, 2015:1603; WHO, 2006:10). The weakness of a good medicine supply system is ADRs (Alomar, 2014:84). Although the pharmacovigilance system has grown since 1961, public health systems are still struggling to implement pharmacovigilance with success (WHO, 2006:10).

2.6 The benefits of pharmacovigilance

The majority of all ADRs are potentially preventable (Hardmeier *et al.*, 2004:664; Muñoz-Torrero *et al.*, 2010:1257; WHO, 2008a). The successful implementation of pharmacovigilance results in reduced drug-related risk and improved patient and drug safety (Nyakiba *et al.*, 2014:523). The aims of pharmacovigilance are as follow:

- To improve patient care and safety regarding the safe use of drugs.
- To improve public health and safety.
- To contribute to the benefit-risk assessment of a drug.
- To promote the safe, rational and effective use of medicine.
- To improve pharmacovigilance understanding, clinical training and education for healthcare professionals and promote communication to the public (WHO, 2002b:8).

ADRs leads to hospital admission and extended hospital admission days, patient distress, an increased financial burden, morbidity and mortality (Bouvy *et al.*, 2007:755; Budnitz *et al.*, 2015:448; Classen *et al.*, 1997:305; Hire *et al.*, 2013:386; Leendertse *et al.*, 2011:37; Meier *et al.*, 2015:176; Pirmohamed *et al.*, 2004:15; Rottenkolber *et al.*, 2012:870). The outcome of ADRs, namely mortality, morbidity and cost, can be reduced with pharmacovigilance (Khan, 2013:45; Singh & Bhatt, 2012:228;).

Statistics given on ADR reports do not support the severity of the problem and the extra cost of managing these ADR events results in a liability for the health systems (Metha, 2011:247; Raine, 2012:1). There is a perception that pharmacovigilance is an expensive system, but the cost is low compared to the burden of ADR cost (Suyagh *et al.*, 2015:148; WHO, 2006:22; WHO, 2007:22). The management of ADRs can increase a budget by 15-20%. Hospitalisation and loss of productivity are more expensive than drugs (Nyakiba *et al.*, 2014:522).

Pharmacovigilance is a constant risk-benefit assessment, but the perception of risk is not constant between the different stakeholders, and that is why communication regarding these risks is so important (WHO, 2012:13). The communication in a pharmacovigilance system spreads information regarding the effectiveness and risk of drugs (WHO, 2002b:19). A good pharmacovigilance communication system is an intelligent, evidence-based use of medicine, to contribute to the prevention of ADRs (Rajesh *et al.*, 2011:678).

The monitoring of ADRs generates an information system regarding the quality and safety of drugs, creates risk-management plans, contributes to the prevention of ADRs and improves awareness of ADRs among healthcare professionals (Sahu *et al.*, 2014:696). A good information system may result in the improvement of health outcomes (WHO, 2006:31). The early detection of ADRs may lead to increased prevention of harm, improve rational use of drugs, and contribute to patient adherence. Pharmacovigilance is a system that improves international communication regarding the safety of drugs (Waller & Evans, 2003:17).

2.7 Good pharmacovigilance practices

Good pharmacovigilance practice depends on complete data reports of ADRs (Dogra *et al.*, 2013:81). Increase in the quality of ADR reports improves the quality of pharmacovigilance (Dogra *et al.*, 2013:8; Lindquist, 2004:865). The quality of the report indicates the association between the product and the ADE (Dogra *et al.*, 2013:81). The core of the problem with the pharmacovigilance system is to improve risk management, and good pharmacovigilance practices will make this goal achievable. A good pharmacovigilance practice programme will identify risk factors; this will minimise or avoid harm (Rajesh *et al.*, 2009:678).

Good pharmacovigilance practice should be the main focus at each pharmacovigilance training session (WHO, 2006:24). A good pharmacovigilance system can only be obtained with clear, detailed SOPs (WHO, 2006:24). These SOPs should include:

- The terms generally used in pharmacovigilance.
- The responsibilities and communication system of the stakeholders in the pharmacovigilance framework.
- The guidelines for the process of pharmacovigilance.
- A clear explanation regarding the ADR report form.
- Practicalities to complete the ADR report form.
- A description of the indicators that will be used to monitor the progress of the system.

2.7.1 Terms generally used in pharmacovigilance

The terms used to report the hazardous events should be universal (Biffignandi, 2009:4; De Ponti, 2013). Different terms used to describe ADEs result in confusion among healthcare professionals (Rehan *et al.*, 2009:3). These different terms, with distinctive meanings, used to detect signals are an international challenge (Biffignandi, 2009:4; Lindquist, 2004:829).

Table 2.1: Pharmacovigilance terms

Terms used in pharmacovigilance	Definitions
Adverse event or experience	Adverse event is any unpleasant medical incident associated with the use of a medical product, but there is not necessarily an association with the medical product (Gagnon <i>et al.</i> , 2012:145; MCC, 2014:4; Nebeker <i>et al.</i> , 2004:795).
Adverse drug event	Adverse drug event is known harm that is caused by the drug or indicates incorrect drug use (Nebeker <i>et al.</i> , 2004:796)
Serious adverse event	Serious adverse event is an unpleasant medical incident that is life threatening, requires hospitalisation, leads to a congenital anomaly or birth defect, or results in death at any dose (Dogra <i>et al.</i> , 2013:71; FDA, 2014:1; MCC, 2014:5):
Adverse effect	Adverse effect is related to the use of a drug that results in a dangerous or unwanted reaction. This effect includes medication errors that result in adverse drug effects (Edwards & Aronson, 2000:1255).
Adverse drug reaction	An adverse drug reaction (ADR) indicates the response to a drug. The drug may be toxic or may have been used accidentally, and the term also includes the lack of efficacy of the drug used. It includes overdose, misuse and abuse of drugs (Gagnon <i>et al.</i> , 2012:146; MCC, 2014:4; Nebeker <i>et al.</i> , 2004:795).
Unexpected adverse drug reaction	Unexpected adverse drug reaction is an adverse reaction that is not consistent with the product market agreement (Edwards & Aronson, 2000:1256).
Signal	A signal requires more than one report to indicate a need for a review of reaction between an adverse event and a drug. The relationship between the event and the drug is unknown or previous documentation of information was incomplete (WHO, 2002b:42).
Side effect (known side effects: preventative/ non- preventative)	Side effect is a predictable dose-dependent medical event that is not the principal effect for which the use of the drug was intended (Nebeker <i>et al.</i> , 2004:796) Preventative: injury due to an error, allergic reaction in a patient known to be allergic (Von Laue <i>et al.</i> , 2003:409). Non-preventative: injury with no error involved. Allergic reaction in a patient not known to be allergic (Von Laue <i>et al.</i> , 2003:409).
Medication error	Medication error, occur when a physician's order is misread or a dangerous dose is used to treat the patient This inappropriate use of drugs and failure in the treatment has the potential to lead to harm to the patient (Ferner & Aronson & 2006:1011; Von Laue <i>et al.</i> , 2003:408).

Adverse effect is the chosen term worldwide (Edwards & Aronson, 2000:1255; Nebeker *et al.*, 2004:795). The terms adverse drug reaction and adverse effect are similar, but these terms should be distinguished from adverse drug events. ADR is distinguished by the suspicion of a relationship between the drug and the reaction (Edwards & Aronson, 2000:1255; Nebeker *et al.*, 2004:795). This term is preferred over terms such as toxic or side effect. The definition and classification of each term support the WHO preference for adverse effect (Edwards & Aronson, 2000:1255).

Drug reactions include all adverse events associated with drug administration, regardless of etiology (Riedl & Casullis, 2003:1781). Medication error and side effects indicate the possibility of harm to the patient (Nebeker *et al.*, 2004:795). Potential adverse drug event is circumstances that have the possibility of resulting in ineffective treatment by the use of drugs but that did not harm the patient (Nebeker *et al.*, 2004:796). The inappropriate or irrational use of medicines has been observed and the origin of this problem can be due to the inappropriate prescribing, dispensing or selling of medicine (Halloway & Van Dijk, 2011:2). This underlines the need to improve the appropriate use of medicine as quality care is an apprehension to HCPs (Halloway & Van Dijk, 2011:2). The rational use of medicines refers to the correct medicine being provided to the patient, and being consumed in the correct dosage for the specific individual for a suitable time, with the lowest costs for the patient and the community (Halloway & Van Dijk, 2011:2).

The relationship between inappropriate drug use, medication error, ADEs and ADRs is as follows:

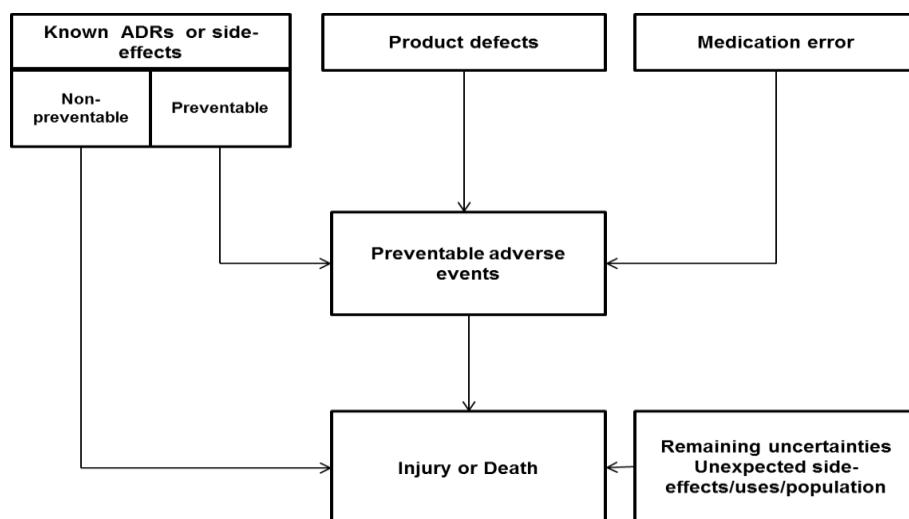


Figure 2.1: The relationship of terms used in pharmacovigilance (adapted from WHO, 2008b)

2.7.2 The pharmacovigilance framework

Universal terminology and the difference between countries indicate that good pharmacovigilance practices require an established national comprehensive pharmacovigilance system. The Strengthening Pharmaceutical Services (SPS) programme designed a model to indicate the relationship and responsibilities of the stakeholders in pharmacovigilance to support the success of the system (SPS, 2010:5).

The WHO provides a clear outline for a functional pharmacovigilance system (WHO, 2010:2). The minimum requirements for a pharmacovigilance system include:

- An existing national pharmacovigilance centre.
- One staff member should be a full time employee.
- Stable basic funding should be available to ensure the functioning of pharmacovigilance.
- A mandate that defines the structures and roles of all the stakeholders in the pharmacovigilance framework.
- These mandates should be developed in collaboration with the WHO programme for international drug monitoring.
- There should be an existing national spontaneous reporting system and a national individual case safety report.
- A national database or system is required to collect and manage the ADR reports.
- The existence of a national ADR or pharmacovigilance advisory committee is required.
- This committee is responsible for causality assessment, risk assessment, investigation in case reports, crisis management and communication.
- To ensure an effective routine and crisis communication, a functional communication strategy should be implemented.

2.7.3 The process and responsibilities of pharmacovigilance

The aim of pharmacovigilance can only be achieved if the process of pharmacovigilance is understood. The process of pharmacovigilance starts with the doctors, dentist, nurses and consumers (SPS, 2010:5). These reactions are related to a specific batch of drugs (Singh & Bhatt, 2012:231). A detailed description of the ADRs and the result of the examination and test

are required. The description of the ADRs includes the type and severity of reaction, the place of the reaction and the appearance of the reaction (WHO, 2002b:16). Information about the suspected product is essential. The name of the brand, manufacturer or active ingredient should be identified (WHO, 2002b:16)

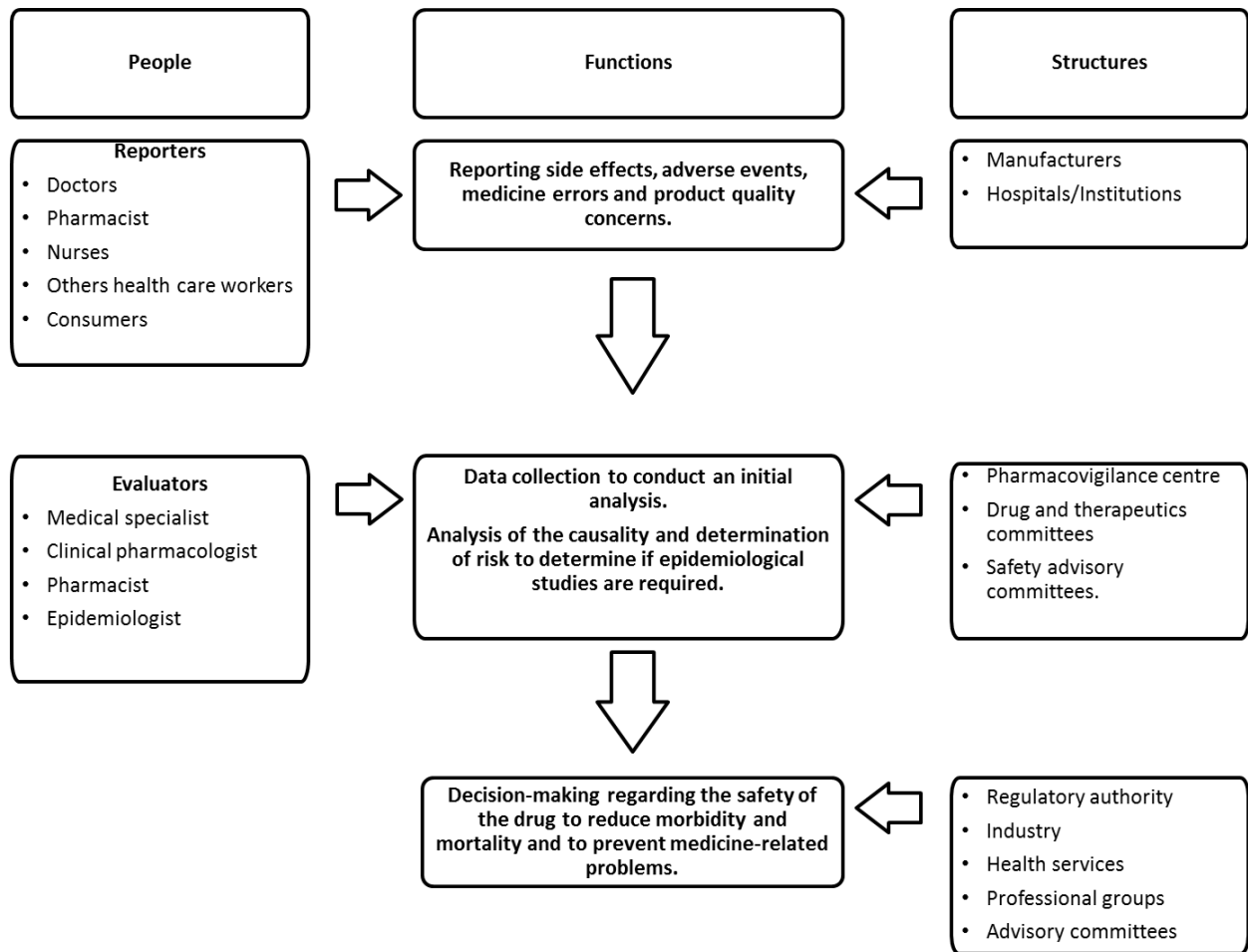


Figure 2.2: The pharmacovigilance framework (adapted from SPS, 2010)

The process of pharmacovigilance in public health facilities starts with the reporting of recognised side effects and suspected adverse effects. The PHC, district health officer/programme manager and hospital are responsible for the detection, investigation, and management and reporting of ADRs. It is the responsibility of the district health officer to manage these activities to prevent delayed reports of ADRs (SPS, 2010:6).

The second step in the process is the evaluation of data collected. An analysis should be conducted to determine the risk of the event. This step will also indicate if further epidemiological studies are required (SPS, 2010:5). The last step is to make a decision to improve the safety of the drug. This includes the possible amendment of package inserts, schedule changes, risk management, withdrawal from the market or product recall (SPS,

2010:5). Evaluators of adverse drug events include medical specialists, clinical pharmacologists, pharmacists and epidemiologist. Data collection of an event is the responsibility of pharmacovigilance centres, drug and therapeutic committees, and safety advisory committees. The process is concluded with the insight from regulatory authority, industry, health services, professional groups, advisory committees and the media (SPS, 2010:6).

“Pharmacovigilance is nobody’s individual privilege” (UMC, 2000:6). The WHO (2006:24) states that an effective pharmacovigilance system requires individuals with different educational experience. The responsibility of pharmacovigilance is shared between manufacturers, drug regulators, public health programmes, clinical institutions, academic researchers, healthcare workers, media and patients (Suleman, 2010:56). The success of spontaneous reporting can be increased if the healthcare professionals understand the importance of pharmacovigilance (Ruud *et al.*, 2010:346). Pharmacovigilance should be included in the national drug policy, regulation of medicines, clinical practice and disease control public health programmes (WHO, 2004a:10). The WHO (2004a:10; 2002a:11) identified the following stakeholders to contribute to the growth of pharmacovigilance:

(a) The WHO Quality Assurance and Safety: Medicines Team

This medicine team is part of the Department of Essential Drugs and Medicines Policy in the WHO Health Technology and Pharmaceuticals cluster. This team provides leadership and assistance to countries regarding drug safety (WHO, 2002a:9). The leading goal of the quality assurance and safety team is to ensure the quality of pharmaceutical products in public health (WHO, 2014:5).

(b) The Uppsala Monitoring Centre

The key function of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) is to control the international database of ADR reports obtained from national centres (WHO, 2002a:9). The UMC is responsible for maintaining the WHO Global Individual Case Safety Report (ICSR) database, Vigibase. This database is a global source of post-marketing surveillance reports (UMC, 2012:1). The Vigibase had received 10 million ADR reports by the end of October 2014 (Olsson, 2015:5). Healthcare services regarding the safe use of medicine indicate an improvement in the use of this electronic medical record database (Kiguba *et al.*, 2014:1).

It is the responsibility of the UMC to collect and analyse data from ADR reports and provide information concerning the safety of a drug to all the stakeholders in pharmacovigilance

(Lindquist, 2008:409). The UMC should provide training opportunities to support and improve pharmacovigilance (Lindquist, 2008:409).

(c) The national pharmacovigilance centres

Pharmacovigilance is an indispensable part of drug regulation (WHO, 2002a:20). The national government should accept the responsibility to improve drug safety and establish a multidisciplinary national pharmacovigilance centre to manage ADRs (Gagnon *et al.*, 2012:150; WHO, 2004a:11).

The management and improvement of pharmacovigilance, considered to be a luxury discipline, are not included in public health budgets (WHO, 2006:32). The government of each country should develop regulations and guidelines to monitor drug safety and include guidelines for reporting ADRs (WHO, 2010:2). France, Sweden and Italy share their commitment to pharmacovigilance by making ADR reporting mandatory in these countries (Hazell & Shakir, 2006:386). The WHO (2006:48) developed a clear mandate regarding the responsibilities of a national pharmacovigilance centre.

Responsibilities of stakeholders at the national pharmacovigilance centre are as follows:

- To encourage the reporting of ADRs.
- To collect and evaluate the ADR reports.
- To compare, analyse and evaluate the patterns of ADRs.
- To separate ADR reports containing valuable information from low-quality reports.
- To provide recommendations to respond to ADRs.
- To initiate studies to determine the importance of suspected ADRs.
- To communicate the risk of ADRs to the WHO programme for international drug monitoring, prescribers, manufacturers and the public (WHO, 2006:23).

These centres are used for the post-marketing observation of products (WHO, 2002a:11). ADR reports must be sent to each country's national pharmacovigilance programme units. It is the responsibility of these units to monitor the ADRs (Stenver, 2008:184). The national pharmacovigilance units report their findings to the WHO-ADR Monitoring Centre in Sweden. The WHO unit reports the information about the ADR to all the other national pharmacovigilance units in other countries (Bandekar *et al.*, 2010:1182; Metha, 2011:247).

The national pharmacovigilance centre can encourage the report of ADRs through educated healthcare professionals in healthcare facilities (WHO, 2010:2). It is the responsibility of the national pharmacovigilance centre to evaluate the system and to determine if the reporting is complete and correct, with immediate feedback to reporters, and to ensure actions are taken to manage these ADRs according to standards (WHO, 2006:48).

(d) Pharmaceutical industry, hospitals and academia

It is compulsory for pharmaceutical companies in all countries to test new drugs during a clinical trial and to determine the benefit-harm-risk profile of a new product before the product is approved by drug regulating authorities (Arora, 2008:13; Hauben *et al.*, 2005:930; Rashmi *et al.*, 2011:43). Data regarding the safe use of medicine gathered during the pre-authorisation phase of drug development is the responsibility of pharmaceutical manufacturers (MHRA, 2012:129; WHO, 2002b:12).

Regional pharmacovigilance centres have been identified in different countries. These centres are established in hospitals, academic institutions and pharmaceutical manufacturers (Dal Pan, 2014:1; Jeetu & Anusha, 2010:316). The responsibilities of these regional centres are to collect and analyse the ADR reports before sending them to the national pharmacovigilance centre (Dal Pan, 2014:1). Clinical pharmacology and pharmacy departments can be rewarded for their contribution to develop pharmacovigilance as a discipline (WHO, 2002b:12). Undergraduate education for healthcare professionals regarding pharmacovigilance requires more attention. A good theoretical pharmacovigilance education provides a secure groundwork for future clinical practice (Upadhyaya *et al.*, 2012:310; Yamamoto, 2013).

(e) Health professionals

The WHO (2002c:13) requests all healthcare systems to participate in spontaneous reporting of ADRs. These healthcare systems include all public and private hospitals, general practitioners, nursing homes, retail dispensaries and clinics for traditional medicine (WHO, 2002a:13). Drug safety should be the main focus in patient care (Alomar, 2014:83; Ulfvarson, 2007:31). Pharmacovigilance should be an obligation for HCPs, specifically in hospitals and primary healthcare facilities (Ruud *et al.*, 2010:346). In the past, healthcare professionals were the main contributors to ADR reporting. The active participation of healthcare professionals is the key to the success of pharmacovigilance (Reddy *et al.*, 2014:35; WHO, 2002b:13). Pharmacists, general practitioners and nurses in the public health programme are key players for the success of pharmacovigilance (Gupta & Udupa, 2011:1064; Hartzema *et al.*, 2008:205; Rajesh *et al.*, 2011:679). The implementation of pharmacovigilance relies on HCPs, and their lack of interest

in pharmacovigilance is a major reason for the failure of pharmacovigilance in many countries (WHO, 2006:12; WHO, 2006:32).

Pharmacists' participation in pharmacovigilance is vigorous (Reddy *et al.*, 2014:35). The pharmacist as a healthcare professional is not only responsible for the dispensing of drugs according to required standards, but is now a consultant on pharmacotherapy for medical practitioners and patients. Pharmacists should be seen as the experts in medicine and they should play an exceptional role in pharmacovigilance, but there is little indicating that pharmacists are active in the reporting of ADRs in South Africa (Granás *et al.*, 2007:430; Suleman, 2010:57). According to Granás *et al.* (2007:433), the pharmacist has the correct attitude to report ADRs, but they lack the experience. The future pharmacist needs a strong academic basis to recognise, prevent and report ADRs (Reddy *et al.*, 2014:35). Pharmacists contribute to the reduction in the risk of ADRs and improve the awareness of ADR reporting by training the nurses and the general practitioners (Palaian *et al.*, 2011:229).

Clinicians' lack of expertise to detect ADRs may influence the management of these reactions (Hire *et al.*, 2013:386). To improve ADR reporting, general practitioners need to understand the importance of pharmacovigilance (Hazell & Shakir, 2006:393). The safe use of drugs relies on high-quality prescribing that includes a benefit-risk assessment of the drug, from general practitioners and this standard requires concentrated insight into ADRs monitoring, detecting and reporting (Hazall & Shakir, 6002:393; WHO, 2006:10). Patients are exposed to possible further drug-related harm as the result of inappropriate management of ADR, because of the inability of clinicians to identify or detect ADRs (Hire *et al.*, 2013:386).

It is the responsibility of the nurses to administer the drugs and monitor the patient for signs and symptoms to ensure the safe use of drugs (Conforti *et al.*, 2012:597; Hughes & Blegen, 2008:397). The broad scope of healthcare practice, including the prescription and administration of drugs and the monitoring of patients, depends on nurses as the first HCPs to observe ADRs in most cases (Alan *et al.*, 2013: 616; Gabe *et al.*, 2011:385; Palaian *et al.*, 2011:229; Ulfvarson *et al.*, 2007:533). Although nurses are allowed to prescribe limited drugs, pharmaceutical companies have the tendency to exclude them from their marketing group after the clinical development of a new drug and this leads to the lack of monitoring the safety of the drugs. Nurses have a substantial role in the detection of ADRs and should be included in training and education opportunities for pharmacovigilance (John *et al.*, 2012:5; Ulfvarson *et al.*, 2007:536).

(f) Patients

Patients are the most important stakeholders because they benefit from the drug and they experience the adverse effects (Jeetu & Anusha, 2010:316; Van Grootheest & De Jong-van den

Berg, 2004:363). Health professionals rely on the explanation from the patient during the investigation of complaints (Hazell & Shakir, 2006:386; WHO, 2002b:12). Patients want to share their experience with ADRs, and spontaneous reporting of ADRs enables willing patients to report their ADRs in the US, Canada, Australia and New Zealand (Dal Pan, 2014:2; Van Grootheest & De Jong-van den Berg, 2004:365; Van Hunsel *et al.*, 2012:46). Patient reporting of ADRs can contribute to the value of pharmacovigilance (Jeetu & Anusha, 2010:316; Van Hunsel *et al.*, 2012:58).

2.7.4 The ADR report

A good-quality report form is required to report ADRs. According to the WHO (2000:7), an ADR report form is a “notification relating to a patient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine”. Although the WHO sets guidelines for these forms, there are still differences between countries (Bandeekar *et al.*, 2010:1182). To report these events, the WHO provided minimum information requirements for a report form (WHO, 2002c:16). Different forms are designed by different countries due to the economic state, different diseases, ethnic groups, dietary factors and the development level of new drugs (Palaian *et al.*, 2011:229; SPS, 2010:5; WHO, 2006:10). These report forms should include at least four sections, with sufficient information (WHO, 2002c:16):

Patient information	Adverse event or product problem	Outcome of the event	Reporter
<ul style="list-style-type: none"> • Patient identifier • Date of birth/age • Gender • Weight 	<ul style="list-style-type: none"> • Description of the event • The date of the event • The date of the report • Relevant test done or laboratory data • Patient history 	<ul style="list-style-type: none"> • Suspected medication(s) • Name of the drugs • Dose, frequency and route used for all medication used • Start date of therapy • The diagnosis for use of drugs • The outcome after use of drug is stopped or dose is reduced • The batch number of drugs used • The expiration date of drugs used • Description if the event reappeared after reintroduction of drug • Concomitant medical products and therapy dates 	<ul style="list-style-type: none"> • Name, address and telephone number of HCP • HCP occupation and speciality

Figure 2.3: The minimum requirements for ADR report form

The identification of patient risk factors can prevent harm to the patient (De Ponti, 2013). Risk factors may include impaired renal function, exposure to the alleged drug prior to this event, all allergies and any social use of drugs (WHO, 2002c:16).

Age is an important risk factor, because elderly or infant patients are excluded from clinical trials, and the drug safety data on these age categories is just estimated (Alomar, 2014:86; Meyboom *et al.*, 1999:444). Laboratory results like creatinine clearance indicate the ability of the kidney to excrete drugs (Alomar, 2014:87). If changes in creatinine clearance occur, the use of a drug could result in decreased therapeutic effects or toxicity (Alomar, 2014:87). Gender influences the activity of drugs. There is a clear difference between male and female weight, body composition, gastro-intestinal factors, metabolism and renal function (Alomar, 2014:86). The metabolisms of drugs are different in males and females, as the female hepatic enzyme CYP3A4 is more active (El-Eraky & Thomas, 2003:198).

The name of the suspected drug, with information regarding the purpose, dose, route of administration, frequency of use, and the start and end date of the drug used, are necessary information to indicate the relationship between the adverse effect and the drug used (Meyboom *et al.*, 1999:443; Singh & Bhatt, 2012:231). In the same way, concomitant drug information is also important and is used to determine the relationship between the adverse reaction and the drug, and the possibility of drug-drug interactions. This indicates the difference between a medication error and an adverse reaction (Singh & Bhatt, 2012:231). The dosage, route of administration and the frequency of the use of the drug are the parameters that reveal the relationship between medication error and an ADR (Bandekar *et al.*, 2010:1182). Poly-pharmacy, known as the use of multiple drugs, increases the risk of ADRs (Bushardt *et al.*, 2008:338; Meyboom *et al.*, 1999:443). In the event that a reaction is caused by a specific batch of drugs, the product and manufacturer information is used to trace that specific batch of drugs (Singh & Bhatt, 2012:231).

It is important for healthcare professionals to know what to report (WHO, 2002c:15):

- Reporting recognized side effects and suspected adverse effects should include all suspected reactions of new drugs, including minor reactions.
- Serious or unexpected/expected events of well-known drugs should be reported.
- The HCP should report a reaction when an increased frequency of the same reaction is detected.
- Drug-drug/drug-food/drug-food supplements should be reported.
- ADRs that originate from drug abuse or the use of drugs during pregnancy or lactation should be reported.
- Medication errors or overdose ADRs should be reported.

- Lack of efficacy or suspected pharmaceutical details should be reported.
- Any event that is regarded as clinically important information should be reported (WHO, 2002c:15).

The details of the reporter should be included to enable the national pharmacovigilance centre to acknowledge receipt of the report and to contact the reporter if any other details are required during the evaluation of the ADR report form (MHRA, 2015).

De-challenge and re-challenge activities are required to determine the causality of an ADR. These activities are not common in all countries. The USA, Canada, India, Malaysia and Sweden report de-challenge information and Argentina, New Zealand, USA, UK, Canada, India, Malaysia, Singapore, Sweden and South Africa report re-challenge information (Singh & Bhatt, 2012:231). The pharmacovigilance system requires causality assessment criteria to determine the relationship between the drug that was used and the adverse event that occurred (Hire *et al.*, 2013:386, Nebeker *et al.*, 2004:796; WHO, 2002d:1). Causality assessment of an ADR contributes the benefit-risk profile of a drug (Macedo *et al.*, 2003:137). The medical history of a patient, gender, maternity status, allergy status, relevant laboratory data and social factors, alcohol use and smoking are important for causality assessment (Singh & Bhatt, 2012:231). The World Health Organisation and the Uppsala Monitoring Centre (UMC) identified four levels of causality assessment criteria (WHO, 2002d:2).

To determine the grades of certainty that the ADR is linked to the use a specific drug the causality assessment criteria indicate the time relationship between the reaction and the use of the drug, the pathophysiology of the reaction, the conflicting cause of a reaction and the response of the de-challenge or the re-challenge of an ADR (Nebeker *et al.*, 2004:796; WHO, 2002d:1).

Table 2.2: WHO-UMC causality assessment criteria

Level of causality assessment	Assessment criteria
Certain	<p>This is a clinical event that occurred in a credible time relationship with the use of a drug and there is no other explanation for the event (WHO, 2002d:2).</p> <p>All laboratory tests indicate an abnormality and the event indicates a definite pharmacological or phenomenological reaction (WHO, 2002d:2).</p> <p>This criterion also includes the possible response to the withdrawal of a drug (WHO, 2002d:2).</p> <p>If the re-challenge of this event is necessary, the second administration of this drug will indicate the same results (WHO, 2002d:2).</p>
Probable/likely	<p>This is a clinical event that occurred in a rational time relationship with the use of a drug (WHO, 2002d:2).</p> <p>All laboratory tests indicate an abnormality (WHO, 2002d:2).</p> <p>It is not likely that this event was caused by another drug or a competing disease.</p> <p>When therapy is discontinued and/or the dose of the therapy has been reduced, the reaction is a clinically reasonable response to the withdrawal of a drug (Nebeker <i>et al.</i>, 2004:796; WHO, 2002d:2).</p> <p>This assessment does not require the re-challenge of the event (WHO, 2002d:2).</p>
Possible	<p>This is a clinical event that occurred in a rational time relationship with the use of a drug (WHO, 2002d:2).</p> <p>All laboratory tests indicate an abnormality (WHO, 2002d:2).</p> <p>There is a probability that this reaction was caused by another drug or competing disease.</p> <p>There is no definite information regarding the withdrawal of therapy (WHO, 2002d:2).</p>
Unlikely	<p>The time relationship between the administration of the drug and the reaction is doubtful, but still possible (WHO, 2002d:2).</p> <p>There is credible explanation that correlates the cause of this reaction to another drug or disease (Nebeker <i>et al.</i>, 2004:796; WHO, 2002d:2).</p>

2.8 The South African perspective

2.8.1 The current scenario of pharmacovigilance in South Africa

In 2010 the WHO established that a national pharmacovigilance centre should have the selected staff, basic finances, clear directives, definite structures and integration with the WHO programme for international drug monitoring (WHO, 2010:4). The centre needs a national reporting system and a form to report ADRs. A national database should be implemented to collect and manage ADR reports. The centre requires assistance for the management of ADRs

from a pharmacovigilance advisory committee, and a definite communication strategy should be identified (WHO: 2010).

The pharmacovigilance system includes all individuals and resources required to protect patients from drug-related harm (SPS, 2011:21; WHO, 2004a:1). The National Department of Health needs to clarify and operationalize public health programmes and services management (Mehta *et al.*, 2014:10). Data regarding the safety of drugs in South Africa is based on clinical trials conducted in other parts of the world, and as mentioned, these trials are short and limited to different population groups (Suleman, 2010:56). This highlights the need to be vigilant during Phase 4 of the clinical trials (Department of Health, 2013b:21). The responsibility of pharmacovigilance in South Africa is shared among the Medicines Control Council (MCC), public health programmes, the pharmaceutical industry and the Essential Drugs Programme of the Department of Health (Mehta *et al.*, 2014:104).

In South Africa, pharmacovigilance is used to ensure the quality and efficacy of medicines as a function of the regulatory authority MCC and is implemented as a national and provincial programme to monitor all drugs used in public health (Dheda, 2013:1; Mehta *et al.*, 2014:105). The MCC implemented the National Adverse Drug Event Monitoring Centre (NADEMC) at the University of Cape Town and designed guidelines to assist stakeholders to report ADRs (Maigetter *et al.*, 2015:6; MCC, 2014:4). The NADEMC is responsible for the collection of data and the management of the national ADR database (Mehta, 2011:249). Although the guidelines for a functional pharmacovigilance system indicate that only one staff member is required to work full time, the one full-time pharmacist at the centre cannot administrate all the data (Maigetter *et al.*, 2015:6). The NADEMC is struggling to employ new staff members, because pharmacovigilance is perceived to be an administrative profession (Maigetter *et al.*, 2015:6). It is the responsibility of the one full-time pharmacist and the six members of the pharmacovigilance advisory committee to review the ADR reports and provide recommendations to the MCC about the registration of the drug and the safety of the drug on the market (Maigetter *et al.*, 2015:6; Mehta, 2011:249). The advisory committee consults with a clinical committee if a label of a drug needs to be changed (Maigetter *et al.*, 2015:6; Mehta, 2011:249; Yadav, 2008:9).

Public health programmes are allowed to have a system for pharmacovigilance that is disease-specific (SPS, 2010:10). In Bloemfontein, the Department of Health implemented a monitoring centre for ARTs for pregnant women and in Pretoria, at the Medunsa University; a pharmacovigilance unit has been implemented to monitor youth and adult monitoring of ART ADRs (Misra, 2004). Although the pharmacovigilance programmes in South Africa generate potentially useful information, the communication between these programmes is inadequate (Dheda, 2013:1; Maigetter *et al.*, 2015:6; Mehta *et al.*, 2014:104). The South African

Department of Health has successfully implemented a decentralised patient-centred pilot pharmacovigilance programme for anti-retroviral therapy (ART) reactions in Mpumalanga to strengthen the pharmacovigilance programme (Dheda, 2013:357). This programme has now been expanded to the North West Province with the support of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) programme. This support from the SIAPS in the North West Province led to the training of 118 HCPs, the establishment of 20 cluster pharmacovigilance centres and the production of new ADR forms, specifically for ART ADRs (SIAPS, 2014:2). This resulted in an increased number of reports – from zero reports in 2012 to 422 ADR reports in August 2014 (SIAPS, 2014:2).

The Department of Health (2013b:21) stated “that it is a moral and professional responsibility of the HCP to report adverse drug reactions”. As it is not compulsory for healthcare professionals to report ADRs, this needs to be a culture among healthcare professionals. HCPs in the public health system in South Africa are not trained to identify or report an ADR (SIAPS, 2014:1). The pharmaceutical industry, however, is obligated to report ADRs and provide a periodic safety update report at well-defined times to indicate the safety of the drug world-wide after registration of the drug (MCC, 2014:6; Misra, 2004).

The government of South Africa does not perceive the importance of pharmacovigilance and the Department of Health does not have sufficient funding to improve the safety of medicine (Dheda, 2012:1; Maigetter *et al.*, 2015:6). The MCC guidelines urge HCPs to report ADRs, even if they are unsure if the reaction is related to the drug, but only the serious ADRs are evaluated due to the workload (Department of Health, 2012:395; Maigetter *et al.*, 2015:7). The electronic database of South Africa is not working and an electronic submission of an ADR report leads the system being overloaded (Maigetter *et al.*, 2015:7). South Africa’s pharmacovigilance system is still in transition and there is a general culture of under-reporting of ADRs in South Africa (Ruud *et al.*, 2010:345; Yadav, 2008:10).

The requirements of the WHO for a functional national pharmacovigilance system are compared with the pharmacovigilance system in South Africa (Maigetter *et al.*, 2015:300; WHO, 2010) in Table 2-3.

Table 2.3: National pharmacovigilance centre of South Africa

WHO	South Africa
Established national pharmacovigilance centre	National Adverse Drug Event Monitoring Centre (NADEMC).
Legal or structural framework	Periodic safety updates are mandatory in South Africa, but no policy exists.
Designated staff (at least one should be full time)	Staff members at the NADEMC include: one full-time pharmacist and six external experts from the pharmacovigilance advisory committee.
Stable basic funding	The Department of Health does not have a separate budget for pharmacovigilance.
Clear mandates and well-defined structures and roles	The activities in South Africa are scattered and duplicated and recruitment for the pharmacovigilance system is slow.
Collaborating with the WHO programme for international drug monitoring	The NADEMC do not have the capacity to analyse the data collected.
National spontaneous reporting system in existence with a national ADR reporting form	A spontaneous reporting system is active in South Africa at present, but there is no functional electronic system.
A national database or system for collecting and managing ADR reports	The South African database is not compatible with the international ADR database and it is difficult to access and analyse the data.
A national pharmacovigilance advisory committee for feedback and recommendations on safety issues	There is an external pharmacovigilance committee due to a lack of manpower at the NADEMC.
Validate causality, participate in crisis management and crisis communication	External pharmacovigilance members cannot participate in NADEMC-related activities.
A communication strategy that is clear, both for routine and crisis communication	The NADEMC has a communication strategy, but no therapeutic or drug bulletin has been published and there is no public relations officer.

2.8.2 The ADR process in South Africa

ADR reports must be sent to each country's national pharmacovigilance programme unit. It is the responsibility of these units to evaluate and monitor the adverse reaction. When the NADEMC receives a report, the applicant is informed of the receipt, with the number assigned to the report. This number is used to minimise duplication of the report and should be used if the

applicant provides more information about the same report (Yadav, 2008:9). The national pharmacovigilance units report their findings to the WHO ADR Monitoring Centre in Sweden (Gupta & Udupa, 2011:1064; Margetter *et al.*, 2015:6; Mehta, 2011:249). The WHO unit reports to all the other national pharmacovigilance units in other countries about the reaction (Bandekar *et al.*, 2010:1182).

2.8.2.1 The ADR report form

The WHO provides guidelines with regard to reporting ADRs, but there are no international standards for reporting these reactions (Singh & Bhatt, 2012:229). The South African guidelines for reporting an ADR are similar to the WHO guidelines, but there is still a need for universal guidelines (Singh & Bhatt, 2012:229). ADRs can be reported on the National MCC ADR report form or on the decentralised ART ADR report form in the DKKD (MCC, 2014:9). In South Africa an expected/unexpected ADR should be reported within 15 calendar days from the identification of the reactions. The reports should be submitted by mail or facsimile (MCC, 2014:11).

2.8.2.1.1 Patient information on the ADR report

The patient information is required to identify a patient (MCC, 2014:6). The patient information on the ART form is more complete, as the MCC form does not include allergy or pregnancy risk factors. All other risk factors (date of birth, age, gender, weight, height) are included on both the South African forms (Table 2.4). The height and the weight of a patient are used to determine the body mass index (BMI) of a patient and the BMI of a patient is used to determine the correct dosage for administration of a drug for a specific patient (Singh & Bhatt, 2012:230). Pregnant women are excluded from clinical trials (Alomar, 2014:86). The pregnancy status will also influence the causality assessment of an ADR, as signs of vomiting and nausea could be due to the pregnancy and not the ADR (Alomar, 2014:86; Bandekar *et al.*, 2010). The allergy status and history of drug use will influence the causality assessment of an ADR (Singh & Bhatt, 2012:230). The MCC and ART ADR report form requires more patient information to be completed than initially required by the WHO (WHO, 2002c:16) (Table 2.4).

Table 2.4: ADR report form: Patient information

WHO	South African form (MCC)	South African form (ART)
Patient information	Patient information	Patient information
Patient identifier	Patient name or initials	Patient name or initials
	Patient reference number	Patient reference number
Date of birth	Date of birth	Date of birth
Age	Age	Age
Gender	Gender	Gender
Weight	Weight	Weight
	Height	Height
		Allergy
		Pregnant

2.8.2.1.2 Adverse Event and Product quality information

Different ADRs that should be reported in South Africa include:

- Adverse experiences with medications, medical devices, and complementary/alternative medicine.
- Especially ADRs to newly marketed products, serious reactions and interactions between products and ADRs that are not clearly reflected in the package insert.
- Product-quality problems such as suspected contamination, questionable stability, defective components, poor packaging and labelling and therapeutic failures.
- Even if you are not certain if the product caused the event and if you do not have all the details (Department of Health, 2012:391).

The MCC and ART ADR report forms adhere to all the WHO requirements for an ADR report form (Table 2.5). The ART ADR report form is more user friendly than the MCC ADR report form in identifying the ADR that occurred (Table 2.5). The MCC requires an original-word description of the event and the medicine name (MCC, 2014:9). The ART form provides a list of possible reactions that can occur, with extra space for other reactions excluded from the list. The MCC form and the ART form require an indication of whether any laboratory tests were done, but the ART provides you with the test that should be done for the convenience of the HCP. The MCC encourages HCPs to include laboratory results and post-mortem reports and to release a summary of any other clinical information (MCC, 2014:9).

Table 2.5: ADR report form: Description of ADR or product quality problem

WHO	South African form (MCC)	South African form (ART)
ADE/product problem	ADR/product-quality problem	ADRs
Description of event	Description of reaction or problem	Description of reaction tick box
Date of event	Date of onset of event Time of onset of reaction	Date of onset of reaction
Relevant tests/laboratory data	Include relevant tests/laboratory data	Laboratory results: include baseline and current results

The MCC and the ART ADR report form indicates the outcome of the ADRs as required by the WHO (WHO, 2002c:16). Possible ADR outcomes are provided on both the MCC and the ART ADR report form (Table 2.6). The ART form also provides a clear category with possible actions to be taken when an ADR occurs and the reporter is required to indicate any drugs used to treat the ADR (Table 2.6). The MCC ADR report form only require the reporter to indicate the events after the drug has been stopped or after the ADR has been re-challenged (Table 2.6.). The ART ADR report form includes a section for other clinical information as required by the WHO (WHO, 2002c:16). The ART-relevant clinical history information is used by the pharmacovigilance advisory committee to evaluate the ADR.

Table 2.6: ADR report: adverse drug reaction outcome and other information

WHO	South African form (MCC)	South African form (ART)	
Adverse reaction outcome	Adverse reaction outcome	Adverse reaction outcome	
Outcome attributed to the adverse drug event	Death	Intervention required	
	Disability	Patient counselled	
	Life-threatening	Additional clinical visit	
	Congenital anomaly	Hospitalisation	
	Required intervention to prevent permanent impairment/damage	Referred to expert	
		Additional lab request	
	Other	Other	
		Action taken	
Event abated after use stopped or dose was reduced	Event abated after stopping medicine	Discontinued suspected drug	Decreased dose
Event reappeared after reintroduction of the treatment	Event reappeared on re-challenge	Treated ADR (dose and name)	Other
		Patient outcome	
		Medication used to treat the ADR	
Other relevant patient information		Relevant clinical history	
		Date patient commenced ARTs	
		Initial regime	
		How long patient been diagnosed with HIV (years/months)	
		How long patient has been on ART treatment (years/months)	
		Concomitant medical conditions	
		Early warning of drug resistance	

2.8.2.1.3 ADR report form: suspected medicine

Neither the MCC nor the ART ADR report form demonstrates a perfect correlation with the WHO requirements for a report form (Table 2.7) (WHO, 2002c:16). The MCC and the ART ADR

forms do not include the expiration date of suspected drugs (WHO, 2002c:16). Product-quality problems are not addressed in the ART form, and this form does not include the batch numbers of the suspected drugs. This will have a negative impact on product recall.

The ART and MCC forms include dosage, route of administration, the start date of the therapy and the date when the therapy was stopped (Table 2.7). The ART form requests the details of the prescriber for the different drugs that are used, but the reporter is not required to indicate the reason for the use of each drug. The incorrect dosage/route of administration/frequency should be assessed as a medication error and not as an ADR (Nebeker *et al.*, 2004:795). The ART form includes more information to identify medication error compared to the MCC form.

Table 2.7: ADR report form: suspected medicine

WHO	South African form (MCC)	South African form (ART)
Suspected medication	Medicine/vaccines/devices	Medicines (and concomitant medicines, including herbal products, if known)
Name (INN and brand)	Trade name	Medicines (all the drugs the patient is using)
Batch number	Batch number	
Dose	Daily dosage	Dose
Frequency		Interval
Route of administration	Route of administration	Route of administration
Therapy start date	Date started	Date started
	Date stopped	Date stopped
		Prescriber
Diagnosis for use	Reason for use	
Expiration date		

2.8.2.1.4 Who should report ADRs in South Africa?

Pharmacovigilance should be an obligation for HCPs, specifically in hospitals and primary healthcare facilities (Ruud *et al.*, 2010:346). The applicant must identify themselves and they are required to indicate initials, address, contact number and qualification. The HCPs are allowed to only use their initials to ensure the confidentiality of the reporter (MCC, 2014:9). The reporter will not experience negative consequences when an ADR is reported. The report is stored on a secure database and any form of identification of the patient and the HCP will be removed before the ADR is communicated to other stakeholders in the pharmacovigilance framework (Department of Health, 2012:391). The identification of the reporter on the South African forms complies with the requirements of the WHO (Table 2.8) (WHO, 2002c:16). The

NADEMC will be able to identify and contact the reporter to provide confirmation of receipt or to obtain any additional information.

Table 2.8: ADR report form: reporter

WHO	South African form (MCC)	South African form (ART)
Reporter	Reporter	Reporter
Name	Name	Name
Address	Address	Facility
Telephone number	Telephone number	Telephone number and email address
Speciality and occupation	Qualifications	Qualifications
	Signature	Signature
Date of report	Date of signature	Date of signature

2.8.2.2 Reporting ADRs

The WHO also provides guidelines regarding the procedure to report ADRs (WHO, 2000:8). This information that indicates the responsibility reporter ADRs, how to report ADRs, what should be reported and where to report an ADR are compared to the South African guidelines in Table 2.9.

Table 2.9: Reporting ADRs

Reporting	International	South Africa
What should be reported	New drugs: all suspected reactions, including minor reactions (WHO, 2002c:15)	New drugs: report all suspected reactions including minor reactions (Department of Health, 2013b:24)
	Well known-drug: serious and suspected/unsuspected (WHO, 2002c:15)	Well-known drug: all non-serious or unexpected (Department of Health, 2013b:24)
	Amplified occurrence of reactions observed. (WHO, 2002c:15)	Amplified occurrence of reactions observed (Department of Health, 2013b:24)
	Drug abuse, pregnancy or lactation(WHO, 2002c:15)	ADRs from drug abuse, pregnancy or lactation (Department of Health, 2013b:24)
	Suspected ADRs associated with withdrawal (WHO, 2002c:15)	
	ADR from overdose or medication error(WHO, 2002C:15)	ADRs from overdose or medication error (Department of Health, 2013b:24)
	Lack of efficacy (WHO, 2002c:15)	Lack of efficacy (Department of Health, 2013b:24)
	Suspected pharmaceutical defects (WHO, 2002c:15)	Suspected pharmaceutical defects (Department of Health, 2013b:24)
		Report reactions that are related with drug-drug interaction, drug-food or food-drug interactions (Department of Health, 2013b:24)
Who can report	HCPs: Medical practitioners, pharmacist, nurse, pharmacist assistant, pharmaceutical technicians/assistants, clinical officers and others Manufacturers, public and private health centres (WHO, 2000:8)	HCPs: medical practitioners, pharmacist, nurses, dentist and allied healthcare professionals (Department of Health, 2013b:24; MCC, 2014:7)
How to report	Complete an ADR report form (MCC, 2000:7)	Complete MCC ADR form or ART ADR form and send form by post or facsimile (MCC, 2014:9)
Where it can be reported	Completed ADR form should be sent to pharmacovigilance centre (WHO, 2002c:17)	Completed ADR form should be sent to NADEMC (MCC, 2014:9)

2.9 Factors influencing the success of pharmacovigilance

2.9.1 Prevalence of ADR

In 1968 when the WHO initiated the pharmacovigilance programme, only 10 countries participated in the programme to improve the safety of drugs, and today 120 countries have implemented the pharmacovigilance programme as part of their healthcare system. The UMC

currently provides access to 10 000 000 ADR reports (Berhe *et al.*, 2015:5). South Africa, the first African country to join the pharmacovigilance programme in 1992, has submitted a total of 16 000 individual case safety reports to the UMC database since 1992. This is the largest number of reports in Africa (Isah *et al.*, 2012:28; Olsson, 2011:11).

The global patterns of ADRs indicate that 85% of ADR reports from 2000 until 2009 were received from high-income countries like the UK, US, France, Germany, Canada and Australia (Aagaard *et al.*, 2012:1174). The US made the largest contribution of ADR reports to the database and submitted 406 274 reports from 2000 until 2009 (Aagaard *et al.*, 2012:1175). South Africa, classified as an upper high-income group, submitted 5 518 reports from 2000 until 2009 (Aagaard *et al.*, 2012:1176).

ADRs have been classified as the sixth leading cause of mortality in 2002 (Meier *et al.*, 2015:176; Khan 2013:45). Hospital admissions due to ADRs have increased in the past 15 years (Abdel-Latif & Abdel-Wahab, 2015:155; Meier *et al.*, 2015:176; Reddy *et al.*, 2014: 34; Singh & Bhatt, 2012:228). ADRs led to 3.6% hospital admissions in Europe, 5.64% in the US, 3.3% in Australia and 6.3% in South Africa (Bouvy *et al.*, 2015:448. Budnitz *et al.*, 2007:755; Hodgkinson, 2009:19; Metha *et al.*, 2008:369)

In France the most frequent ADRs involve cardiovascular and antineoplastic drugs, and geriatric patients experience more ADRs than children or adults (Bénard-Larivière *et al.*, 2015:109). A study in Namibia indicated that 90% of the ADRs include severe and particular tinnitus, hearing loss. Gastro-intestinal-related ADRs and joint pain were experienced in patients with drug-resistant tuberculosis (Sagwa *et al.*, 2012:10). An assessment of ADRs in internal medicine units in Spain indicated that, during a 10-week study, post-antibiotic diarrhoea, bleeding due to anti-thrombotic therapy and rash were the most frequently observed ADRs (Muñoz-Torrero *et al.*, 2010:1260).

Rosiglitazone, an anti-diabetic drug, released on the market in 1999, was linked to cardiac ADRs by the UMC in 2003 (Berthet *et al.*, 2011:1; Summers *et al.*, 2013:52). Further studies indicated that the risk of cardiac problems increased by 43% in 2008. This drug was withdrawn from the international market in 2010 and from the South African market in 2011 (Berthet *et al.*, 2011:1; Summers *et al.*, 2013:52).

The high prevalence of malnutrition, tuberculosis and HIV/AIDS results in different ADRs in developing countries from those in developed countries (Masenyetse *et al.*, 2015:3). In South Africa, neuropathy is the most common ADR in patients using ARTs (Berhe *et al.*, 2015:797; Fyzoo, 2014:13; Masenyetse *et al.*, 2015:5). In 2010, healthcare facilities in KwaZulu-Natal indicated an increase in ADR reports from 430 in 2007 to 16 367 (Fyzoo, 2014:7).

2.9.2 Global problems with pharmacovigilance

In 2011, UMC received 4,7 million reports from 96 countries. Although this is supposed to be an effective number, only 6–10% of ADRs are reported (Gupta & Udupa, 2011:1064). This highlights the concern of under-reporting (Gupta & Udupa, 2011:1064).

Three categories have been identified to assess the awareness of pharmacovigilance: theoretical and practical understanding of pharmacovigilance (knowledge), the trend to respond in a positive or negative way towards pharmacovigilance (attitude) and the application of knowledge and experience regarding pharmacovigilance (practice) (Abudakar *et al.*, 2014:118; Gupta & Udupa, 2011:1065; Molokhia *et al.*, 2009:76).

(a) Knowledge

Knowledge concerning pharmacovigilance includes awareness of the system, definition of the terms used in the system, the process on how to report and where to report the ADRs and the purpose of pharmacovigilance (Abdel-Lafit & Abdel-Wahab, 2015:156; Abubakar *et al.*, 2014:122).

Previous studies indicated that HCPs do not know what to report or how to report ADRs. This lack of understanding of pharmacovigilance is a major obstacle to improving the safety of drugs (Department of Health, 2013b:18; Khan, 2013:49; Palaian *et al.*, 2011:232; Su *et al.*, 2010:220). If HCPs are aware of the pharmacovigilance system, basic information on the national pharmacovigilance system will be known. This information includes the purpose of the national pharmacovigilance centre, where the centre is located and how to contact the centre (Abubakar *et al.*, 2014:127; Adhikary *et al.*, 2013:1029; Palaian *et al.*, 2011:232). The relationship between the reaction and the drug are not clear to the HCPs, and this leads to the decision to oversee the reaction (Gupta & Udupa, 2011:1065; Kiguba *et al.*, 2014:6; Palaian *et al.*, 2011:232). The inability of HCPs to identify ADRs and uncertainty regarding drug-induced events lead to under-reporting (Department of Health, 2013b:18; Khan, 2013:46; Ruud *et al.*, 2010:348).

(b) Attitude

HCPs are unwilling to report or unable to report ADRs (Steurbaute & Hanssens, 2014:860). Although HCPs view ADR reporting as a professional obligation, willing ADR reporting is still poor (Abubakar *et al.*, 2014:127; Adhikary *et al.*, 2013:1027; Palaian *et al.*, 2011:23). In South Africa the problem is that the reporting of ADRs is not mandatory (Department of Health, 2013b:18). The lack of reporting is seen as a culture among HCPs and they have the desire to be rewarded to increase the ADR reporting rate (Gupta & Udupa, 2011:1064). The ADR report guidelines specify that non-serious reactions should not be overseen or excluded, but HCPs

have the perception that there is no necessity to report a well-known ADR, and they have the tendency to report only unusual ADRs (Abubakar *et al.*, 2014:123; Desai *et al.*, 2011:132; Khan, 2013:46; ; Palaian *et al.*, 2011:232; Pimpalkhute *et al.*, 2012:59; WHO, 2002c:15)

The insecurity of HCPs is an important personal factor that leads to global under-reporting of ADRs (Gupta & Udupa, 2011:1065). These insecurities include the fear of legal action that may influence their professional future or the fear and anxiety to appear incompetent in their profession (Desai *et al.*, 2011:132; Gupta & Udupa, 2011:1064; Karelia & Puparava, 2014:51; Muraraiah *et al.*, 2011:420). The guidelines for reporting also require HCPs to report medication errors, and HCPs are reluctant to admit that a mistake has been made (Department of Health, 2012:391; Steurbaute & Hanssens, 2014:860; WHO, 2002c:15). Feedback on the reporting of ADRs is insufficient and this influences the attitude of HCPs towards the system (Palaian *et al.*, 2011:232; Ramesh & Parthasarathi, 2009:12).

(c) Practice

HCPs did not receive sufficient training when the pharmacovigilance programme was implemented and they do not have adequate expertise to identify ADRs (Adhikary *et al.*, 2013:1029; Granas *et al.*, 2007:43). Abubakar *et al.* (2014:124) indicated that HCPs do not lack awareness regarding the pharmacovigilance system. The shortage of staff and increased number of patients create a stressful environment for public HCPs (Ruud *et al.*, 2010:346). The reporting of ADRs and the paperwork are time consuming (Gupta & Udupa, 2011:1065; Muraraiah *et al.*, 2011:421; Pimpalkhute *et al.*, 2012:59; Ruud *et al.*, 2010:248). In previous studies HCPs claimed they did not have the time to report the ADRs, ADR reports are unavailable and there is no functional pharmacovigilance system in the healthcare facilities. These factors are causing a roadblock to the success of pharmacovigilance (Gupta & Udupa, 2011:1065; Khan, 2013:46,49; Muraraiah *et al.*, 2011:419; Palaian *et al.*, 2011:232; Upadhyaya *et al.*, 2012:307; Upadhyaya *et al.*, 2015:32).

2.10 Factors that encourage ADR reporting

The roles and responsibilities of the key stakeholders in the pharmacovigilance framework need to be clarified and pharmacovigilance systems in each country need to be assessed regularly (Jeetu & Anusha, 2010:318; Van-Lierop & Bunyan, 2008:1). There should be a risk-management plan for every new drug and this plan should ensure proactive data collection of a high quality (Van-Lierop & Bunyan, 2008:1).

The most significant encouraging factor to reporting an ADR is patient safety (Kiguba *et al.*, 2015:5). HCPs are more likely to report ADRs if the reactions are serious or unusual and they

are more inclined to report an ADR if they are sure they have diagnosed the reaction correctly (Adhikary *et al.*, 2013:130; Kiguba *et al.*, 2015:5; Upadhyaya *et al.*, 2015: 31).

To improve ADR reporting, an improvement in the knowledge, attitudes and practices of HCPs is compulsory (Gupta & Udupa, 2010:1065). Although the awareness of ADRs seems to be clear, the number of ADR reports is still very low (Rajadhyaksha, 2012:85). Hospital management, pharmaceutical companies and drug regulatory agencies should promote pharmacovigilance education (Abubakar *et al.*, 2014:125; Jeetu & Anusha, 2010:318). Inclusion of pharmacovigilance as a science in undergraduate programmes will increase the awareness and the knowledge of the system. Increased pharmacovigilance knowledge will most likely have a positive influence on the attitude of HCPs (Isah *et al.*, 2012:32).

If a new public health programme is introduced, training should be compulsory and it should be repeated more than once (Adhikary *et al.*, 2013:1030; John *et al.*, 2012:138; Kiguba *et al.*, 2015:6; Ruud *et al.*, 2010:351; Van-Lierop & Bunyan, 2008:1). The focus of frequent pharmacovigilance training should be on expanding HCPs' knowledge regarding the safe use of drugs to prevent drug-related harm to patients (Adhikary *et al.*, 2013:1030; Dheda, 2013:363; Jeetu & Anusha, 2010:318; John *et al.*, 2012:13;). These training sessions should also include causality assessment of ADRs and completing a good quality ADR report (SIAPS, 2014:1). Practical instructions should explain how to complete the ADR report form, and provide an overview of the guidelines for reporting an ADR (Adhikary *et al.*, 2013:1029; Muraraiah *et al.*, 2011:420; Nyakiba *et al.*, 2014:527). After every training session, a post-training assessment is required to determine if the training will have a positive impact on the pharmacovigilance system, because the benefit of one training session decreases over time (Dheda, 2013:363).

The support of the government, definite guidelines and good financial assistance are required (Van-Lierop & Bunyan, 2008:1). Each country should earmark a budget for pharmacovigilance, because a suitable budget to monitor and prevent ADRs is less expensive than treating ADRs (Sainul, 2013:11). Pharmacovigilance will be improved if more ADR monitoring units and effective pharmacovigilance systems in hospitals are available (Abdel-Latif & Abdel-Wahab, 2015:160; Abubakar *et al.*, 2014:125; Dheda, 2013:363; Kiguba *et al.*, 2015:6; Muraraiah *et al.*, 2011:419). Decentralised cluster pharmacovigilance units have the potential to identify gaps in the pharmacovigilance system (Nyakiba *et al.*, 2014:528; SIAPS, 2014:2). Monthly cluster meetings and good communication flow between cluster units and NADEMC will support the success of pharmacovigilance (Dheda, 2013:363; Molokhia *et al.*, 2009:90).

The Department of Health (2012:391) reassures HCPs in their reporting guidelines that the reporting of an ADR will not result in any negative consequences for the HCP. This provision of legal support for HCPs will encourage them to report ADRs without fear of legal action

(Abubakar *et al.*, 2014:125). The reporting of an ADR should be made mandatory in every healthcare programme, but this should be accompanied by regular feedback from the national pharmacovigilance centre or health authorities (Kiguba *et al.*, 2014:7; Van-Lierop & Bunyan 2008:1). The pharmacovigilance system cannot be successful without regular feedback to all stakeholders in the system (Sainul, 2013:11). A periodic update on ADRs will create awareness of the pharmacovigilance system and encourage HCPs to report ADRs (Aguilera *et al.*, 2005:656; Dal Pan, 2014:1; Nyakiba *et al.*, 2014:528). Open and free communication is required between the public and the pharmacovigilance stakeholders to improve the awareness of pharmacovigilance and improve drug safety (Van-Lierop & Bunyan, 2008:1).

The possibility of a reward for reporting can influence the rate of ADR reporting (Adhikary *et al.*, 2013:1030; Desai *et al.*, 2011:132; Kiguba *et al.*, 2014:6). Acknowledgment of receipt of ADR reports and regular feedback on ADR reports motivate HCPs to report ADRs, and the information on the ADR from the stakeholders is a persuasive incentive for HCPs in the healthcare facilities (Ramesh & Parthasarathi, 2009:12; Suleman, 2010:58).

There must always be enough reporting forms, and a telephone line to report ADRs may improve the system (Adhikary *et al.*, 2013:1030; Muraraiah *et al.*, 2011:420; Palaian *et al.*, 2011:233). Spontaneous reporting of ADRs will improve if patients are included as a reporter in the pharmacovigilance system (Arlett & Kurz, 2011:16; Dal Pan, 2014:1). The reporting system should be easy to use and easy to understand for patients and HCPs, and sufficient resources should be provided to patients to encourage ADR reporting (Steurbaut & Hanssens, 2014:860; Sainul, 2013:13).

2.11 Chapter summary

In this chapter the researcher defined the basis of pharmacovigilance as part of therapeutic risk management. Good pharmacovigilance practices, including the benefits of the system, the responsibilities of all the stakeholders in the system and the process of ADR reports, were identified. The ADR report form was analysed to highlight the importance of all the sections included in the ADR form, and the different terms used on the ADR report form were identified and explained. The current South African pharmacovigilance practices were evaluated and the current MCC national ADR report form and the ARV report form were compared to international guidelines. The researcher identified the prevalence of ADRs and global problems that influence the pharmacovigilance system. This chapter also identified possible factors that can lead to a more successful pharmacovigilance system.

CHAPTER 3 RESULTS AND DISCUSSION

3.1 Introduction

In this chapter, results and the discussion of the empirical investigation are presented in manuscript format. The author's guidelines for the two manuscripts are attached in Annexures K and L.

Manuscript 1 was submitted to the *Health Policy and Planning Journal* under the title "*Healthcare professionals' awareness of, experiences with and perceptions of the pharmacovigilance system in the public health sector in South Africa*". The author guidelines for this journal can be accessed at

http://www.oxfordjournals.org/our_journals/heapol/for_authors/index.html

Manuscript 2 was submitted to the *Drug Safety Journal* under the title "Evaluation of the completeness of adverse drug reactions forms in public health facilities in South Africa". The author guidelines for this journal can be accessed at:

<http://www.springer.com/adis/journal/40264>.

Parts of the results from Manuscript 2 were presented on a poster at the 4th International Conference and Exhibition on Pharmacovigilance and Clinical Trials from 10 to 12 August 2015 in London, UK (Annexure M), and at the Academy of Pharmaceutical Sciences Conference from 17 to 19 September 2015 in Johannesburg, South Africa (Annexure N).

3.2 Manuscript 1

Healthcare professionals' awareness of, experiences with and perceptions of the pharmacovigilance system in the public health sector in South Africa

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Abbreviated running title

Evaluation of the pharmacovigilance system in South Africa

Keywords: healthcare professionals, perception, pharmacovigilance, adverse drug reaction report, South Africa, public health sector.

Key Messages:

- Healthcare professionals influence the success of the pharmacovigilance system.
- Healthcare professionals' awareness of, and attitudes towards the pharmacovigilance system were positive.
- The lack of time, an increased workload, insufficient feedback on reports and the lack of incentives are professional factors that discourage ADR reporting among healthcare professionals.
- Adverse drug reactions reporting should be mandatory and a pharmacovigilance specialist should be employed in each sub-district to improve the pharmacovigilance system.

Acknowledgements

The authors would like to thank all healthcare professionals who participated in the study. The authors appreciate the correspondence between Mrs R van Reenen and the research team and the healthcare facilities. The authors also thank Wilna Liebenberg for the language editing of the manuscript. This work was supported by the National Research Foundation of South Africa.

Word count excluding references/tables/figures/abstract: 3295

Abstract

Healthcare professionals are the main contributors towards the spontaneous adverse drug reaction (ADR) report database. Their interest in the system influences the success of pharmacovigilance. The purpose of this study was to investigate healthcare professionals' awareness of; experiences with and perceptions regarding factors that contribute to the successful implementation of pharmacovigilance. A self-administered questionnaire, accompanied by an information letter about the study, was provided to medical practitioners (n=52), pharmacists (n=15), and professional nurses (n=53) in the Tlokwe Local Municipality health sub-district in South Africa. The response rate was 40.8% (n=49). Most healthcare professionals were aware of which ADRs should be reported and what actions should be taken when an ADR occurs. The lack of time to complete an ADR report (56.3%), the possibility of an increased workload (54.2%); insufficient feedback on reports (77.1%) and the lack of incentives (71.4%) are professional factors that discourage ADR reporting among healthcare professionals. ADR reporting should be mandatory (95.5%) and a pharmacovigilance specialist should be employed in each sub-district (89.8%) to improve the future of pharmacovigilance. Healthcare professionals' awareness of and attitudes towards the pharmacovigilance system were positive. Discouraging ADR reporting factors may be resolved in future by means of training.

Introduction

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (Arlett and Kruz 2011). The benefits of a newly developed drug are influenced by the nature of clinical trials, the use of traditional and complementary medicines, the lack of training of prescribers, patient diets, genetics, disease patterns, drug manufacturing, distribution and storage. When new drugs are exposed to different and larger populations than in a controlled clinical trial, they have possibility of leading to unidentified new adverse effects, interactions and risk factors. Consequently, to ensure the safety of drugs in patient care, healthcare professionals need to monitor the patient and report any ADRs that occur (WHO 2004; Equale *et al.* 2008; Sauer *et al.* 2008; WHO 2012; Alomar 2014; Department of Health 2013).

The large number of congenitally deformed infants that resulted from the use of thalidomide for morning sickness and nausea amongst pregnant woman increased international awareness of adverse drug reactions (ADRs) in 1961 (WHO 2004). The application of the practice and science of pharmacovigilance also resulted in the market withdrawal of propoxyphene and rosiglitazone in 2010 due to the increased risk of heart attacks, stroke and death (Department of Health 2013).

Pharmacovigilance is not a priority to government authorities and public health programme managers, and this raises concerns regarding the global state of pharmacovigilance (Ulfvarson *et al.* 2007; WHO, 2006). In addition, the concept of pharmacovigilance is misunderstood by healthcare professionals, patients and society, and this delays the integration of the pharmacovigilance system in public health programmes (Ulfvarson *et al.* 2007; WHO 2006).

Healthcare professionals are the main contributors to the spontaneous ADR report database, and their limited interest in the pharmacovigilance system influences the successful implementation of the system (WHO 2006; WHO 2002a; Hartzema *et al.* 2008; Gupta and Udupa 2011; Rajesh *et al.* 2011; Reddy *et al.* 2014). Nurses involved in the prescribing and administration of drugs and monitoring of patients are often the first healthcare professionals to observe ADRs (Alan *et al.* 2013; Khan 2013). Medical practitioners can prevent and reduce ADRs and further drug-related harm to patients if they are devoted to high-quality prescribing that includes a benefit-risk assessment of the drug, including monitoring and management of ADRs (WHO 2002a; Hazell and Shakir 2006). Pharmacists, considered as the experts on medicines, should possess a strong academic background to monitor and reduce ADRs (Reddy *et al.* 2014; Granas *et al.* 2007; Palaian *et al.* 2011).

Studies conducted in Saudi Arabia, India and Uganda highlighted that healthcare professionals lacked understanding of the pharmacovigilance system and did not know what to report or how to report ADRs (Rajesh *et al.* 2011; Reddy *et al.* Khan 2013; Adhikary *et al.* 2013). Three categories have been identified to evaluate the pharmacovigilance system with reference to the healthcare professionals. Healthcare professionals can be assessed on their theoretical and practical understanding of the system (knowledge), the trend to respond in a positive or negative way towards pharmacovigilance (attitude), and the application of knowledge and experience regarding pharmacovigilance (practice) (Gupta and Udupa 2011; Abubakar *et al.* 2014; Wu *et al.* 2010). Basic knowledge regarding the purpose of pharmacovigilance and the location and contact details of the national pharmacovigilance centre indicates the healthcare professionals' awareness of pharmacovigilance (Palaian *et al.* 2011; Adhikary *et al.* 2013; Abubakar *et al.* 2014). A general culture of under-reporting is common among healthcare professionals, even though ADR reporting is perceived to be a professional obligation. Healthcare professionals seek rewards to improve voluntary ADR reporting (Gupta and Udupa 2011). Although the ADR report guidelines provide a clear indication that all non-serious reactions, known reactions and serious reactions should be reported, healthcare professionals report more unusual ADRs than well-known reactions (WHO 2002; Palaian *et al.* 2011; Khan 2013; Abubakar *et al.* 2014; Desai *et al.* 2011).

Personal insecurities of healthcare professionals that are identified as global obstacles in ADR reporting include the anxiety of seeming incompetent in their profession, the fear of legal action if an ADR occurred while a patient was under their care, or the admission of guilt if a medication error leads to an ADR (WHO 2002a; Gupta and Udupa 2011; Desai *et al.* 2011; Muraraiah *et al.* 2011; Karelia *et al.* 2014; Steurbaut and Hanssens 2014). Healthcare professionals in Turkey and India were in agreement that the ADR report form is too difficult and time-consuming to complete (WHO 2002a; Toklu *et al.* 2008). The ADR reporting rate in Qatar and Nepal will increase if ADR reports are more accessible to healthcare professionals and if they receive sufficient feedback on ADR reports (Palaian *et al.* 2011; Wilbur 2013). Education, training and improved clinical knowledge are required to increase the recognition and reporting of ADRs (Granias *et al.* 2007; Adhikary *et al.* 2013; John *et al.* 2012).

Different motives that prevent healthcare professionals from reporting ADRs have been identified globally, yet no attempt has been made to identify similar reasons in the Tlokwe Local Municipality in the DKKD in South Africa (Department of Health 2013; Hazell and Shakir 2006). The purpose of this study was to investigate healthcare professionals' awareness of, experiences with and their perceptions regarding factors that contribute to the successful implementation of pharmacovigilance in the Tlokwe Local Municipality in the South African public health sector.

Methods

Study design, setting and population

A cross-sectional research study was conducted to evaluate the perception of healthcare professionals regarding the pharmacovigilance system in the Tlokwe Local Municipality in the North West Province in South Africa. A self-administered questionnaire was designed for the purpose of this study. All medical practitioners (n=52), pharmacists (n=15) and professional nurses (n=53) employed on a permanent or temporary contract in the public health sector in the Tlokwe Local Municipality, who were involved in prescribing and/or dispensing medicines and who were directly involved with the identification and confirmation of ADRs were included in the study. This study was approved by the Health Research Ethics Committee at the North-West University (NWU-00003-15-S1) and the North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation.

Questionnaire development

The development of a questionnaire for this study was based on a comprehensive review of literature of similar studies conducted to determine the perceptions of healthcare professionals of pharmacovigilance. In addition standard operating procedures and guidelines for ADR reporting provided by the World Health Organization (WHO) and the South African Department of Health and Medicines Control Council (MCC) were used (Gupta and Udupa 2011; Rajesh *et al.* 2011; Reddy *et al.* 2014; Cosentino *et al.* 1997; Bateman *et al.* 1992; WHO 2002b; Department of Health 2012; MCC 2014; Neuman 2014; Bowling 2009). A preliminary questionnaire was reviewed by one statistician from the North-West University, one medical practitioner from the Department of Health in the Dr Kenneth Kaunda district, three voluntary personnel from the School of Pharmacy at the North-West University and two nurses from the School of Nursing at the North-West University to determine whether the participants understood the questions correctly. Feedback from these groups was used to improve the structure of the questionnaire to ensure the content and face validity of the questionnaire.

The questionnaire consisted of five sections with close-ended questions and one section that included open questions (Bowling, 2009). **Section A** collected demographic information about the participant, i.e. gender, age, qualification, current working environment and experience in practice. **Section B** and **Section D** evaluated the healthcare professionals' awareness of the procedure for reporting ADRs and their actual experience with ADR reporting with a yes (1) or no (2) response category. In **Section C**, a five-point Likert scale (strongly disagree =1, strongly agree = 5) was used to evaluate healthcare professionals' general view on ADR reporting and indicate their agreement on possible future improvements for the pharmacovigilance system (Neuman, 2014). In **Section E**, healthcare professionals were asked to indicate their

agreement/disagreement with respect to general factors that may discourage them to report ADRs. **Section F** included open questions to provide healthcare professionals with the opportunity to give a free response on the instructions and guidelines on the completion of an ADR report form. Space was provided for any future recommendations to improve ADR reporting in their sector. The answers from the open-ended questions were grouped according to different themes and a number was assigned to each theme for data analysis (Bowling, 2009).

Data collection

The questionnaires, accompanied by a cover letter with all the relevant information regarding the study, were delivered to the healthcare facilities and distributed by an independent mediator. The questionnaires were collected from the healthcare facilities after five days. No personal questions were included in the questionnaire and no individual participant could be traced after completion of the questionnaire.

Data analysis

Descriptive statistics such as frequencies and percentages were calculated by using SAS Version 9.1.3 (SAS Institute, USA). The age groups of healthcare professionals were indicated in range years and the years of experience in practice were determined independently for different healthcare facilities. The categories agree and strongly agree and strongly disagree and disagree in Section C were grouped together into two categories of agree and disagree. No inferential statistics were used in the study due to the small number of participants in the pharmacist category compared to the other healthcare professional categories.

Results

In this study 120 healthcare professionals were invited to participate in the study. The response rate was 40.8% (n=49). The respondents represented 23 medical practitioners, 16 professional nurses and 8 pharmacists. Two of the respondents did not indicate their profession, but they were included in the analysis of the total number of healthcare professionals. The majority of healthcare professionals were female (73.5%) and 73.9% had 10 years' or less of experience in practice.

Table 1 Demographic information

	Healthcare professionals	
	N=49	%
Gender		
Male	13	26.5
Female	36	73.5
Age (years)		
≥20 – ≤ 29	20	40.8
>29 – ≤ 39	18	36.7
>39 – ≤ 49	6	12.2
>49 – ≤ 59	5	10.2
Healthcare profession		
Medical practitioner	23	48.8
Nurse	16	34.0
Pharmacist	8	17.0
Current working environment		
Primary health clinic	15	30.6
Public hospital	18	36.7
Other (e.g. community day centre, mobile clinic, community health centre)	16	32.6
Experience in practice (years)		
< 1 – ≤ 10	34	73.9
> 10 – ≤ 20	9	19.6
> 20 – ≤ 30	2	4.4
> 30 – < 40	1	2.2

Table 2 Healthcare professionals' awareness of what should be reported.

	Correct response	Correct response from different healthcare professionals			*Total correct response
		Medical practitioners n=23 (%)	Professional nurses n=16 (%)	Pharmacist n=8 (%)	
Which ADRs should be reported?					
Suspected ADR caused by a new drug	Yes	23 (100.0)	16 (100.0)	7 (87.5)	48 (98.0)
Any unfamiliar drug reaction not previously stated	Yes	23 (100.0)	15 (93.8)	7 (87.5)	46 (97.9)
A well-known ADR	Yes	16 (69.6)	13 (81.3)	4 (50.0)	34 (70.8)
A reaction caused by an interaction between drugs	Yes	19 (82.6)	13 (81.3)	5 (62.5)	38 (80.9)
A reaction caused by a drug-disease interaction	Yes	16 (69.6)	14 (87.5)	7 (87.5)	38 (82.6)
A reaction caused by a drug-food interaction	Yes	18 (78.3)	12 (75.0)	7 (87.5)	38 (84.4)
Only serious ADRs	No	17 (73.9)	9 (56.3)	5 (62.5)	32 (71.1)
Any teratogenicity (birth defect)	Yes	20 (87.0)	14 (87.5)	6 (75.0)	42 (87.5)
ADR occurring due to medication error	Yes	15 (65.2)	13 (81.3)	4 (50.0)	33 (73.3)
Which product quality problems have to be reported?					
Product contamination	Yes	23 (100.0)	15 (93.8)	6 (75.0)	45 (93.8)
Disputed product quality problem	Yes	22 (95.7)	13 (81.3)	7 (87.5)	43 (91.5)
Defective components	Yes	23 (100.0)	16 (100.0)	7 (87.5)	47 (97.9)
Poor packaging and labelling of products	Yes	20 (87.0)	14 (87.5)	6 (75.0)	42 (87.5)
Therapeutic failures	Yes	12 (52.2)	16 (100.0)	5 (62.5)	34 (70.8)

* Total number of respondents with correct response independent of healthcare profession

There were two respondents who did not indicate their healthcare profession Non-response is not indicated in this table

Table 3 Healthcare professionals' actions, minimum requirements and the responsibility to report adverse drug reactions

	Correct response	Correct response from different healthcare professionals			*Total correct response
		Medical practitioners n=23 (%)	Professional nurses n=16 (%)	Pharmacist n=8 (%)	
Possible actions when an ADR occurs					
Report ADR on ADR reporting form	Yes	21 (91.3)	12 (75.0)	6 (75.0)	41 (85.4)
Report ADR on ADR reporting form as well as in patient's file (or file a copy of it in the patient's file)	Yes	23 (100.0)	15 (93.8)	8 (100.0)	47 (100.0)
Report ADR only in the patient's file	No	21 (91.3)	11 (68.8)	6 (75.0)	39(84.8)
Nothing	No	22 (95.7)	12 (75.0)	7 (87.5)	42 (93.3)
Change therapy	Yes	22 (95.7)	10 (62.5)	7 (87.5)	40 (88.9)
Determine the seriousness of the event	Yes	21 (91.3)	12 (75.0)	1 (12.5)	41 (91.1)
Ask patient to contact doctor	Yes	16 (69.6)	6 (37.5)	6 (75.0)	28 (60.9)
Healthcare professional should contact the physician	Yes	19 (82.6)	12 (75.0)	6 (75.0)	38 (82.6)
Minimum requirements for ADR to be reported					
The name address and qualification of reporter	Yes	21 (91.3)	15 (93.8)	7 (87.5)	44 (95.7)
Patient identified by surname, initials, reference number or age and gender	Yes	21 (91.3)	15 (93.8)	8 (100.0)	46 (95.8)
The suspected product that caused the ADR	Yes	22 (95.7)	14 (87.5)	8 (100.0)	45 (97.8)
The suspected ADR observed	Yes	22 (95.7)	14 (87.5)	8 (100.0)	45 (97.8)
Therapeutic failures	No	9 (39.1)	1 (6.25)	2 (25.0)	12 (27.3)
Who should report an ADR?					
Medical practitioner	Yes	23 (100.0)	15 (93.8)	8 (100.0)	48 (98.0)

	Correct response	Correct response from different healthcare professionals			*Total correct response
		Medical practitioners	Professional nurses	Pharmacist	
		n=23 (%)	n=16 (%)	n=8 (%)	
Pharmacist	Yes	22 (95.7)	14 (87.5)	8 (100.0)	46 (95.8)
Professional nurse	Yes	22 (95.7)	15 (93.8)	8 (100.0)	47 (97.9)
Dentist	Yes	21 (91.3)	15 (93.8)	6 (75.0)	43 (93.5)
Physiotherapist	No	10 (43.4)	4 (25.0)	6 (75.0)	21 (46.7)
Patient	No	11 (47.8)	3 (18.8)	4 (50.0)	19 (43.2)

* Total number of respondents with correct response independent of healthcare profession

*There were two respondents who did not indicate their healthcare profession ** Non-response is not indicated in this table

Awareness of ADR reporting

Types of ADRs that should be reported

The results in Table 2 reveal that the majority of healthcare professionals (>80%) were aware that the following ADRs should be reported:

- Unfamiliar and suspected ADRs caused by a new drug or that were not previously stated.
- ADRs caused by drug-drug interactions, drug-disease interaction and drug-food interaction.
- Any teratogenicity.

Less than 30% of the healthcare professionals were not aware that well-known reactions, less serious ADRs and those caused by medication errors should also be reported. Pharmacists were mostly unaware of these requirements (Table 2).

Product quality problems that should be reported

Most healthcare professionals (>85%) were aware that product contamination, disputed products, defective components and poor packaging or labelling of products have to be reported as a product quality problem (Table 2). Only 62.5% of pharmacists and 52.2% of medical practitioners knew that therapeutic failures should also be reported as a product quality problem.

Who is responsible for reporting ADRs?

The majority of healthcare professionals indicated that medical practitioners (98.0%), pharmacists (95.8%), professional nurses (97.9%) and dentists (93.5%) are responsible for ADR reporting (Table 3). More than 50% of healthcare professionals did not know that physiotherapists and patients are not allowed to report ADRs. The pharmacists had the highest awareness of this restriction in the ADR reporting guidelines.

Minimum requirements for reporting an ADR

The results in Table 3 show that healthcare professionals have a good awareness of the minimum requirements for ADR reporting. However, most of the healthcare professionals (>60%) incorrectly included a therapeutic failure as a minimum requirement for reporting an ADR.

Possible steps to follow when an ADR is detected

The results in Table 3 indicate that the majority of healthcare professionals knew that an ADR should be reported on an ADR report form (85.4%) and in the patient's file (100.0%). The overall awareness regarding where an ADR report should be sent and where the centre is located was inadequate. Only 11.1% of healthcare professionals knew that ADR reports should be sent to the NADEMC in Cape Town (n=7, 15.2%) within 15 days (n=2, 4.2%).

Healthcare professional's experience with ADR reporting

The results in Figure 1 reveal that 64.6% of healthcare professionals had reported an ADR in the past. Most medical practitioners (78.3%) and 62.5% of the pharmacists had experience with ADR reporting. Only 43.8% of professional nurses indicated that they had reported an ADR in the past. Six of the eight pharmacists (75.0%) had received training in reporting an ADR, while half of the medical practitioners (52.2%) had received training to identify an ADR. Professional nurses had the least training on how to report (37.5%) and to identify (31.5%) an ADR.

Sixty-five per cent of healthcare professionals indicated that enough ADR report forms were available and they had sufficient access to these forms (68.7%) (Table 4). The healthcare professionals indicated that more standard operating procedures (SOP) were provided to report an ADR (52.1%) than SOPs to assist them with the completion of the ADR report forms (39.6%). However, the instructions for reporting an ADR were understandable to 85.4% of the healthcare professionals.

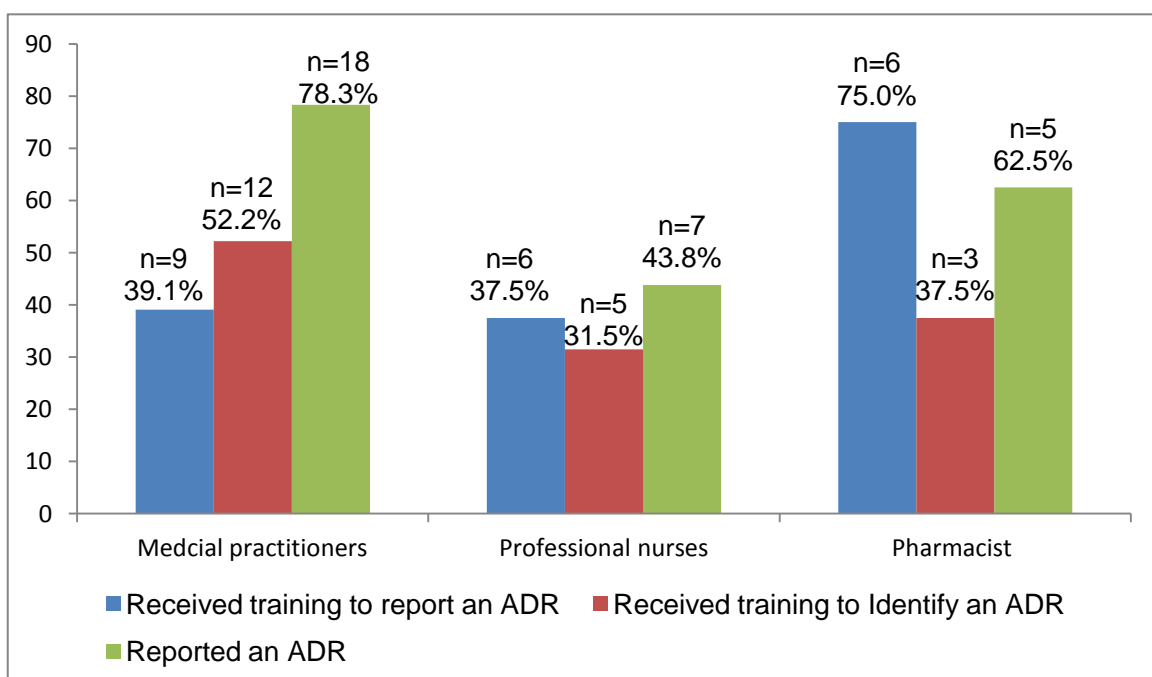


Figure 1 Healthcare professionals' history of adverse drug reaction reporting and training to identify and report adverse drug reactions

Table 4 Healthcare professionals' view on ADR reporting

Healthcare professionals reflect their views on ADR reporting.	Medical practitioners n=23(%)			Professional nurses n=16 (%)			Pharmacists n=8 (%)			All healthcare professionals n=49 (%)		
	Disagree	Uncertain	Agree	Disagree	Uncertain	Agree	Disagree	Uncertain	Agree	Disagree	Uncertain	Agree
The awareness of ADR reporting, in health facilities is effective.	8 (34.8)	7 (30.4)	8 (34.8)	5 (31.3)	4 (25.0)	6 (37.5)	3 (37.5)	3 (37.5)	2 (25.0)	17 (35.5)	14 (29.2)	17 (35.4)
You are provided with sufficient access to ADR reporting forms.	8 (34.8)	1 (4.3)	14 (60.9)	3 (18.8)	2 (12.5)	10 (62.5)	0 (0.0)	0 (0.0)	8 (100.0)	12 (25.0)	3 (6.3)	33 (68.7)
You have received adequate training to identify ADRs (pharmacological knowledge)	8 (34.8)	3 (13.0)	12 (52.2)	8 (50.0)	2 (12.5)	5 (31.3)	3 (37.5)	2 (25.0)	3 (37.5)	29 (43.7)	7 (14.6)	20 (41.7)
You have received adequate training to report an ADR	13 (56.5)	1 (4.3)	9 (39.1)	8 (50.0)	1 (6.3)	6 (37.5)	1 (12.5)	1 (12.5)	6 (75.0)	24 (50.1)	3 (6.3)	21 (43.7)
Your current working environment provides healthcare professionals with visible standard operating procedures to report ADRs.	10 (43.5)	3 (13.0)	10 (43.5)	4 (25.0)	4 (25.0)	7 (46.8)	0 (0.0)	1 (12.5)	7 (87.5)	15 (31.3)	8 (16.7)	25 (52.1)
Your department receives general feedback on ADRs reported from the	14 (60.9)	8 (34.8)	1 (4.3)	8 (50.0)	6 (37.5)	1 (6.3)	4 (50.0)	4 (50.0)	0 (0.0)	39 (58.4)	18 (37.5)	2 (4.2)

Healthcare professionals reflect their views on ADR reporting.	Medical practitioners n=23(%)			Professional nurses n=16 (%)			Pharmacists n=8 (%)			All healthcare professionals n=49 (%)		
	Disagree	Uncertain	Agree	Disagree	Uncertain	Agree	Disagree	Uncertain	Agree	Disagree	Uncertain	Agree

National
Pharmacovigilance
Centre.

* Total number of respondents with correct response independent of healthcare profession *There were two respondents who did not indicate their healthcare profession

** Non-response is not indicated in this table

Table 5 Factors discouraging ADR reporting

Factors discouraging ADR reporting	Medical practitioner n=23 (%)		Professional nurse n=16 (%)		Pharmacist n=8 (%)		Healthcare professionals n=49 (%)	
	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree
You are not confident about when to report an ADR.	11 (47.8)	12 (52.2)	8 (50.0)	8 (50.0)	3 (37.5)	5 (62.5)	24 (49.0)	25 (51.0)
You do not know where to find an ADR reporting form.	8 (37.9)	15 (65.2)	5 (32.3)	11 (68.8)	1 (12.5)	7 (87.5)	16 (32.7)	33 (67.3)
You do not receive feedback from the National Pharmacovigilance Centre.	19 (39.1)	3 (13.0)	11 (68.8)	5 (32.2)	6 (75.0)	2 (25.0)	37 (77.1)	11 (22.9)
Reporting an ADR is time-consuming.	13 (56.5)	9 (39.1)	8 (50.0)	8 (50.0)	6 (75.0)	2 (25.0)	27(56.3)	21 (43.8)
Completing an ADR report form increases your workload.	14 (60.9)	9 (39.1)	6 (37.5)	9 (56.3)	6 (75.0)	2 (25.0)	26 (54.2)	22 (45.8)
ADR reporting is not an essential part of your healthcare practice.	2 (8.7)	21 (91.3)	0 (0.0)	16 (100.)	0 (0.0)	8 (100.)	2 (4.1)	47 (95.9)
All drugs on the market are safe to use.	0 (0.0)	23 (100.)	5 (32.2)	11 (68.8)	0 (0.0)	8 (100.)	6 (12.2)	43 (87.8)
You fear the possibility of legal liability if you report an ADR.	2 (8.7)	21 (91.3)	3 (18.8)	13 (81.3)	1 (12.5)	7 (87.5)	6 (12.2)	43 (87.8)
You fear that the ADR is caused by a medication error.	3 (13.0)	20 (87.0)	5 (32.2)	11 (68.8)	1 (12.5)	7 (87.5)	9 (18.4)	40 (81.6)
You have a lack of motivation to report ADRs.	7 (30.4)	16 (69.6)	5 (32.2)	11 (68.8)	3 (37.5)	5 (62.5)	15 (30.6)	34 (69.4)
There are no ADR reporting forms available in your department.	6 (26.0)	17 (73.9)	2 (12.5)	14 (87.5)	1 (12.5)	7 (87.5)	10 (20.4)	39 (76.6)
There are no guidelines available in the facility to assist healthcare professionals in reporting ADRs.	12 (52.2)	10 (43.5)	4 (25.0)	12 (75.0)	0 (0.0)	8 (100.)	17 (35.4)	31 (64.6)
Do you understand that the reporting of ADRs is an obligation?	22 (95.7)	1 (4.3)	13 (81.3)	3 (18.8)	7 (87.5)	1 (12.5)	44 (89.9)	5 (10.2)

Factors discouraging ADR reporting	Medical practitioner n=23 (%)		Professional nurse n=16 (%)		Pharmacist n=8 (%)		Healthcare professionals n=49 (%)	
	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree
You do not receive incentives (e.g. financial or other recognition) for the reporting of ADRs.	16 (69.6)	7 (30.4)	11 (68.8)	5 (32.2)	6 (75.0)	2 (25.0)	35 (71.4)	14 (28.6)

*Total number of respondents independent of healthcare profession. Two respondents did not indicate their healthcare profession

** Non-response is not indicated in this table

Factors influencing the reporting of ADRs

Factors that influence healthcare professionals in reporting ADRs are indicated in Table 5. These factors are grouped together under professional and personal factors that influence ADR reporting.

Professional factors that influence ADR reporting

The time required to report an ADR and the possibility of an increased workload discourage more than 50% of medical practitioners and pharmacists from reporting ADRs. Less than 50% of professional nurses perceived an increased workload as a discouraging factor.

The majority of healthcare professionals (77.1%) indicated that the lack of feedback from the pharmacovigilance centre and the lack of incentives (71.4%) were discouraging factors for ADR reporting. A shortage of ADR report forms in different departments (76.6%), the unavailability of guidelines to assist with ADR reporting (64.6%) and uncertainty as to where to find an ADR report (67.3%) appeared not to be discouraging factors for healthcare professionals for reporting an ADR.

Personal factors that influence ADR reporting

Only 12.2% and 18.4% of the healthcare professionals agreed that fear of legal liability and fear that the ADR may have been caused by a medication error respectively were discouraging factors for reporting ADRs. The majority of healthcare professionals (69.4%) did not perceive a lack of motivation to be a discouraging factor. They regarded ADR reporting as an obligation (89.4%) and an essential part of their healthcare practice (95.9%). The lack of confidence to report an ADR was also not a factor that discouraged ADR reporting for pharmacists (62.5%) and medical practitioners (52.2%). Most of the healthcare professionals knew that all drugs on the market were not safe to use.

The future of pharmacovigilance

The majority of healthcare professionals agreed with the following possible improvements in ADR reporting:

- ADR reporting should be compulsory (n=47, 95.5%)
- Enriched motivation from the NADEMC (n=42, 85.7%)
- A less-complicated ADR reporting form (n=38, 77.5%)
- An electronic ADR reporting system (n=38, 77.5%)

- A toll-free number to NADEMC (n=42, 89.8%)
- A pharmacovigilance specialist employed in each sub-district (n=44, 89.8%)

Discussion

This study evaluated healthcare professionals' awareness and perception regarding the pharmacovigilance system and determined factors that discourage ADR reporting. Possible factors to improve ADR reporting among healthcare professionals in the Tlokwe Local Municipality sub-district in the public healthcare sector were also identified.

The awareness concerning what should be reported, the responsibility to report an ADR and the minimum information required to report an ADR was satisfactory, as most of the healthcare professionals provided the correct answer for this information. The South African guidelines for reporting ADRs request any suspected ADR (serious, unfamiliar or well-known ADRs) to be reported (Desai *et al.* 2011; Muraraiah *et al.* 2011). Other studies indicated that healthcare professionals are more motivated to report serious ADRs and they do not comprehend the necessity to also report a well-known ADR (MCC 2014; Su *et al.* 2010; Vallano *et al.* 2005). This study, however, indicated that healthcare professionals support the South African guidelines regarding which ADRs should be reported (Desai *et al.* 2011). Nonetheless, the awareness to not report only serious ADRs but to also report well-known ADRs can be improved among these healthcare professionals, especially the professional nurses. A therapeutic failure is not a minimum requirement for an ADR report and can be reported as a product quality problem. Therefore the awareness to report therapeutic failure should be increased to prevent drug-related harm to a patient (MCC 2014; MCC 2004; Juhlin *et al.* 2015). The majority of healthcare professionals agreed that an ADR that has occurred should be reported and the pharmacists indicated the highest awareness of the minimum requirements for reporting an ADR. The majority of the pharmacists in this study were also aware that, in contrast to Denmark and the Netherlands, it is not the responsibility of a patient to report an ADR (Blenkinsopp *et al.* 2007). In South Africa, patients cannot report an ADR without consulting a healthcare professional (MCC 2004).

Even though most healthcare professionals claimed to have reported an ADR, the awareness concerning where the report should be sent was inadequate, even though it is stated on the back of the ADR report forms (MCC 2014). In Bosnia and Nepal, pharmacists (25.0%) indicated the lowest history of ADR reporting, in contrast to the total pharmacists (75.0%) who had reported an ADR in this study. Like the studies in Bosnia (10.7%) and Nepal (17.0%), this study also highlighted that nurses had the lowest history of ADR reporting (Santosh *et al.* 2013; Amrain *et al.* 2014).

Most of the pharmacists had received training in reporting ADRs, and this could explain their good awareness of the minimum requirements for reporting an ADR. This study supported the results of a study in the Eastern Cape in South Africa and in Sweden that nurses required more training regarding the identification and reporting of ADRs (Ruud *et al.* 2010; Ekman *et al.* 2012). Pharmacovigilance training programmes should be provided regularly. The training programme should include the aim of pharmacovigilance, the responsibilities of all the stakeholders involved in pharmacovigilance, what to report, how to report an ADR, where to report an ADR, and what happens to the report (Karelia *et al.* 2014; Dogra *et al.* 2013). Healthcare professionals should also be educated to recognise an ADR. To ensure that the training sessions are effective, a post-training assessment should be done (Dheda 2013).

Like in Nepal, the lack of feedback on ADR reports is not uncommon in South Africa and the implementation of a Drug Bulletin to spread drug safety information can improve the report rate of ADRs (Santosh *et al.* 2013; Maigetter *et al.* 2015). The feedback in Sweden is done by sending a letter to the reporter to inform them of the result of the evaluation of the report and this is believed to contribute to the high ADR report rate in Sweden (Santosh *et al.* 2013). As a method of providing incentives, healthcare professionals should be acknowledged for their submitted ADRs in an attempt to improve the report rate (Ramesh and Parthasarathi 2009). The lack of time to report an ADR and the perception that it might increase the workload were the other main barriers leading to under-reporting of ADRs that were identified in this study and in other studies (John *et al.* 2012; Cosentino *et al.* 1997; Santosh *et al.* 2013; Kiguba *et al.* 2014).

Personal insecurities that refer to the fear of legal liability were not identified as a problem in this study (Gupta and Udupa 2011; Desai *et al.* 2011; Steurbaut and Hanssens 2014; Santosh *et al.* 2013). The unavailability of the ADR report forms, which was a significant problem in Saudi Arabia and Nepal, was also not acknowledged to be a problem in this study and the majority of healthcare professionals had sufficient access to ADR report forms (Khan 2013; Desai *et al.* 2011; Santosh *et al.* 2013; Ramesh and Parthasarathi 2009). Comparable to other studies, the healthcare professionals' attitude towards pharmacovigilance was positive. Most healthcare professionals agreed that ADR reporting was a professional obligation and they comprehended that ADR reporting was an essential part of healthcare practice (Gupta and Udupa 2011; Wilbur 2013; Su *et al.* 2010; Ramesh and Parthasarathi 2009). Pharmacovigilance is implemented to monitor the use and effect of drugs on the market, as all drugs cannot be regarded as safe after clinical trials, and it is satisfactory that healthcare professionals in the Tlokwe Local Municipality were in total agreement with this principle (WHO 2006).

The implementation of mandatory ADR reporting in healthcare practices has the possibility of improving ADR reporting, and the healthcare professionals' agreement in this study that ADR reporting should be mandatory indicated that they were committed to the system (Santosh *et al.*

2013; Amrita *et al.* 2012; Hardeep and Rakesh 2013). A less complicated ADR report form was requested by most healthcare professionals, even though the instructions for reporting an ADR were understandable to the majority of respondents. Healthcare professionals indicated that they would prefer the guidelines for reporting an ADR (51.6%) to be on the front of each ADR report, but the guidelines for reporting an ADR are available on the back of each ADR report form. This information indicates what should be reported, with clear instructions on what should be done with the ADR report form (MCC 2014). The pharmacovigilance system in South Africa could benefit from an electronic system, but an evaluation of the system stated that ADR reports should be submitted manually, as the current system does not have the capacity to handle electronic submissions (Maigetter *et al.* 2015). Effective pharmacovigilance units in facilities or different sub-districts were suggested as a possible contribution to the improvement of ADR reporting (Abubakar *et al.* 2014; Muraraiah *et al.* 2011; WHO 2002b; Ramesh and Parthasarathi 2009).

Study limitation

The response rate in the study could have been better. The study population included healthcare professionals from only one public health sub-district, and the results cannot be generalised to the rest of the healthcare professionals in the public health sector in South Africa.

Conclusion

The healthcare professionals' overall awareness of the pharmacovigilance system is satisfactory. The overall attitude towards pharmacovigilance is positive and should be used as a stepping stone towards improving the pharmacovigilance system. The factors that discourage healthcare professionals from reporting ADRs are more related to professional factors than personal factors. The identified problems may be addressed and improved by means of pharmacovigilance training.

Funding: This study was supported by the National Research Foundation of South Africa.

Conflict of interest: The authors have no conflicts of interest directly relevant to the content of this study.

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3.3 Manuscript 2

Evaluation of the completeness of adverse drug reaction forms in public health facilities in South Africa

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Abstract

Background: Pharmacovigilance aims to generate drug safety information by means of adverse drug reaction (ADR) report forms. Good-quality ADR report forms are a requirement for a good pharmacovigilance system.

Objective: The aim of this study was to assess and compare the completeness of the contents of the ADR report forms completed in the Dr Kenneth Kaunda (DKK) health district in South Africa with the minimum WHO requirements.

Method: A cross-sectional study was conducted in the DKK district in South Africa. The Medicines Control Council (MCC) and anti-retroviral (ART) ADR report forms received between 2010 and 2014 were evaluated. The completeness was assessed by reviewing the elements of the ADR forms, and the number of fields that had been completed. Descriptive statistics were reported.

Results: A total of 1 454 MCC and 92 ART ADR report forms were available for evaluation. On the MCC and ART ADR report forms the sections regarding ADR outcomes were fully completed on respectively 57.9% and 13.0% of the ADR reports. The least fully completed section on the MCC ADR report form was the description of the ADR (0.1%), and on the ART ADR report form the patient information section (1.1%). Seventeen of the MCC ADR report forms reported a product quality problem, but none of these were fully completed.

Conclusion: None of the sections on the MCC and the ART ADR report forms from 2010 until 2014 was fully completed. The absence of information on the ADR report forms limits the expansion of drug safety information.

Key points:

- The completeness of the ADR report form is important for adequate evaluation of the ADR that occurred.
- There is a need to evaluate the completeness of the ADR report forms in other public healthcare facilities in South Africa.
- The incompleteness of the ADR report forms may indicate a need for training among healthcare professionals in an attempt to improve the quality of ADR reporting.

Key words: Adverse drug reaction report, completeness, public health sector, pharmacovigilance, South Africa

1. Introduction

The occurrence of adverse drug reactions (ADRs) leads to an average of 3.6% of hospital admissions in Europe, 5.64% in the US, 3.3% in Australia and 6.3% in South Africa. In addition, these harmful or unpleasant reactions caused by the use of drugs also lead to a prolonged hospital stay, an unexpected economic burden on the healthcare system and patients, unwanted patient distress and a possible rise in the mortality and morbidity rate [1-11]. These consequences and the occurrence of ADRs confirm the need for a system that enables the early detection of drug safety problems [11-15].

Pharmacovigilance was established as a part of the drug safety regulation system due to the limited drug safety data available from clinical trials. This post-marketing surveillance system expands the drug safety information from the clinical trials through the collaboration between science and activities that include the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem to ensure the safety of drugs and improve patient care [8, 13, 16-18].

The World Health Organization (WHO) created minimum requirements for a successful pharmacovigilance system, including standard minimum requirements for an ADR report form. All the countries participating in the pharmacovigilance programme design their own ADR report form as a fundamental step to establishing a good pharmacovigilance system [14, 19]. The voluntary spontaneous reporting of ADRs can be enforced at a regional or national level in a country. This method of ADR reporting is considered to be the basis of pharmacovigilance and is the most widespread economical method used to report ADRs in developed and developing countries. The spontaneous ADR reports contribute to the WHO's global individual case safety report (ICSR) database system, VigiBase [12, 14, 20-23]. The majority (85%) of ADR reports in VigiBase were received from the US, UK, France, Germany, Canada and Australia [20, 24]. South Africa also utilises the spontaneous reporting of ADRs to contribute to the WHO database. The South African Medicines Control Council (MCC) and the Essential Drug Programme of the South African Department of Health designed an ADR report form according to the minimum WHO standards [25-26]. In an attempt to improve the effectiveness of the pharmacovigilance system in South Africa, ADRs can be reported on the national MCC ADR report form or on the regional antiretroviral therapy (ART) ADR report form [26-28].

Due to the unknown mechanism that results in ADRs, a standard ADR report form should contain all the important factors required to evaluate the risk of a specific ADR [33]. The identification of risk factors will aid in the prevention of drug-related harm to patients [15, 34]. Patient information variables include risk factors such as gender, weight, height and age [35]. The exclusion of elderly and infant patients from clinical trials confirms the age category of a

patient as a risk factor for ADRs. The dosage regimens for drugs on the market are only an estimate for these age groups. Gender is included as a risk factor due to the difference between the male and female body weight, body composition, gastro-intestinal factors, metabolism and renal function that influence the activity of drugs [36-37]. The height and weight of the patient are used to calculate the body mass index (BMI) to determine the correct dosage of a drug for patients, especially for infants and children [11, 47, 49].

Drug variables include all the drugs used by the patient and a signal that indicates which of these drugs were responsible for the ADR. The reason for the use of each drug, the dosage form, route of administration, frequency of use and the start and end date of the administration of the drugs should also be on the ADR report form [11, 35, 37]. These drug variables and the description of the ADR are used to determine the relationship between the ADR and the drugs that were administered and the possibility of drug-drug interactions or medication errors [11, 27]. If a product quality problem led to an ADR, it is important to include the batch number of the drug to enable that specific batch of drugs to be traced to prevent any further drug-related harm to patients [11]. Administrative variables include the details of the reporter and are used to acknowledge the receipt of the report and to contact the reporter if the evaluators of the ADR report require any additional information [33].

A good pharmacovigilance system relies on the quality of the information from the ADR reports that are used to generate an information system on the quality and the safety of drugs used by different populations in different countries. The investigation of these reported ADRs can lead to informative proposals to ensure the safe use of drugs, or to changes on the package inserts, and changes in the scheduling status or manufacturing of the drug to reduce or to prevent these ADRs in the future [14, 25, 28-32]. Inadequate data from incomplete ADR reports limits the value of the data [42-44]. The quality of an ADR report is based on the degree to which the ADR report form meets the completeness requirements of the form. The quality of the ADR report form increases if there is more information available on the ADR report forms [38-41].

As is mentioned in the text above, the information from the ADR report form is used to make critical decisions. An evaluation of the completeness of ICSRs submitted to VigiBase indicated that only 23% of the reports in 2012 were considered to be good-quality ADR reports, and 66% of these high-quality reports were from Europe [43]. The quality of 1 520 completed ADR reports used in publications was evaluated in Europe, North America and Asia in 2002. The patient and drug variables were completed in >90% and 70% of the published reports [45]. The assessment of the completeness of ADR report forms in Mexico in 2007 and 2008 indicated that 32% and 44% of these reports were incomplete [46]. In Saudi Arabia, from 2009 until 2012 only 38% of the completed ADR report forms contained high-quality patient information [47]. The completeness of the ADR report form is also a problem in South Africa because of incomplete

patient and relevant laboratory information [48]. These studies concluded that incomplete information on these forms could not be used for a thorough evaluation to identify significant risk signals regarding the drugs that had caused the ADRs [30, 35, 46, 48].

The aim of this study was to assess and compare the completeness of the contents of the ADR report forms completed in the Dr Kenneth Kaunda (DKK) health district in the North West Province in South Africa with the minimum WHO requirements.

2. Method

2.1 Research design and study setting

A cross-sectional research design was used to conduct the study. Two different checklists for the MCC and the ART ADR report forms were specifically developed to evaluate the completeness of the available ADR reporting forms, independent of pharmacological category or drug use, from 2010 until 2014 in the DKK district. All the available completed ADR report forms from three public hospitals and their connected primary healthcare clinics in the DKK district were evaluated.

2.2. Data collection tool

The MCC and the ART ADR report forms were used as criteria to create two checklists for evaluating the MCC and the ART ADR report forms. The face validity of the evaluation forms was confirmed by a statistician. Table 1 provides the six sections on the MCC ADR report form and the checklist concerned; and the eight sections on the ART ADR report form and the checklist concerned. On these checklists, yes/no categories were used to determine the completeness of each of the aspects on the ADR form (Table 1). On the MCC ADR report form patient information is required in **Section I**. **Section II** (medicine/vaccine/devices) describes the medicine currently being used by the patient, including the dosage, duration of use and the reason for using the drug. **Section III** describes the ADR outcome and product quality problems, and provides the date and time of the reaction. **Section IV** indicates the type of ADR and information regarding the treatment of the reaction. Product quality problems are evaluated in **Section V**. **Section VI** requires the information of the healthcare professional who were responsible responsible for the completion of the ADR report form. The reporter is obliged to include their name, qualification, address, contact number, date of reporting and a signature.

On the ART ADR report form **Sections I and II** are the same as those on the MCC ADR report form. **Section III** describes the date of the reaction and the type of reaction that occurred. The ART ADR report form does not include a section to report product quality problems; but laboratory tests, relevant clinical history and drug-resistance warnings are described in

Sections IV, V and VI. Section VIII on the ART ADR report form is the same as **Section VI** on the MCC ADR report form. The quality assessment regarding the completeness of the ADR report form included all the categories provided on the South African ADR report forms [26].

2.3. Data collection and administration

The evaluation of the ADR report forms was done on hard copy in the hospitals to ensure the safety of the information. The completed checklist did not contain personal information of patients, healthcare professionals or the public healthcare institution (primary healthcare clinic or hospital) in order to increase the anonymity of each facility. A coding scheme was designed as an important feature to indicate whether the information required on the ADR form had been completed or not. The data was uploaded to the data coding sheet that has been designed as a Microsoft Excel template. The completeness of the information of the MCC and ART ADR report forms was also compared to the standards provided by the WHO (Fig 1) [15].

Patient information	Adverse event or product quality problem	Outcome of the event	Reporter details
<ul style="list-style-type: none"> • Patient identifier • Date of birth/age • Gender • Weight 	<ul style="list-style-type: none"> • Description of the event • The date of the event • The date of the report • Relevant test done or laboratory data • Patient history 	<ul style="list-style-type: none"> • Suspected medicine(s) • Name of the drugs • Dose, frequency and route used for all medications. • Start date of therapy • The diagnosis for the drugs used • The outcome after use of drug is stopped or dose is reduced • The batch number of drugs used • The expiration date of drugs used • Description if the event reappeared after reintroduction of drug • Concomitant medical products and therapy dates 	<ul style="list-style-type: none"> • Healthcare professional's name • Healthcare professional's address • The telephone number of the reporter • Healthcare professional's occupation and specialty

Figure 1 The World Health Organization's minimum required information for an adverse drug reaction report form

2.4. Statistical analysis

Descriptive statistics, frequencies and percentages for all elements of the checklist were calculated by using the SAS Version 9.1.3 (SAS Institute, USA).

3. Results

A total of 1 454 MCC and 92 ART ADR report forms were available for evaluation. The overall completeness of the different sections on the ADR report forms was determined according to the South African guidelines that require an ADR report form to be as complete as possible [25]. The completeness of different categories on the respective ADR report forms was also compared to the WHO requirements (Fig 1).

3.1. Overall completeness of ADR report forms

As is shown in Table 1, all the categories in the section on ADR outcome and the administrative details of the reporter were fully completed on 57.9% and 35.4% of the MCC ADR report forms. The sections that describe the medicine/devices/vaccine used by the patients, the description of the ADR and patient information were fully completed on 2.1%, 0.1% and 8.4% of the MCC ADR report forms. On the ART ADR report forms, the ADR outcome and the administrative details of the reporter were fully completed on 13.0% and 51.1% forms. The categories in the sections of the medicine/vaccines/devices used by the patient, the description of the ADR and patient information were fully completed on 9.8%, 46.7% and 1.1% of the ART ADR report forms (Table 1). The respective sections on laboratory results, relevant clinical history and early-warning drug resistance were fully completed on 26.1%, 56.5% and 22.8% of the ART ADR report forms (Table 1). None of the 17 MCC ADR report forms that reported a product quality problem were completed according to the South African requirements [26].

Table 1 The completeness of different sections of the MCC and ART ADR report forms

Section	MCC ADR report form	Completeness n=1 454 (%)	Section	ART ADR report form	Completeness n=92 (%)
I	Patient information	122 (8.4)	I	Patient information	1 (1.1)
II	Medicine/vaccine/ devices used by the patient	30 (2.1)	II	Medicine/vaccines / devices used by the patient	9 (9.8)
III	Adverse drug reaction/ product quality problem	2 (0.1)	III	Adverse drug reaction	43 (46.7)
IV	Adverse drug reaction outcome	842 (57.9)	IV	Laboratory results	24 (26.1)
V	Product quality problem	0 (0)	V	Adverse drug reaction outcome	12 (13.0)
VI	Reporting doctor/ pharmacist/ nurse	514 (35.4)	VI	Relevant clinical history	52 (56.5)
			VII	Early warnings for drug resistance	21 (22.8)
			VIII	Reporting doctor/ pharmacist/nurses	47 (51.1)

MCC ADR report form: Medicines Control Council adverse drug reaction report form

ART ADR report form: Anti-retroviral adverse drug reaction report form

3.2. Completeness of different categories in each section on the ADR report form according to the WHO and the South African guidelines

Patient information

As is shown in Table 2 the three best-completed categories regarding patient information on the MCC and ART ADR report forms were the patient identifier, date of birth and gender while the weight of the patient was more complete on the ART ADR report form (69.9%) than on the MCC ADR report form (38.0%). The height, allergy and pregnancy status of the patient, indicated in Table 3, are not a requirement of the WHO. However, the height of the patient was reported on 9.6% and 44.6% of the MCC and ART report forms respectively (Table 3). The pregnancy and allergy status of a patient were reported on 70.7% and 69.9% of ART ADR report forms (Table 3).

Adverse drug reaction or quality problem

The description of the ADR was reported on 89.9% of the MCC and 80.4% of the ART ADR report forms, whereas the date on which the reaction occurred was more complete on the ART ADR report forms (59.8%) than on the MCC ADR report forms (13.4%) as can be seen in Table 2. The time at which the reaction occurred, as indicated in Table 3 is required only by the MCC ADR report form and was reported on 3.0% of the forms.

The MCC ADR report form has a separate section to report a product quality problem related or unrelated to an ADR. Of the 1 454 MCC ADR report forms, 17 recorded a product quality problem and six of these product quality problems had resulted in an ADR. The trade name, dosage form and strength of a drug and an indication as to whether or not the suspected product was available for evaluation were reported on only 17.7% of these 17 MCC ADR report forms (Table 4).

Outcome of the event

With regard to all the drugs used by the patient, the name of the drugs was indicated on 96.9% of the MCC and 93.5 % of the ART ADR report forms (Table 1). The suspected drug that had caused the ADR was indicated on only 3.4% of the MCC ADR report forms and on 21.7% of the ART ADR report forms. The daily dosage, route of administration of drug and start date of therapy were completed on 93.8%, 89.5% and 66.4% of the MCC ADR report forms. The dosage, interval, route of administration and start date of therapy were completed on 91.3%, 85.9%, 91.3% and 81.5% of the ART ADR report forms (Table 1). The diagnosis for the drugs used and the batch number of the drugs were respectively completed on 67.1% and 2.4% of the MCC ADR report forms (Table 2). The prescriber of the drug indicated in Table 3 and the

outcome after the intervention of the drug indicated in Table 2 were completed on 67.4% and 18.5% of the ART forms. As is shown in Table 2, neither the MCC ADR report form nor the ART ADR report forms was required an indication of the expiry date of the drugs. However, the description of events after the ADR had been re-challenged was completed on 6.5% and 34.8% of the MCC and ART ADR report forms (Table 2).

Reporter

As is shown in Table 2 and Table 3, the name, occupation and address of the reporter were completed on 97.0%, 96.4% and 96.6% of the MCC ADR report forms and on 94.6%, 71.7% and 98.9% of the ART ADR report forms.

Table 2 Completeness of ADR report form according to the WHO requirements

ADR report form requirements according to WHO	MCC	ART
	completeness n=1 454 (%)	completeness n=92 (%)
Patient information		
Patient identifier	1 436 (98.8)	90 (97.8)
Date of birth	1 313 (90.3)	85 (92.4)
Gender	1 384 (95.2)	84 (91.3)
Weight (kg)	553 (38.0)	64 (69.6)
Adverse drug reaction or quality problem		
Product quality problem	17 (1.0)	N/A
Description of reaction	1 292 (89.9)	74 (80.4)
Date of reaction	95 (13.4)	55 (59.8)
Report date	1 364 (93.8)	88 (95.7)
Relevant test done		
<i>Baseline test</i>	N/A	35 (38.0)
<i>Current test</i>	N/A	57 (61.9)
Patient history		
<i>Date patient initiated ARTs</i>	N/A	71 (77.2)
<i>Initial regimen</i>	N/A	64 (69.6)
<i>How long has patient been diagnosed with HIV?</i>	N/A	64 (69.6)
<i>How long has been patient been on ART treatment?</i>	N/A	63 (68.5)
Outcome of the event		
Suspected medicine	50 (3.4)	20 (21.7)
Name of drugs	1409 (96.9)	86 (93.5)
Dosage and frequency		
<i>Daily dosage</i>	1369 (93.8)	N/A
<i>Dosage</i>	N/A	84 (91.3)
<i>Interval</i>	N/A	79 (85.9)
Route	1301 (89.5)	84 (91.3)
Start date of therapy	966 (66.4)	75 (81.5)
Diagnosis of drug used	975 (67.1)	N/A
Outcome after drug intervention	N/A	17 (18.5)
Batch number of drug	35 (2.4)	N/A
Expiry date	N/A	N/A
Description after re-challenge	94 (6.5)	32 (34.8)
Concomitant drugs	N/A	N/A
Reporter		
Name	1411 (97.0)	87 (94.6)
Address	670 (46.1)	58 (80.4)
Telephone number	1364 (38.8)	48 (52.2)
Occupation	1401 (96.4)	66 (71.7)

MCC ADR report form: Medicines Control Council adverse drug reaction report form

ART ADR report form: Anti-retroviral adverse drug reaction report form

N/A: Not applicable was assigned to all categories not included on the original adverse drug reaction report form

Table 3 Completeness of the additional information available on the MCC and ART ADR report form

Information available on South African forms not required by World Health Organization	MCC complete n=1 454 (%)	ART complete n=92 (%)
Patient information		
NHLS lab no	N/A	6 (6.5)
Height	140 (9.6)	41 (44.6)
Allergy	N/A	56 (60.9)
Pregnancy	N/A	65 (70.7)
Adverse drug reactions or quality problems		
Time of onset of reaction	44 (3.0)	N/A
Medicine/vaccines/devices		
End date of therapy	1 369 (94.2)	76 (82.6)
Prescriber of drugs	N/A	62 (67.4)
Outcome of the event		
Comments for history, allergies, previous exposure and baseline test results	717 (49.3)	N/A
Early warning drug resistance		
Patient ART pick-ups for 3 months (dates)	N/A	55 (59.8)
Interval for scheduled consultations	N/A	29 (31.5)
Most recent consultation dates (last 3)	N/A	58 (63.0)
Reporter		
Signature	1404 (96.6)	91 (98.9)

MCC ADR report form: Medicines Control Council adverse drug reaction report form

ART ADR report form: Anti-retroviral adverse drug reaction report form

N/A: Not applicable was assigned to all categories not included on the original adverse drug reaction report form

Table 4 Product quality problem information from the MCC ADR report form.

Product quality problem information	Completed MCC ADR report forms n=17 (%)
Trade name	3 (17.7)
Batch number	2 (11.7)
Registration number	2 (11.7)
Dosage form and strength	3 (17.7)
Expiry date	2 (11.7)
Size/type of container	2 (11.7)
Product available for evaluation	3 (11.7)

MCC ADR report form: Medicines Control Council adverse drug reaction report form

4. Discussion

The evaluation of the content of the completed ADR report forms assessed the quality of completeness of each ADR report form. Even though most of the different categories in each section on the MCC and the ART ADR report form were completed, the overall completeness of these different sections was not satisfactory.

Similar to the quality of the ADR report forms in Saudi Arabia, the quality of the patient information section on the MCC and the ART ADR report forms was disappointing [47]. Patient information required for the identification of a patient and to avoid duplication of the evaluation of an ADR was fully completed on only 8.4% of the MCC and 1.1 % of the ART ADR report forms respectively [26]. In contrast, except for the weight of the patient, the other patient information categories required by the WHO were indicated on more than 90% of the MCC and the ART ADR report forms. The height and the weight were completed on 38.0% and 9.6% of the MCC ADR report forms and on 69.6% and 44.6% of the ART ADR report forms. The height and the weight categories were complete on only 28.3% and 21.1% of the Saudi Arabian ADR report forms, therefore these categories were more complete on the MCC and the ART ADR report forms [47].

The pregnancy and allergy status of patients that is used during the causality assessment of the ADR is not a requirement on the MCC ADR report form, but was completed on 70.7% and 60.9 % of the ART ADR report forms. It was difficult to assess the allergy and pregnancy status from the MCC ADR report form, because this form provides only a comment block where the pregnancy and allergy status of a patient can be recorded in a narrative form [27, 39]. The quality assessment of the ADR report form was done on the information provided on the forms, and if a category was incomplete, it influenced the quality of the report. However, the quality of the assessment regarding the completion of an ADR report form will improve if a *not applicable* or an *unknown* option is provided for the allergy and pregnancy status [40].

The section describing the ADR that occurred was more complete on the ART ADR report forms (46.7%) than on the MCC ADR report forms (2.1%). This could be related to the difference in these two ADR report forms. The completeness of this section on the MCC ADR report forms was based on the following five categories: adverse drug reaction/product quality problem, time of the ADR, the date the ADR occurred and description of the reaction. However, this same section on the ART ADR report form included only the description of the ADR and the date on which the ADR occurred. The ART ADR report form provided a list of possible ADRs with sufficient space to indicate other reactions, while the MCC ADR report form required a written description of the reaction. Nonetheless, there was not a remarkable difference concerning the completion of this category between the MCC (89.9%) and the ART (80.4%) ADR report forms

[30]. The date when the ADR occurred, used during causality assessment of the ADR, was more frequently completed on the ART (59.8%) than on the MCC (13.4%) ADR report forms. The completeness of this category was lower than the completeness of the Saudi Arabian ADR reports (62.7%) [47]. However, the date when the ADR occurred was more complete on the ART ADR report form than on ADR reports in the United States (19.0%) [50]. In Norway, physicians indicated the date of the ADR on 86% of the ADR report forms, whereas pharmacists indicated the date of the ADR on only 49% of the ADR report forms [51]. The section on relevant clinical history on the ART ADR report form was also required for causality assessment by the pharmacovigilance advisory committee and healthcare professionals [48]. The MCC ADR report form provided only a comment space to indicate whether possible laboratory tests had been done, and compared to the ART ADR report form, more definite categories are required for this information on the MCC ADR report form. The quality of the completeness of the ART ADR report form can also be improved with the inclusion of a *not applicable* or an *unknown* option to be chosen in this section [40].

During a quality assessment of published case reports and Saudi Arabian ADR reports, the drug suspected of causing the ADR was indicated on 99.0% of published case reports and 67.2% of the Saudi Arabian ADR report forms, while the suspected drug was indicated on only 3.4% of the MCC and 21.7% of the ART ADR report forms [47, 52]. The route of administration of the drug on the MCC (89.5%) and the ART (91.3%) ADR report forms was more complete than in published case reports, which indicated the route of administration on only 37% of the ADR report forms [52]. An ADR could be re-challenged to determine the certainty of the relationship between the ADR that occurred and a suspected drug by administering the same drug again after complete withdrawal [54]. During the evaluation of the MCC and ART ADR report forms, the completeness of the category concerning the description of the event that occurred after an ADR had been re-challenged was mandatory. However, it is not always possible to re-challenge an ADR. For example, the administration of a vaccine cannot be withdrawn, therefore this category could be considered as an optional category during the evaluation of the completeness of the ADR report form [40, 41, 54].

If a product quality problem is detected or a product quality problem results in an ADR, it should be reported as a suspected ADR. The report of product quality problems is a requirement of the WHO and can only be reported on the MCC ADR report form. Product quality problems such as suspected contamination, inconsistent stability, defective components, inadequate packaging or labelling and therapeutic failures due to lack of efficacy of the drug should be reported [25-26]. On 17 of the MCC quality report forms evaluated, the information required to trace the batch of drugs was incomplete and any possible future drug-related harm caused by those specific drugs cannot be prevented with these reports [26]. The lack of detailed information on the product

quality report forms obstructed the evaluation of the report and should be improved to minimise drug-related harm to a patient as a result of a product quality problem [53].

The occupation of the healthcare professional was more complete on the MCC (96.5%) and the ART (71.1%) ADR report forms compared to the Saudi Arabian ADR report forms (15%) [47]. The name and signature of the reporter were completed satisfactorily on the MCC and ART ADR report forms, but indication of the address and telephone number of the reporter showed room for quality improvement.

5. Conclusion

The completeness of an ADR report form is an important quality parameter in the pharmacovigilance system [43]. The completion quality of both the MCC and the ART ADR report forms in this study was generally low. This may be the result of a lack of awareness and knowledge regarding the importance of the different types of information needed for the evaluation of the ADR that occurred. All the information required on the ADR report forms is important and the ADR report form needs to be as complete as possible [26]. Therefore, in an attempt to improve the completion quality of the ADR report forms, training should be provided to healthcare professionals. This training should focus on the completion of all the categories in the different sections on the MCC and the ART ADR report forms. In an attempt to improve the pharmacovigilance system, future studies should also evaluate the clinical information on the ADR report form and should be implemented in all public healthcare facilities in South Africa.

Acknowledgement

The authors would like to thank the managers of all the facilities in the DKK district for making the data available. The authors appreciate correspondence between Mrs R van Reenen and the research team and the healthcare facilities. The authors also thank Wilna Liebenberg for the language editing of the article.

Compliance with ethical standards

Funding: This study was supported by the National Research Foundation.

Conflict of interest: Authors have no conflicts of interest directly relevant to the content of this study.

Ethical approval: The necessary permission and ethical clearance were obtained from the Health Research Ethics Committee (HREC) at the North-West University (NWU-00003-15-S1) and the North West Department of Health: Policy, Planning, Research, Monitoring and

Evaluation (PPRM&E) directorate. Goodwill permission was also obtained from the managers of all facilities included in the study.

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CHAPTER 4 CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

The conclusion and key findings from the literature study and the empirical investigation are discussed in this chapter. Significant limitations to the study and recommendations for possible future studies regarding pharmacovigilance are included in this chapter.

4.1 Literature review objectives

4.1.1 Conceptualisation and comparison of good pharmacovigilance practice with international and national guidelines.

Good pharmacovigilance practices are based on the completeness of ADR reports for the effective identification of risks and the prevention of drug-related harm (Dogra *et al.*, 2013:18; Rajesh *et al.*, 2009:678; WHO, 2006:24) (Section 2.7). The principles of good pharmacovigilance practice are conceptualised according to the terms used in pharmacovigilance (Section 2.7.1); the minimum requirements for a functional pharmacovigilance system (Section 2.7.2); the responsibilities of all stakeholders in the pharmacovigilance framework (Section 2.7.3); the process of ADR reporting; the ADR report (Section 2.7.3); and the guidelines for completing an ADR report form (Section 2.7.4).

The stakeholders include the WHO quality assurance and safety medicine team, the Uppsala Monitoring Centre (UMC), national pharmacovigilance centres, pharmaceutical industries, hospitals and academia, healthcare professionals and patients (Section 2.7.3). The WHO quality assurance and safety medicine team provides global leadership to improve drug safety (WHO, 2002a:9; WHO; 2014:5). All the ADR reports are sent to the UMC for evaluation and to expand the international ADR database (WHO, 2002a:9). It is the patient's responsibility to inform their healthcare professional if an ADR occurs (Section 2.7.3). Once a pharmacovigilance system is established, it is the responsibility of the healthcare professional to start the flow of the ADR report system as seen in Figure 2.2 (Section 2.7.3). The National Pharmacovigilance Centre receives ADR reports from healthcare professionals and pharmaceutical companies and are responsible for the motivation of ADR reporting and evaluation of ADR reports (WHO, 2001:2; WHO, 2006:48) (Section 2.7.3).

A functional pharmacovigilance system consists of an available national pharmacovigilance centre with sufficient manpower to manage the ADR system, basic funding, an existing spontaneous ADR reporting system, a national ADR database and clear mandates concerning the responsibilities of stakeholders and communication between these stakeholders (WHO, 2010:2) (Section 2.7.2). The pharmacovigilance system in South Africa only meets four of these nine requirements (Table 2.3 and Section 2.7.2 and 2.8.1).

These concepts of good pharmacovigilance practice were compared to the current pharmacovigilance status of South Africa and the conclusion was drawn that pharmacovigilance activities in South Africa lack continuity (Section 2.8.1).

4.1.2 Evaluation of the current South African ADR reporting form with international guidelines

In the DKKD there are two ADR report forms available: the MCC and the ART ADR report forms (Annexure D and C) (Section 2.8.2.). These ADR report forms were compared to the minimum requirements for an ADR report form provided by the WHO, as indicated in Figure 2.3 (Section 2.7.4). The comparison was divided into different categories: patient information (Table 2.4 and Section 2.8.2.1.1), ADR/product quality problem (Table 2.5 and Section 2.8.2.1.2), ADR outcome and other information (Table 2.6 and Section 2.8.2.1.3), medicine suspected to have caused the ADR (Table 2.7 and Section 2.8.2.1.3), and the details of the ADR reporter (Table 2.8 and Section 2.8.2.1.4). The MCC and ART ADR report forms contain more information than required by the WHO in the patient information, ADR/product quality and ADR reporter details sections.

However, in contrast to the MCC ADR report form, the ART ADR report form cannot be used to report a product quality problem (Table 2.5). The ART ADR report form also makes no provision for indicating the diagnosis for the drugs used by patients, the batch number of drugs or the expiry date of the drugs (Table 2.5). This evaluation concluded that even though there is not perfect correlation between the MCC and ART ADR report forms, these forms comply with most of the WHO requirements for an ADR report form (Section 2.8.2). The guidelines used to report an ADR in South Africa are also compared to international guidelines in Table 2.9 and specify what should be reported, who can report an ADR, when and where an ADR should be reported and how to report an ADR. These guidelines should also be used as basic principles in pharmacovigilance training.

4.1.3 Description of the relationship between inappropriate drug use, medication errors, ADEs (preventative and non-preventative) and ADRs through an extensive literature review

The review of this objective provides a clear distinction between the different definitions of the terms used in pharmacovigilance (Table 2.1 and Section 2.7.1.1). The term adverse effect is universally preferred (Edwards & Aronson, 2000:1255). Adverse drug reaction also refers to adverse effect, but these two terms are different from an adverse event. Preventable events include medication errors, known side-effects of a drug, product quality problems and the inappropriate use of drugs (Section 2.1.1 and Figure 2.1).

4.1.4 Identification of the prevalence of ADRs globally and in South Africa

It is evident that ADRs can be fatal or they may result in increased hospital admissions, extended hospital stays and increased and unexpected healthcare costs for health providers and patients in the UK, USA, France, Spain, Germany and South Africa (Bouvy *et al.*, 2015:448; Budnitz *et al.*, 2007:755; Davies *et al.*, 2009; Leendertse *et al.*, 2011:37; Metha *et al.*, 2008:369; Rottenkolber *et al.*, 2012:870; Pirmohamed *et al.*, 2004; Singh & Bhatt, 2012) (Section 2.9.1). In South Africa, the most prevalent ADRs are related to drugs used in tuberculosis and HIV/AIDS treatment, thus supporting the development of the ART ADR report form (Berhe *et al.*, 2015:797; Fyzoo, 2014:13; Masenyetse *et al.*, 2015:3-5) (Section 2.9.1 and Section 2.8.1). This objective concluded that the scope of pharmacovigilance should be applied to prevent ADRs and reduce their consequences (Section 2.9.1).

4.1.5 Identification of possible challenges for the successful implementation of pharmacovigilance, specifically in the public health sector of South Africa

This objective established that the major concern with the spontaneous ADR reporting system was the general under-reporting rate of ADRs and the quality of the ADR report forms (Section 2.1 and Section 2.9.2). The effect of healthcare professionals' knowledge concerning pharmacovigilance, their attitude towards pharmacovigilance and their experience and practice relating to pharmacovigilance were identified as challenges in pharmacovigilance practices globally (Section 2.9.2). In addition to these factors, the South African pharmacovigilance system is also influenced by the inadequate infrastructure and resources in the public health sector. The NADEMC does not have basic funding to improve pharmacovigilance, the limited manpower at the centre does not have the capacity to analyse the data and no electronic system is available (Section 2.8.1).

4.2 Empirical investigation

4.2.1 Step 1: The perception of healthcare professionals of pharmacovigilance, with special reference to the Tlokwe Local Municipality

4.2.1.1 Evaluate current pharmacovigilance practices from the perception of healthcare professionals (general practitioners, hospital pharmacists and professional nurses) in the Tlokwe Local Municipality against national and international guidelines.

This study investigated healthcare professionals' awareness, experience and perception of pharmacovigilance in the Tlokwe Local Municipality (Manuscript 1)

The awareness of ADR reporting was based on the South African ADR reporting guidelines (MCC, 2004; MCC, 2014). This included the awareness of the type of ADRs and product quality problems that should be reported and the minimum requirements for reporting an ADR. Healthcare professionals were asked to indicate who was responsible for reporting an ADR and the possible steps that should be taken when an ADR occurs. The healthcare professionals' experience with pharmacovigilance investigated healthcare professionals' training history for reporting and identifying an ADR and their history of actual ADR reporting. Professional and personal factors that influence ADR reporting were also determined.

The overall awareness of ADR reporting was good, but it can be improved (Table 2 and Table 3 in Manuscript 1). The majority of healthcare professionals knew which ADRs to report, but the awareness of reporting a well-known ADR (70.8%) and an ADR caused by a medication error (73.3%) can be improved. The South Africa ADR reporting guidelines indicate that any product quality problem should be reported as a suspected ADR (MCC, 2012:9). Healthcare professionals should be aware that therapeutic failure is not a minimum requirement for reporting an ADR (27.3%) (Section 2.8.2.2). The responsibility for reporting an ADR appears to be clear to healthcare professionals, but it should be emphasised that patients in South Africa are required to consult a healthcare professional to report an ADR (MCC, 2004:2). The instructions regarding what should be reported and where to send the completed ADR report are on the MCC ADR report form, nonetheless the awareness that ADRs should be sent to the NADEMC was still low (11.1%).

Professional nurses did not receive adequate training to report (37.5%) or identify ADRs (31.5%), and this explains their low history of ADR reporting (43.8%). Medical practitioners received more training in identifying ADRs (52.2%) than in reporting ADRs (39.1%), while pharmacists received more training in reporting ADRs (75.0%) than in identifying ADRs (31.7%). The availability of SOPs for reporting an ADR (52.1%) and SOPs for completing an ADR report form (39.6%) should be increased and equal training opportunities should be provided to all healthcare professionals to enable them to identify and report ADRs.

Professional and personal factors that influence ADR reporting were identified in this study. Personal factors that influence ADR reporting indicated a positive attitude towards pharmacovigilance. The majority of healthcare professionals have enough confidence to report ADRs and only a few healthcare professionals fear legal liability when they report an ADR (12.2%) or fear that they might have caused the ADR due to a medication error (18.4%). Healthcare professionals understand that ADR reporting is an obligation (89.9%) and an essential part of healthcare practices (95.9%). According to the healthcare professionals, the ADR report forms are available and they have sufficient access to these forms. Professional factors that discourage ADR reporting include time to complete an ADR report form (56.3%), the

possibility of an increased workload (54.2%), the lack of feedback from the NADEMC (77.1%), and lack of reimbursement (71.4%). These problems can be resolved through the recommendations made in Section 4.2.4.

4.2.1.2 Determine, from the perception of healthcare professionals, possible factors that can contribute to the successful implementation of pharmacovigilance in the Tlokwe Local Municipality

Healthcare professionals' adequate awareness of ADR reporting and their positive attitude towards the pharmacovigilance system provide a stable foundation for improving ADR reporting in the Tlokwe Local Municipality. Healthcare professionals comprehend their responsibility to report ADRs. Healthcare professionals indicated that a pharmacovigilance specialist in each sub-district in the DKKD (89.8%) and mandatory ADR reporting (95.5%) can possibly improve ADR reporting in the future. The availability of ADR report forms and sufficient access to these forms can also be considered as factors that contribute to the success of pharmacovigilance. Even though the majority of healthcare professionals (85.4%) understood the instructions for completing an ADR report form; most healthcare professionals requested a less complicated ADR report form (95.5%). Although the medical practitioners, professional nurses and the pharmacists did not lack motivation to report an ADR, the majority would appreciate feedback from the NADEMC. These factors were indicated by the healthcare professionals as possible factors that could contribute to the successful implementation of pharmacovigilance in the Tlokwe Local Municipality.

4.2.2 Step 2: Evaluate the completeness of the content of the completed ADR forms, available in the DKKD.

4.2.2.1 Evaluate the completeness of the content of the completed ADR forms available in the DKKD and compare these forms with the minimum requirements for an ADR report form according to the WHO

A total of 1 454 MCC and 92 ART ADR report forms were available to evaluate the completeness of the content on the ADR report forms (Manuscript 2). The overall completeness of the six sections on the MCC ADR report form and the eight sections on the ART ADR report form were not satisfactory. None of these sections was fully completed on any of the available ADR report forms (Manuscript 2).

On the MCC ADR report form (Manuscript 2) the least completed section was the description of a product quality problem and the best completed section was the outcome of the ADR. On the ART ADR report forms the least completed section was the patient information and the best completed section was relevant clinical history clinical history (Manuscript 2).

The MCC and ART ADR report forms contains more information categories than required by the WHO (WHO, 2002c:16). The MCC and the ART reports adhere to these requirements, except for the following:

- The MCC ADR report form does not contain a clear category to describe the outcome after drug intervention.
- The expiry date on the MCC ADR report form is required only if a product quality problem is reported and is not included in the sections that describe all the medication/vaccines/devices used by the patient.
- The ART ADR report cannot be used to report a product quality problem and there is also no category to report the batch of the drugs that are used by the patient.
- The ART ADR report forms require the identification of the prescriber for each drug used by the patient, but do not indicate the reason for the use of the drugs.
- There is also no clear category on the MCC and ART report forms to indicate concomitant drugs used by the patient.

4.2.3 Make recommendations for the training of healthcare professionals and the improvement of the pharmacovigilance system in the DKKD with special reference to the Tlokwe Local Municipality

It is evident from the results in Manuscript 1 and Section 4.2.1 that healthcare professionals in the Tlokwe Local Municipality require training to improve the pharmacovigilance system. The incompleteness of the ADR report forms (Manuscript 2) in the DKKD supports the need to develop guidelines to improve the quality of ADR reports. The recommendations from the healthcare professionals should also be considered during the development of these guidelines (Manuscript 1 and Section 4.2.1). It is suggested that training in pharmacovigilance should be implemented quarterly and should include the following:

- Pre-training assessment on the information that will be presented in the training should be performed to determine participants' background knowledge on this specific information.
- Describe the factors that influence the effectiveness and safety of drugs (Section 2.2.1). Include the prevalence of ADRs in South Africa (Section 2.9.1) and the consequences of ADRs (Section 2.6) to increase healthcare professionals' awareness of the need for pharmacovigilance.

- Elaborate on the need for pharmacovigilance by including the aim and the benefits of pharmacovigilance to indicate how pharmacovigilance is applied to reduce or prevent ADRs and the relevant consequences (Section 2.6).
- Apply the pharmacovigilance framework (Section 2.7.2 and Figure 2.2) to give an overview of important individuals, functions and structures required for a successful pharmacovigilance system.
- Explain the responsibilities of all the stakeholders, including the people and the structures, in the pharmacovigilance system (Section 2.7.3). According to the results from Manuscript 1 the responsibilities of different healthcare professionals should be included. This highlights the inclusion of each healthcare professional in the pharmacovigilance system (Section 2.7.3) and also indicates the exclusion of patients.
- The evaluation of the MCC and ART ADR report forms (Manuscript 2) indicated that healthcare professionals may not understand the importance of all the information on the report forms. The training should include the fundamentals of the ADR report. The importance of all the information on the ADR report form should be explained to the healthcare professionals (Section 2.7.4) in an attempt to improve the quality of completed ADR report forms.
- Make use of Table 2.8 (Section 2.8.2) as a clear explanation of what to report, who can report, when to report, how to report and where to report ADRs according to the South African guidelines (Section 4.2.1).
- Include the terms used in pharmacovigilance (Table 2.1 and Section 2.7.1.1) to determine the type of event that occurred and the causality assessment criteria (Table 2.2 and Section 2.7.4) to recognise an ADR and to determine the degree of certainty that the ADR is related to the drugs used (Table 2.2 and Section 2.7.4) (Section 2.10).
- Each training session should include practical examples of different ADRs. These examples should also be included in the pre- and post-training assessments (Section 2.10).
- After the training sessions, a post-training assessment on the above-mentioned information should be compared to the pre-training assessment and can be used to determine if the training was successful (Section 2.10).

Other relevant recommendations include the following:

Each healthcare facility should provide a form of acknowledgement to healthcare professionals that report ADRs and this acknowledgement should be seen as an incentive gesture (Ramesh & Parthasarathi, 2009:12) (Section 2.10 and Section 4.2.2). Also improve the communication between all stakeholders in the pharmacovigilance system (Section 2.7.2 and Figure 2.2) (Section 2.10). Improve the awareness of ADRs in healthcare facilities by means of posters.

4.3 Limitations

The time available to conduct the study led to the involvement of a small target population in a small geographical area. More health districts should be included in the study to generalise the study results to other areas in the North West province and the rest of the South African public health sector. The low response rate in Step 1 could be due to the time healthcare professionals had available to complete the questionnaire or they decided not to participate in the study. The evaluation of the ADR report forms was restricted to a yes/no indication of the completion of the form. A more thorough evaluation that includes clinical information will provide an even stronger illustration of the quality of the ADR report forms.

4.4 Strengths

To the best of our knowledge this was the first study conducted in the Tlokwe Local Municipality in the DKKD to evaluate pharmacovigilance practices. This study was also at the request of the Head of Pharmaceutical Services in North West Province. The results of this study could contribute to the implementation of the decentralised pharmacovigilance system in the North-West Province (Section 2.8.1). The recommendations from the study can be used as a reference for future training in pharmacovigilance and future studies in other healthcare districts.

4.5 Recommendations for future studies

The research regarding pharmacovigilance in South Africa is limited. The following are recommended areas for future studies in pharmacovigilance:

- Implement a similar study in the public and/or the private health sector in other districts in North-West Province or the rest of South Africa.
- Evaluate the effectiveness of the decentralised pharmacovigilance system in South Africa (Section 2.8.1).
- Develop an adequate training tool from the recommendations of this study and determine the improvement in knowledge and perception of healthcare professionals before and after the training sessions.

- Evaluate the status of pharmacovigilance awareness in final-year under-graduate students in different healthcare professions.
- The basis of Step 2 of this study can be used to assess the clinical information on the ADR report forms.

4.6 Chapter Summary

This study succeeded in achieving the literature and empirical investigation objectives.

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ANNEXURE A: QUESTIONNAIRE

Questionnaire:

Evaluation of the perception of the health care professionals regarding the pharmacovigilance system in the Tlokwe Local Municipality in the North West Province

For office use only

Questionnaire number	
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LETTER OF INVITATION TO PARTICIPATE IN A RESEARCH QUESTIONNAIRE

Dear Colleague

The North-West University is appealing to you for participation in a *Magister Pharmaciae* research study:

Evaluation of the pharmacovigilance system in the Dr Kenneth Kaunda District

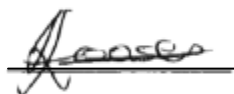
Adverse drug reaction reporting is an essential part of risk management in healthcare. Your perception, as healthcare professional, will provide insight into the current status of the adverse drug reporting system and it will require twenty minutes of your time to participate in this study.

Your insight will be of great value to generate future recommendations for pharmacovigilance in the Tlokwe Local Municipality.

Please note that your participation is voluntary and information from the questionnaire will remain confidential. Your opinion on the status of the pharmacovigilance system in the Tlokwe Local Municipality will not influence you in a negative way, because no personal information is asked in the questionnaire and you will not be identified.

Thank you in advance for your consideration of this initiative. We are looking forward to your participation in our study.

Yours sincerely



Lizané Goosen
M. Pharm student

Prof MS Lubbe
Study Supervisor

Evaluation of the perception of the health care professionals regarding the pharmacovigilance system in the Tlokwe Local Municipality in the North West Province

Section A: Demographic information

1. Gender:

Male	1
Female	2

2. Age (in years): _____

3. Indicate your specialised area (indicate more than one, if applicable):

Medicine		Nursing		Pharmacy	
General Medicine	1	Primary Care Nursing	11	Pharmacist	24
General Surgery	2	Midwifery	12	Clinical Pharmacist	25
Obstetrics and Gynaecology	3	Paediatric Nursing	13	Radio-pharmacist	26
Paediatrics	4	Medical-Surgical Nursing	14	Community service Pharmacist	27
Family Medicine	5	Community Health Nursing	15		
Mental Health	6	Psychiatric Nursing	16		
Orthopaedics	7	Emergency/Trauma Nursing	17		
Orthopaedic Trauma	8	Orthopaedic Nursing	18		
Primary Health Care	9	Ophthalmic Nursing	19		
Anaesthetics	10	Reproductive health and HIV/AIDS counselling services	20		
		Forensic Nursing	21		
		Critical Nurse specialist	22		
		Nephrology Nursing Specialist	23		
Other	28	Other	28	Other	28

Please specify other: _____

4. Current working environment :

(Indicate more than one if applicable).

Working environment	
Satellite clinic	1
Mobile clinic	2
Primary health clinic	3
Community day centre	4
Community health centre	5
Institutional pharmacy in a public hospital	6
Public hospital	7
Other	8

Please specify other: _____

5. Experience in practice:

(Indicate in years all categories applicable)

Department of practice	Number of years
Community pharmacy	
Institutional pharmacy in a public hospital	
Public hospital	
Mobile clinic	
Primary health clinic	
Community day centre	
Community health centre	
Satellite clinic	
Academia	
Medical aid environment	
Marketing	
Medicine control council	
Pharmaceutical development	
Administration	
Other	

Please specify other: _____

Section B: Adverse drug reaction system and structure

This section highlights the guidelines to report adverse drug reactions.

6. What type of adverse drug reaction should be reported (please answer all the questions):

	Types of adverse drug reactions	Yes	No
6.1	Suspected adverse drug reaction caused by a new drug	1	2
6.2	Any unfamiliar drug reaction not previously stated	1	2
6.3	A well-known adverse drug reaction	1	2
6.4	A reaction caused by an interaction between drugs (drug-drug interaction)	1	2
6.5	A reaction caused by a drug-disease interaction	1	2
6.7	A reaction caused by a drug-food interaction	1	2
6.8	Only serious adverse drug reactions	1	2
6.9	Any teratogenicity (birth defect)	1	2
6.10	Adverse drug reaction occurring due to medication error	1	2

7. Which product quality problem should be reported (*please answer all the questions*):

	A reaction caused by suspected:	Yes	No
7.1	Product contamination as a result of uncleanness in a product that may have occurred during the production, sampling, packaging or repackaging, storage or transport of the product.	1	2
7.2	Disputed product stability (Product stability refers to the extent to which a product preserves the same chemical and physical appearances at the time of its packaging, during the course of storage and use).	1	2
7.3	Defective components (Products containing elements that are harmful to a patient, which result in a defect, e.g. birth defect)	1	2
7.4	Poor packaging and labelling of products	1	2
7.5	Therapeutic failures (Products failing to accomplish the aim of the treatment due to inadequate or inappropriate drug therapy)	1	2

8. Healthcare professional responsible for reporting adverse drug reaction include (*please answer all the questions*):

	Healthcare professional	Yes	No
8.1	Medical practitioner	1	2
8.2	Pharmacist	1	2
8.3	Registered nurse	1	2
8.4	Dentist	1	2
8.5	Physiotherapist	1	2
8.6	Patient	1	2

9. Indicate the steps followed by healthcare professionals when an adverse drug reaction is detected:

(Please answer all the questions)

		Yes	No
9.1	Report adverse drug reaction on adverse drug reaction reporting form	1	2
9.2	Report adverse drug reaction on adverse drug reaction reporting form as well as in patient's file (or file a copy of it in the patient's file)	1	2
9.3	Report adverse drug reaction only in the patient's file.	1	2
9.4	Nothing	1	2
9.5	Change therapy	1	2
9.6	Determine the seriousness of the event	1	2
9.7	Ask patient to contact doctor	1	2
9.8	Healthcare professional should contact the physician	1	2

10. To whom will you send the completed ADR form?

11. Indicate the minimum information required from the healthcare professional on an official adverse drug reaction reporting form:

(Please answer all the questions)

		Yes	No
11.1	The name, address and qualification of reporter	1	2
11.2	Patient identified by surname, initials reference number or age and gender	1	2
11.3	The suspected product that caused the adverse drug reaction	1	2
11.4	The suspected adverse drug reaction observed	1	2
11.5	Therapeutic failures	1	2

12. Each hospital in the DKKD should send their completed adverse drug reactions forms to the National Pharmacovigilance Centre within:

(Choose only one)

10 days	1
15 days	2
20 days	3
30 days	4

13. The National Pharmacovigilance Centre in South Africa is located in:

(Choose only one)

Pretoria	1
Durban	2
Bloemfontein	3
Cape Town	4
Johannesburg	5

Section C: Healthcare professional's perception regarding adverse drug reaction reporting.

In this section, the health professional reflects his/her views on adverse drug reporting.

		Strongly disagree	Disagree	Uncertain	Agree	Strongly Agree
14.	The awareness of adverse drug reaction reporting, in health facilities, is effective.	1	2	3	4	5
15.	You are provided with sufficient access to adverse drug reaction reporting forms.	1	2	3	4	5
16.	You have received adequate training <u>to identify adverse drug reactions</u> (pharmacological knowledge.)	1	2	3	4	5
17.	You have received adequate training <u>to report an adverse drug reaction</u>	1	2	3	4	5
18.	Your current working environment provides the healthcare professionals with visible standard operating procedures to report adverse drug reactions.	1	2	3	4	5
19.	Your department receives general feedback on adverse drug reactions reported from the National Pharmacovigilance Centre.	1	2	3	4	5

The following statements generate possible improvements for adverse drug reaction reporting

		Strongly disagree	Disagree	Uncertain	Agree	Strongly Agree
20.	Adverse drug reaction reporting should be compulsory	1	2	3	4	5
21.	Enriched motivation from the National Pharmacovigilance Centre will increase the reporting of adverse drug reactions	1	2	3	4	5
22.	A less-complicated adverse drug reaction reporting form will increase adverse drug reaction reporting	1	2	3	4	5
23.	An electronic adverse drug reaction reporting system is needed for the success of this system	1	2	3	4	5
24.	A toll-free number to the National Pharmacovigilance Centre will increase adverse drug reaction reporting.	1	2	3	4	5
25.	Each sub-district (Tlokwe, Ventersdorp, Matlosana and Maquassi Hills) will benefit from a pharmacovigilance specialist working in this environment.	1	2	3	4	5

Section D: Adverse drug reaction reporting in practice

The following section focuses on the healthcare professional's experience regarding adverse drug reaction reporting

		Yes	No
26.	Have you ever reported an adverse drug reaction?	1	2
27.	Are there always enough adverse drug reaction reporting forms available?	1	2

Section E: Factors that may influence adverse drug reporting

The following factors may lead to discouragement in adverse drug reaction reporting.

	Discouraging Factor	Agree	Disagree
28.	You are not confident when to report an adverse drug reaction.	1	2
29.	You do not know where to find an adverse drug reaction reporting form.	1	2
30.	You do not receive feedback from the National Pharmacovigilance Centre.	1	2
31.	Reporting an adverse drug reaction is time consuming.	1	2
32.	Completing an adverse drug reaction report form increases your workload.	1	2
33.	Adverse drug reaction is not an essential part of your healthcare practice.	1	2
34.	All drugs on the market are safe to use.	1	2
35.	I fear the possibility of legal liability if I report an adverse drug reaction.	1	2
36.	I fear that the adverse drug reaction is caused by a medication error.	1	2
37.	I have a lack of motivation to report adverse drug reactions.	1	2
38.	There are no adverse drug reactions reporting forms available in my department.	1	2
39.	There are no guidelines available in the facility to assist healthcare professionals in reporting adverse drug reaction.	1	2
40.	Do you understand that the reporting of adverse drug reactions is an obligation?	1	2
41.	I do not receive incentives (e.g. financial or other recognitions) for the reporting of an adverse drug reaction.	1	2

Section F: Open questions

This section focuses on the possible challenges of adverse drug reactions

42. Are the instructions regarding the completion of an adverse drug reaction understandable?

Yes	1
No	2

43. If you indicated “No” in question 42, specify the area beyond your understanding.

44. Have you been provided with standard operating procedures to assist you with the completion of an adverse drug reaction report form?

Yes	1
No	2

45. If you choose “No” in question 44, which method do you prefer as visible standard operating procedures for adverse drug reaction reporting?

Guidelines for adverse drug reporting on a large poster	1
Guidelines provided on the front of each adverse drug reaction report form	2

46. Do you have any recommendations to improve the adverse drug reporting system in the Dr Kenneth Kaunda district?

Please enclose the completed questionnaire in the envelope provided.

Thank you for the time you offered to complete this questionnaire. Your participation is highly appreciated.

ANNEXURE B: INFORMED CONSENT FORM



PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM FOR HEALTH CARE WORKERS IN PRIMARY HEALTH CARE FACILITIES

TITLE OF THE RESEARCH PROJECT: Evaluation of the pharmacovigilance system in the Dr Kenneth District in the North-West Province

REFERENCE NUMBERS: NWU-00003-15-S1

PRINCIPAL INVESTIGATOR: Prof Martie S Lubbe

ADDRESS: North-West University

Faculty of Health Science

Potchefstroom

2522

CONTACT NUMBER: 018-2992288 (Work) 072-592-8288 (cell)

As part of the healthcare professional community in the Tlokwe Local Municipality, you are invited to participate in a research project. I kindly request you to read, thoroughly, through all the information provided regarding the scope of this project. It is important for the study, the researcher and you as participant, that you understand the purpose of the project. Please note that your participation is completely voluntary and you have the right to withdraw from the study at any time. No participant will be negatively influenced if they decide to exercise their rights.

This study has been approved by the **Health Research Ethics Committee of the Faculty of Health Sciences of the North-West University (NWU-00003-15-S1)** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki and the ethical guidelines of the National Health Research Ethics Council. It might be necessary for the research ethics committee members or relevant authorities to inspect the research records

What is the purpose of this study?

- The aim of this study is to evaluate the public health pharmacovigilance system in the Dr Kenneth Kaunda District (DKKD) in the North West Province, with specific reference to the Tlokwe Local Municipality.
- Pharmacovigilance refers to the reporting of adverse drug reactions, to induce the safe use of medicine and the improvement of therapeutic risk management.
- The successful implementation of the pharmacovigilance system will contribute to the improved healthcare of patients.
- The success of the pharmacovigilance system in the Tlokwe Local Municipality will be determined from the perceptions of healthcare professionals.
- The study will make use of a questionnaire that each participant must complete if informed consent is given for participation.

Why have I been chosen to participate in this study?

- Participants in the study must be a pharmacist, general practitioner or registered nurse, on a permanent or temporary contract, directly involved in the prescribing or dispensing of drugs and in the identification and confirmation of adverse drug reactions, in one of the public health institution in the Tlokwe Local Municipality.
- 15 pharmacists, 8 medical practitioners from PHC clinics, 35 medical practitioners from Potchefstroom District Hospital, 9 medical practitioners from Witrand Specialised Hospital and 53 nurses from PHC clinics are invited to participate in the study.

- You have been chosen to participate in this study as your career is an essential part of the public health sector and your insight into therapeutic risk management will be valuable.
- You will be excluded from the study should you fail to sign the informed consent.

What responsibilities will I have if I decide to participate?

- The only responsibility you as health professional will have during this study is to complete the questionnaire regarding your perceptions of the current pharmacovigilance system in the DKKD with special reference to the Tlokwe Local Municipality.
- It is requested that the questionnaire will be completed before.....(date)....
- The researcher will provide enough time to complete the questionnaire for your convenience.
- It is your right to withdraw from the study at any time. It is your responsibility to inform the researcher should you wish to withdraw from the study.

How will this study benefit me directly, if I participate?

- The questionnaire will provide all health care professionals with the opportunity to identify challenges that they experience with the report of ADRs.
- The identification of these challenges may result in the need for further training in the reporting of adverse drug reactions, which will benefit your future career and increase your knowledge.

What are the potential benefits for the community?

- The improvements of the pharmacovigilance system in the Tlokwe Local Municipality will benefit the national pharmacovigilance plan to improve patient care and contribute to treatment policy decision-making.
- Increased knowledge of healthcare professionals in the management of adverse drug reactions and other drug-related problems through pharmacovigilance will improve public health and safety in the use of medicine.
- The development of standard operating procedures from the results from the questionnaire will increase and improve the quality of ADR reporting in the Tlokwe Local Municipality, which can be applied to or used in the DKKD and other health districts in the North West Province.

What is the possible risk that I may experience if I participate?

- None of the questions are structured to hurt you emotionally or physiologically in any way.
- Participation is completely voluntary and you have the right to withdraw from the study at any time.
- No participant will be negatively influenced if they decide to exercise their rights to withdraw from the study.
- There are no personal questions included in the questionnaire.
- The questionnaire will demand 20 minutes from your schedule during the period that is provided to complete the form and this may lead you to find the study inconvenient.
- The level of risk of this study has been identified as a low risk.

What will happen in the unlikely event of some form of discomfort occurring as a direct result of taking part in this research study?

- If you feel that the questions asked hurt you emotionally or physiologically in a way, you are allowed to withdraw from the study or refuse to answer the questions with no fear of any consequences.

Who will have access to the data I am providing as participant?

- The study is being performed under ethical guidelines.
- All raw data is the property of the NWU.
- You are not required to provide your name on the questionnaire form to ensure your anonymity.
- All the records are confidential and your identity will not be revealed in the distribution of findings.
- The researcher and supervisor are the only people who will have access to your questionnaire.
- The data will be stored for five years, in a closed cabinet in the researcher's office and it will be uploaded onto a code sheet on the computer with a passport to ensure confidentiality.

- The Health Research Ethics Committee from NWU may need to request to inspect recorded data to ensure data quality and integrity.

Will I receive any compensation for participation in the research project?

- No incentives will be provided to participants

Is there any cost that I am responsible for should I decide to participate in this study?

- This study will not provide any economic burden to any of the participants.

What can I do if I have any enquires prior to the study?

- If you experience any problems or something is unclear to you regarding the study, you are welcome to contact Professor **MS Lubbe** at 018 299 2288/ martie.lubbe@nwu.ac.za
- You can contact the Health Research Ethics Committee via Mrs Carolien van Zyl at 018 299 2094 or carolien.vanzyl@nwu.ac.za if you have any concerns or complaints that have not been adequately addressed by the researcher.

How will these findings be made available to me?

- The researcher will provide feedback to the DKKD Health Director, PHC Tlokwe Local Municipality Manager, CEO/Clinical head/ Hospital manager of the hospitals and the Therapeutic and pharmaceutical committee of the NW Province.
- The pharmacist in charge at the hospitals and the PHC managers will provide you with the results and recommendations concluded from the study.

INFORMED CONSENT FORM

Declaration by participant

By signing below, I agree to take part in a research study entitled: **Assessment of the District Health Information System in Dr Kenneth Kaunda and Bojanala Platinum District in the North West**

I declare that:

- I have read this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions to both the person obtaining consent, as well as the researcher and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) on (*date*) 20....

.....

Signature of participant

.....

Signature of witness

Declaration by person obtaining consent

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter.

Signed at (*place*) on (*date*) 20....

.....

.....

Signature of person obtaining consent

Signature of witness

Declaration by researcher

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter.

Signed at (*place*) on (*date*) 20....

.....

.....

Signature of researcher

Signature of witness

ANNEXURE C: CRITERIA FOR EVALUATION OF QUESTIONNAIRE

Criteria for face and content validity of the questionnaire	Yes	No	Recommendations
The appearance of the questionnaire is up to standard for health care professionals			
The questionnaire has clear instructions regarding the completion of the form.			
The questionnaire can be completed between 20 and 30 minutes.			
The question sequence is in the correct order			
The questions result in confusion			
The wording of the questions is understandable and will ensure the correct response from participants			
The response categories is easy to understand and to complete			
The response categories will provide the researcher with sufficient data			

ANNEXURE D: MCC ADR REPORT FROM CHECKLIST



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

Checklist for the evaluation of the standard of completion of available ADR report

Criteria are based on the MCC-ADR report form provided by the Department of Health (Department of Health, 2012:389).

		Yes	No	N/A	Comments
Patient information					
1.1	Name/Initials / patient ref no	1	0		
1.2	Age	1	0		
1.3	Weight (kg)	1	0		
1.4	Height (cm)	1	0		
1.5	Sex	1	0		
1.6	Date of Birth	1	0		
Adverse drug reaction problem/ Product quality problem					
2.1	Adverse drug reaction	1	0	2	
2.2	Quality problem	1	0	2	
2.3	Date of onset of reaction	1	0		
2.4	Time of onset of reaction	1	0		
2.5	Description of reaction or problem (Include tests/lab data and dates)	1	0		
Medicines/vaccines/devices					
3.1	Trade name	1	0		
3.2	Batch no	1	0		
3.3	Asterisk: suspected product indicated	1	0		
3.4	Daily dosage	1	0		
3.5	Route	1	0		
3.6	Date started	1	0		
3.7	Date stopped	1	0		
3.8	Reasons for use	1	0		
Adverse reaction outcome					
4.1	Death	1	0	2	
4.2	Life-threatening	1	0	2	
4.3	Disability	1	0	2	
4.4	Hospitalisation	1	0	2	

4.5	Congenital anomaly	1	0	2	
4.6	Other	1	0	2	
4.7	Required intervention to prevent impairment/damage	1	0	2	
4.8	Event reappeared on re-challenge	1	0		
4.9	Treatment of reaction	1	0		
4.10	Recovered.	1	0		
4.11	Sequel	1	0		
4.12	Describe sequel	1	0		
4.13	Comments for history, allergies, previous exposure and baseline test results	1	0		
Product quality problem					
5.1	Trade name	1	0	2	
5.2	Batch number	1	0	2	
5.3	Registration number.	1	0	2	
5.4	Dosage form and strength	1	0	2	
5.5	Expiry date	1	0	2	
5.6	Size/ Type of container	1	0	2	
5.7	Product available for evaluation	1	0	2	
Reporting doctor/pharmacist/nurses					
6.1	Name	1	0		
6.2	Qualifications	1	0		
6.3	Address	1	0		
6.4	Signature	1	0		
6.5	Date	1	0		
6.6	Telephone number	1	0		

ANNEXURE E: MCC ADR REPORT FORM

ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM

(Identities of reporter and patient will remain strictly confidential)

Department
of Health
Logo Here

NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE

Medicines Control Council,
The Registrar of Medicines,
Department of Health

Tel : (021) 447-1518
Fax : (021) 448-6181

In collaboration with the WHO International Drug Monitoring Programme

PATIENT INFORMATION

Name (or initials): Age: Weight (kg) :
Sex: M F DOB :/...../..... Height (cm) :

ADVERSE REACTION/PRODUCT QUALITY PROBLEM

Adverse reaction¹ and/or Product Quality problem² Date of onset of reaction:/...../.....
Time of onset of reaction:h.....min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES/VACCINES/DEVICES (include all concomitant medicines)

Trade Name & Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

<input type="checkbox"/> death	<input type="checkbox"/> life-threatening	Event reappeared on rechallenge: <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> Rechallenge not done	Recovered: <input type="checkbox"/> Y <input type="checkbox"/> N
<input type="checkbox"/> disability	<input type="checkbox"/> hospitalisation		Sequelae: <input type="checkbox"/> Y <input type="checkbox"/> N
<input type="checkbox"/> congenital anomaly	Other:	Treatment (of reaction):	Describe Sequelae:
<input type="checkbox"/> required intervention to
<input type="checkbox"/> prevent permanent impairment/damage

COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

2. PRODUCT QUALITY PROBLEM:

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation?: Y N

REPORTING DOCTOR/PHARMACIST Etc:

NAME:

QUALIFICATIONS:

ADDRESS:

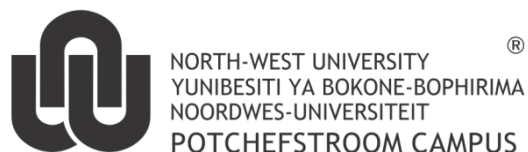
Signature

Date

TEL: (.....)

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ANNEXURE F: ART ADR REPORT FORM CHECKLIST




Checklist for the evaluation of the standard of completion of available ADR report

Criteria are based on the new ARV - ADR report form provided by four hospitals in the DKKD


		Yes	No	N/A	Comments
Patient information					
1.1	Name/Initials/ Patient ref n	1	0		
1.2	NHLS lab No	1	0		
1.3	Allergy	1	0		
1.4	Weight (kg)	1	0		
1.6	Gender	1	0		
1.7	Height (cm)	1	0		
1.8	Date of Birth	1	0		
1.9	Pregnant	1	0		
1.10	Age	1	0		
Medicines/vaccines/devices					
2.1	Medicine	1	0		
2.2	Suspected drug *	1	0		
2.3	Dose	1	0		
2.4	Interval	1	0		
2.5	Route	1	0		
2.6	Date started	1	0		
2.7	Date stopped	1	0		
2.8	Prescriber	1	0		
Adverse reaction outcome					
3.1	Date of onset of reaction (DD/MM/YYYY)	1	0		
3.2	Description of reaction	1	0		
Laboratory results					
4.1	Baseline	1	0		
4.2	Current	1	0		

	Adverse drug reaction outcome			
5.1	Intervention required:	1	0	
5.2	Action taken	1	0	
5.3	Patient outcome	1	0	
	Relevant clinical history			
6.1	Date patient initiated ARVs	1	0	
6.2	Initial regimen	1	0	
6.3	How long has patient been diagnosed with HIV?	1	0	
6.4	How long has been patient been on ARV treatment?	1	0	
6.5	Concomitant medical conditions	1	0	2
	Early warnings for drug resistance			
7.1	Patient ARV pick-ups for 3 months (dates)	1	0	
7.2	Interval for scheduled consultations	1	0	
7.3	Most recent consultation dates (last 3)	1	0	
	Reporting doctor/pharmacist/nurses			
8.1	Name	1	0	
8.2	Qualifications	1	0	
8.3	Facility	1	0	
8.4	Signature	1	0	
8.5	Date	1	0	
8.6	Telephone number	1	0	

ANNEXURE G: ART ADR REPORT FORM



HIV/AIDS AND TB TREATMENT PROGRAMME



DISTRICT: Dr. Kenneth Kaunda

CLUSTER FACILITY NAME: Patchetstroom Hospital/Boni Thlopi Clinic

MAIN TEL NO: _____ MAIN FAX NO: _____

(Please place original form in the patient records and send duplicate to NDOH)

PATIENT DETAILS

Name	<u>C. vd Merve</u>	Patient Ref No	File nr	DOB	
NHLS Lab No		Gender	<u>M/F</u>	Pregnant	<u>Important!!</u>
Allergy		Weight (kg)		Age	
		Height (cm)			

MEDICINES (AND CONCOMITANT MEDICINES, INCLUDING HERBAL PRODUCTS, IF KNOWN)

Medicine	Suspect drug (?)	Dose	Interval	Route	Date started	Date stopped	Prescriber
<u>Write All the drugs the patient is taking!!</u>							
<u>ARV, TB, Blood pressure, cholesterol etc.</u>							

ADVERSE DRUG REACTION

Date of onset of reaction (dd/mm/yyyy) _____

Description of reaction or problem (tick all that apply) – Attach additional information as required

<input type="checkbox"/> Pain/tingling/numbness in extremities	<input type="checkbox"/> Psychosis/hallucinations	<input type="checkbox"/> Unusual bruising	<input type="checkbox"/> Enlarged breast(s)
<input type="checkbox"/> Back pain	<input type="checkbox"/> Fat gain	<input type="checkbox"/> Unusual bleeding	<input type="checkbox"/> Depression
<input type="checkbox"/> Persistent muscle pain	<input type="checkbox"/> Fat loss	<input type="checkbox"/> Rash	<input type="checkbox"/> Heartburn
<input type="checkbox"/> Abdominal pain	<input type="checkbox"/> Fat redistribution	<input type="checkbox"/> Dizziness	<input type="checkbox"/> Headache
<input type="checkbox"/> Impaired concentration	<input type="checkbox"/> Weight loss	<input type="checkbox"/> Problems with breathing	<input type="checkbox"/> Anxiety
<input type="checkbox"/> Unusual fatigue	<input type="checkbox"/> Constipation	<input type="checkbox"/> Nausea	<input type="checkbox"/> Confusion
<input type="checkbox"/> Insomnia/sleep issues	<input type="checkbox"/> Loss of appetite	<input type="checkbox"/> Vomiting	<input type="checkbox"/> Other } <u>Virological Failure!!</u>
<input type="checkbox"/> Hearing loss	<input type="checkbox"/> Fever	<input type="checkbox"/> Diarrhoea	<input type="checkbox"/> Other
<input type="checkbox"/> Ringing in the ears	<input type="checkbox"/> Chills	<input type="checkbox"/> Vision changes	<input type="checkbox"/> Other

LABORATORY RESULTS. SELECT ABNORMAL ONE(S) AND WRITE THE VALUES (BL=BASELINE; CURR=CURRENT)

	Hb	ALT	Neutro	Chol	LACT	K+	Serum Cr	CD4	Viral Ld	Other
BL <u>Baseline</u>										
CURR <u>Current</u>										

ADVERSE REACTION OUTCOME

Intervention Required: Patient counseled Referred to expert

Additional clinic visit Additional lab request Hospitalization Other

Action Taken: Discontinued suspect drug Decreased dose Treated ADR (Name + Dose) Other

Patient Outcome: Write name of drug you used to treat the ADR!!

RELEVANT CLINICAL HISTORY (ATTACH ADDITIONAL INFORMATION)

Date patient initiated ARVs (dd/mm/yyyy) _____ Initial regimen _____

How long has patient been diagnosed with HIV _____ Years _____ Months

How long has patient been on ARV treatment _____ Years _____ Months

Concomitant medical condition(s) (tick all that apply): What medical condition patient has now!

Hypertension Diabetes Kaposi Sarcoma Tuberculosis Other

ADDITIONAL INFORMATION

EARLY WARNINGS FOR DRUG RESISTANCE

In the past 3 months, what are the dates for patient's ARV pick-ups (last 3 dates)? _____

How often is patient scheduled for consultation? Monthly Once every 3 months Other

Please provide the most recent dates (last 3 dates) for patient's clinical consultation _____

REPORTING DOCTOR/PHARMACIST/NURSE

Name	Qualifications	
Facility	E-mail	
Tel	Signature	Date

NB! NB! NB!

ANNEXURE H: ETHICAL LETTER OF APPROVAL HREC



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

Private Bag X6001, Potchefstroom
South Africa 2520

Tel: 018 299-1111/2222
Web: <http://www.nwu.ac.za>

Faculty of Health Sciences
Tel: 018-299 2092
Fax: 018-299 2088
Email: Minrie.Greeff@nwu.ac.za

25 April 2015

Prof MS Lubbe
MUSA

Dear Prof Lubbe

APPROVAL:

**ETHICS APPLICATION: NWU-00003-15-S1 (MS LUBBE-L GOOSEN)
"EVALUATION OF THE PHARMACOVIGILANCE SYSTEM IN THE DR
KENNETH KAUNDA DISTRICT IN THE NORTH WEST PROVINCE"**

Thank you for amending your application. All ethical concerns have now been addressed and ethical approval is granted until 01/02/2018.



Please note that any changes to the approved application must be submitted to the Health Research Ethics Committee for approval before implementation.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Minrie Greeff'.

Prof Minrie Greeff
HREC Chairperson

ANNEXURE I: ETHICAL LETTER OF APPROVAL FROM PPRM&E

	health Department of Health North West Province REPUBLIC OF SOUTH AFRICA	3801 First Street New Office Park MAHIKENG, 2735	Enq: Keitumetse Shogwe Tel: 018 391 4504 kshogwe@nwpp.gov.za www.nwhealth.gov.za	
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POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

Name of researcher : L Goosen
North West University

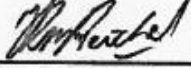
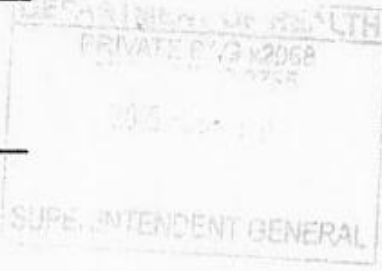
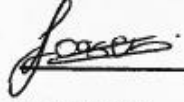
Physical Address (Work/ Institution) Hoffman street 11
Potchefstroom
2531


Subject : **Research Approval Letter- Evaluation of the pharmacovigilance system in the Dr Kenneth Kaunda District in the North West Province.**

This letter serves to inform the Researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities, and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards

 _____ Dr. FRM Reichel Director: PPRM&E		<u>19/06/2015</u> Date
 _____ Researcher		<u>19/06/2015</u> Date


Healthy Living for All

1

ANNEXURE J: AGENDA



Agenda for presentation of pharmacovigilance study in the Dr Kenneth Kaunda District

Date/Time: _____

Location: _____

1. Opening and Introduction:

1.1 Introduction of the research team

2. Study announcement:

2.1 A brief background regarding pharmacovigilance.

2.2 The purpose of the study.

2.3 Study population.

2.4 Participant responsibilities.

2.5 Potential risk of the study.

2.6 Potential benefits of the study.

2.7 Publication of results and access to data.

2.8 Compensation for participation

2.9 Contact information

3. Data collection information

3.1 Informed consent

3.2 Questionnaire distribution

3.3 Collection of questionnaire

4. Ethical considerations

5. Questions

6. Adjourn

ANNEXURE K: ABSTRACT FOR POSTER PRESENTATION AT 4TH INTERNATIONAL CONFERENCE AND EXHIBITION ON PHARMACOVIGILANCE AND CLINICAL TRIALS

Research methodology used to evaluate the pharmacovigilance system in the Dr Kenneth Kaunda district in the North West Province, South Africa

Lizane Goossens BPharm, Martie S Lubbe* PhD, Dorcas Rakumakoe PharmD, Elzabé Bekker BPharm, Ronel van Reenen BPharm, Madeeha Malik PhD. Medicines Usage in South Africa (MUSA), School of Pharmacy, North-West University, Potchefstroom, 2520, South Africa

*Corresponding author: Martie.Lubbe@nwu.ac.za, Tel #: +27 18 299 2288

Abstract:

One of the main reasons for the failure of pharmacovigilance systems is under-reporting, and this has a direct effect on the universal pharmacovigilance system. Professional and personal barriers were identified as a cause for under-reporting of adverse effects. The question arises as to whether these barriers can be drawn to South Africa or if there are other factors that influence the standard of reporting of adverse drug reactions (ADR) in South Africa. The aim is to describe the methodology that will be followed to evaluate the public health pharmacovigilance system in the Dr Kenneth Kaunda District (DKKD) in the North West Province in South Africa. Two steps will be followed: i) Determination from the perception of health care professionals the possible factors that can contribute to the successful implementation of a pharmacovigilance system; and ii) Evaluation of the completeness of the content of the filled-in ADR forms available in the DKKD. A quantitative, non-experimental, cross-sectional research design will be followed to conduct the study in the DKKD in the North West Province in South Africa. The study population for step 1 will include all healthcare professionals (medical practitioners, pharmacists, professional nurses) in the Tlokwe Local Municipality, in the public health sector (hospitals and primary health care clinics) on a permanent or temporary contract. All the completed ADR forms independent of pharmacological category or drug use, from 2010 to 2014 available at the hospitals and primary health care clinics in DKKD will be used as study population for step 2. A self-completion questionnaire will be used to determine the perception of healthcare professionals in Step 1. The focus of the questionnaire will be on the following aspects: i) Demographic information, ii) Adverse drug reaction system and structure, iii) Healthcare professionals' perceptions regarding adverse drug reaction reporting; iv) Adverse drug reaction reporting in practice; v) Factors that may influence adverse drug reporting; v) Challenges of adverse drug reaction reporting. A checklist, based on the standard set by the

South African Department of Health for an ADR report, will be used by the researcher to evaluate the completeness of the ADR reports in the DKKD. The study will help to identify current problems with the ADR documentation system on district level in South Africa.

ANNEXURE L: ABSRTACT FOR PRESENTATION AT ACADEMY OF PHARAMCEUTCAL SCIENCES CONFERENCE

Evaluation of the pharmacovigilance system in the Dr Kenneth Kaunda District in the North West Province, South Africa

Lizané Goosen¹, Martie S Lubbe¹, Elzabé Bekker¹, Dorcas Rakumakoe ¹, Madeeha Malik ¹, Marike Cockeran¹

¹Medicine Usage in South Africa (MUSA), School of Pharmacy, Faculty of Health Sciences, North-West University, Potchefstroom, 2520, South Africa

Purpose: Adverse drug reactions (ADRs) contribute to approximately 6.5% of all hospital admissions and may result in increased patient distress, mortality and morbidity. Pharmacovigilance is the only system that has been developed to identify and reduce the risk of ADRs and improve drug safety after it has been released in the market. This study evaluated the pharmacovigilance system in the public health system in the Dr Kenneth Kaunda District (DKKD) in the North West Province in South Africa.

Methods: Two standardised evaluation forms were specifically developed to evaluate the completeness of the available ADR reporting forms, independent of pharmacological category or drug use, from 2010 until 2014 in the DKKD. Two types of ADR reporting forms were available: Medicine Control Council (MCC) ADR report forms and the antiretroviral therapy (ART) ADR report forms

Results: A total of 1 454 MCC ADR report forms and 92 ART ADR report forms were available for step 2 and these forms were compared with standards required by the World Health Organization (WHO)¹. On the MCC ADR report, the adverse drug reaction outcome section indicates that all categories in this section were completed on 58% (n=842) of the ADR report forms; however, the section to describe the medicine/device/vaccine used in the patient was completed on 2% (n=30) MCC ADR report forms. All categories on patient information on the ART ADR report form were only completed on one (n=1) report.

Conclusions: Healthcare professionals in the public health sectors require training to improve the quality of completed ADR reports.

References

1. Bandekar, M.S. Anwikar, S.R., & Kshirsager, N.A. 2010. Quality check of spontaneous adverse drug reaction reporting forms of different countries. *Pharmacoepidemiology and drug safety*, 19(11):1181-1185.

ANNEXURE M: AUTHOR GUIDELINES FOR HEALTH POLICY AND PLANNING

Health Policy and Planning's aim is to improve the design and implementation of health systems and policies in low- and middle-income countries through providing a forum for publishing high quality research and original ideas, for an audience of policy and public health researchers and practitioners. HPP is published six times a year.

HPP has a double-blinded peer-review policy. All papers, in each of the categories described below, are peer reviewed.

Specific objectives are to:

- Attract high quality research papers, reviews and debates on topics relevant to health systems and policies in low- and middle-income countries;
- Ensure wide geographical coverage of papers including coverage of the poorest countries and those in transition;
- Encourage and support researchers from low- and middle-income countries to publish in *HPP*;
- Ensure papers reflect a broad range of disciplines, methodologies and topics;
- Ensure that papers are clearly explained and accessible to readers from the range of disciplines used to analyse health systems and policies; and
- Provide a fair, supportive and high quality peer review process.

Health Policy and Planning welcomes submissions of the following types: original articles, review papers, methodological musings, research in practice, commentaries, and papers in our series 'How to do (or not to do)...' [for example, see Hutton & Baltussen, *HPP*, 20(4): 252-9] and '10 best resources' [for example, see David & Haberlen, *HPP*, 20(4): 260-3].

Overall quality required for publication in an international journal, authors should address HPP's readership: national and international policy makers, practitioners, academics and general readers with a particular interest in health systems and policy issues and debates in low- and middle-income countries. Manuscripts that fail to set out the international debates to which the paper contributes, and to draw out policy lessons and conclusions, are more likely to be rejected or returned to the authors for redrafting prior to being reviewed. In addition, economists

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Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

- Book chapter

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