Implementation of interventions
to strengthen the pharmacovigilance surveillance system
at Dr George Mukhari Academic Hospital, Gauteng Province

A mini-dissertation submitted by

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Sefako Makgatho Health Sciences University

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Dr M Matlala and Prof RS Summers

2017
DECLARATION

I declare that the mini-dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Pharmacy, School of Pharmacy has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

_________________________________________  ______________________
Nkonde, K (Ms)                                      Date
DEDICATION

This dissertation is dedicated to my loving parents Edmond and Clotilde, for putting me through the best education possible and encouraging me to pursue this degree. I hope this makes you proud. To my beautiful siblings, thank you for supporting me through the overwhelming parts and keeping me level-headed most times. To my many colleagues who endured my numerous rants and near-breakdowns, eternal gratitude for your understanding and giving me the strength to keep pushing. To my beloved friends, I would not have got through this Master’s programme without your encouragement and unwavering love. Finally and without hesitation, to God. May He smile upon us always.

“Sure t’was something different . . . .”
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<th>Description</th>
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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>CEO</td>
<td>Chief Executive Officer</td>
</tr>
<tr>
<td>DGMAH</td>
<td>Dr George Mukhari Academic Hospital</td>
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<tr>
<td>HCP</td>
<td>Health Care Professional</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>MAC</td>
<td>Medical Advisory Committee</td>
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<td>MCC</td>
<td>Medicines Control Council</td>
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<td>NADEMC</td>
<td>National Adverse Drug Event Monitoring Centre</td>
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<td>NCS</td>
<td>National Core Standards</td>
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<td>NDoH</td>
<td>National Department of Health</td>
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<td>NHI</td>
<td>National Health Insurance</td>
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<td>NPC</td>
<td>National Pharmacovigilance Centre</td>
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<tr>
<td>NSAIDs</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>PQP</td>
<td>Product Quality Problem</td>
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<tr>
<td>PTC</td>
<td>Pharmacy and Therapeutics Committee</td>
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<tr>
<td>PMS</td>
<td>Post Marketing Surveillance</td>
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<td>PV</td>
<td>Pharmacovigilance</td>
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<tr>
<td>SA</td>
<td>South Africa</td>
</tr>
<tr>
<td>SMUREC</td>
<td>Sefako Makgatho Health Sciences University Research and Ethics Committee</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>UMC</td>
<td>Uppsala Monitoring Centre</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WIM</td>
<td>Ward Inventory Management</td>
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ABSTRACT

Introduction: Under-reporting of adverse drug reactions (ADRs) by health care professionals is a critical, world-wide problem in healthcare, particularly in developing countries. Spontaneous reporting is low and several obstacles to such reporting have been reported in the literature, including knowledge and attitudes of health care professionals. In South Africa, evidence of a clear pharmacovigilance system to monitor and manage ADRs is a requirement for compliance with the National Core Standards.

Previous research illustrated that ADR reporting can be increased by using a combination of various interventions such as training and giving feedback to health care professionals. In South Africa, attempts have been made by a number of hospitals to improve ADR reporting. In one particular study, the interventions had a significant effect on health care professionals’ overall perceptions regarding ADR reporting and the number of ADR reports submitted. A survey conducted in 2015 at Dr George Mukhari Academic Hospital showed that the majority of health care professionals encountered patients with ADRs in the past, however, only 25% had reported an ADR previously. The majority had little knowledge about ADRs and a negative attitude towards ADR reporting. The aim of this study was therefore to implement interventions to strengthen the pharmacovigilance surveillance system for ADR reporting at Dr George Mukhari Academic Hospital.

Objectives: To determine the rate of ADR reporting and assess the quality of completed ADR reports by HCPs at Dr George Mukhari Academic Hospital for a 9-month period prior to and since the implementation of interventions. To implement interventions and provide supportive training for health care professionals at DGMAH. To evaluate the implementation of the interventions by comparing the ADR reporting rate and the quality of completed ADR reports pre- and post-intervention phases.

Method: A two-phased, operational, intervention study with a pre-post samples design was conducted at Dr George Mukhari Academic Hospital, Gauteng Province, between January 2017 and October 2017, to implement interventions to strengthen the pharmacovigilance surveillance system for ADR reporting. Phase 1 consisted of a retrospective review of ADR reporting records to determine the number and quality of completed reports submitted over a period of nine months. Phase 2 involved two parts. Part 1 consisted of a number of interventions aimed at improving ADR reporting by health care professionals at Dr George Mukhari Academic Hospital over a period of nine months. These interventions included formal supportive trainings in the different departments using a PowerPoint® presentation, informal
The completeness of the different categories was good (75% of categories were more than 50% complete) and the ADR/product quality problem and reporter details sections were completed well (64.2% and 85.7% respectively) according to the World Health Organisation requirements in the post-intervention phase. Adverse drug reaction or product quality problem selected, description of reaction / problem, report date, name, address, qualifications and signature were 100% completed post-intervention. The category on the re-challenge of the
suspect medicine was the least completed in the ADRs submitted before and after the intervention. Of the five reports analysed for the pre-intervention phase, one ADR reported was a product quality problem. Four of the 14 ADRs submitted were recorded as being a product quality problem post-intervention. The section on reporter details was more complete in both phases.

**Conclusion:** Although ADR-reporting did not increase significantly, post-intervention results showed the benefit of implementing interventions to strengthening the pharmacovigilance system. Further training is needed for health care professionals on causality assessments and detection of ADRs as this will lead to improved quality and completeness of the various sections of the reporting form. Ultimately, effective pharmacovigilance will enable better understanding of the trends of medicine use and enable health care professionals to make wise therapeutic decisions on the use of a medicine.

**Recommendations:** Training interventions used in this study should be made a continuous process and conducted over a longer period of time for better knowledge retention. Pharmacovigilance activities should be reinforced by the pharmacovigilance subcommittee of the Pharmacy and Therapeutics Committee with enforced quarterly reports. Dedicated staff members in each department/unit should be working together with the pharmacy and the Pharmacy and Therapeutics Committee to help facilitate and raise awareness about ADR reporting in the hospital. Standard Operating Procedures for ADR reporting at Dr George Mukhari Academic Hospital should be introduced to ensure correct procedures for reporting are followed. Pharmacovigilance training should be incorporated into health care professionals undergraduate programmes to better equip them with pharmacovigilance knowledge at an early stage. A qualitative study involving focus group discussions and in-depth face-to-face interviews with key pharmacovigilance stakeholders to ascertain their knowledge about ADR reporting, attitudes towards the implemented interventions, and suggestions to improve future ADR reporting at Dr George Mukhari Academic Hospital will be conducted as a follow-up to this study.
Chapter 1: Introduction

CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

This chapter provides the background to and rationale for the study. The research question is provided, followed by the aim and objectives of the study. The importance of conducting this study is explained. The chapter ends with the outline of the dissertation.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Pharmacovigilance (PV) is an umbrella term that covers more than just conventional drug therapy. Over the last decade, its concerns have been widened to include herbal, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines (Mkele et al., 2010). Pharmacovigilance involves detection of adverse drug reactions (ADRs) during clinical trials and post-marketing surveillance (WHO, 2002). However, the relatively short duration of clinical trials makes it difficult to detect ADRs with a long latency (Harmark & Van Grootheest, 2008). Therefore, in order to study ADRs, including rare ones as well as those in specific populations, careful monitoring of the drug in the post-marketing phase is essential (WHO, 2002).

Adverse drug reactions impact significantly on public health, they reduce the quality of life for patients and impose a considerable financial burden on health care systems (Molokhia, Tanna & Bell, 2009). Recent estimates suggest that ADRs are the fourth major cause of death in the United States (US) (Mehta et al., 2013; Gupta & Udupa, 2011). These estimates and discoveries are the reason for ADR reporting and PV as a whole.

The effectiveness of PV greatly depends on the number of reports submitted and due to the spontaneous nature of ADR reporting, this method has several limitations, the most notable being under-reporting (Biagi et al., 2013). A number of factors are believed to contribute to under-reporting among health care professionals (HCPs), which is deemed a serious drawback of PV systems (Biagi et al., 2013). Gupta and Udupa (2011) determined that the knowledge of resident doctors at two teaching hospitals in India regarding their responsibility to report, type of event to report, product to be reported and the manner in which to go about reporting ADRs was deficient. This reiterates that there are concerns at the considerable extent of under-reporting of ADRs in hospitals across the world and locally (Lopez-Gonzalez, Herdeiro & Figueiras, 2009)
In South Africa (SA), the National Adverse Drug Event Monitoring Centre (NADEMC) is responsible for the receipt of ADR reports from all over the country and the subsequent follow-up of the submitted reports. Hughes, Whittlesea and Luscombe (2002) determined that the number of reports received in South Africa by NADEMC was a few hundred each year. Furthermore, the World Health Organisation (WHO) Uppsala Monitoring Centre (UMC) advised that the ADR reporting rate for South Africa in 2010 was 58 per million population (2 902 ADR reports) compared to 77 per million population (4 088 ADR reports) in 2011. The population was approximately 50.1 million and 51.8 million in 2010 and 2011 respectively (Maigetter et al., 2015).

South Africa has endeavoured to improve ADR reporting through various means (Meyer et al., 2017). Adverse drug reactions also form part of the safety aspects of the National Core Standards (NCS), which require that all health facilities in South Africa will have to comply with the NCS in future. One aspect of these requirements is to identify and manage adverse events promptly to minimise patient harm and suffering (NDoH, 2013). In such an instance, an active PV system was implemented in two medical wards at Ermelo Provincial Hospital through pharmaceutical care provided by a pharmacist (Ally et al., 2015). The ADR reporting rate (number of reports/number of beds) increased from 0.5% for the 12-week period prior to the operational study to 51.1% during the implementation phase. In July 2013, the National Health Act (Act No. 61 of 2003) was amended to launch an independent public entity, the “Office of Health Standards Compliance”, a regulatory authority put in place to protect and promote the health and safety of patients by monitoring and enforcing compliance by health establishments (NDoH, 2013). There have also been attempts to improve ADR reporting in other hospitals in South Africa (Gauteng Province, 2017). In one study, the interventions had a significant effect on HCPs’ overall perceptions about ADR reporting and increased the ADR reports submitted from 6 to 69 over a period of 18 months (Terblanche et al., 2017b).

In a survey conducted in 2015 at Dr George Mukhari Academic Hospital (DGMAH) to assess the knowledge and attitudes of HCPs towards reporting ADRs, results showed that 88.1% of 84 doctors who participated in the study had encountered patients with ADRs, however only 25% had reported an ADR (Engler et al., 2016). The study further reported that the majority of HCPs had little knowledge of the ADR reporting process and had a negative attitude towards it. At a strategic planning meeting held at DGMAH in February 2016, policy makers identified PV and ADR reporting as one of the aspects that need to be focused on and improved upon. These matters warrant future efforts and endeavours at DGMAH to improve the ADR reporting rate and compliance with the NCS. The present
study used the results of these previous studies as a baseline and motivation to strengthen the PV system at DGMAH, with the implementation of interventions, mainly adapted from the work done by Terblanche and colleagues (2017b) at a district hospital in the Gauteng Province.

Lopez-Gonzalez, Herdeiro and Figueiras (2009) linked knowledge and attitudes of health professionals to ADR reporting as one of the factors for under-reporting. They also illustrated that by making use of various interventions such as training and giving feedback to HCPs, the reporting rate can be sharply increased. This study therefore aimed to strengthen the current PV surveillance system at DGMAH by making use of a number of interventions to improve ADR reporting. This was done through training interventions and various other methods that are known to increase ADR reporting, such as access to report forms in combination with verbal reminders and detailed drug-specific feedback to the reporting HCPs (Johansson et al., 2009).

1.3 RESEARCH QUESTION

What impact will interventions implemented to strengthen the PV surveillance system at DGMAH have on ADR reporting by health care professionals?

1.4 AIM OF THE STUDY

The aim of this study was to implement and evaluate interventions to strengthen the PV surveillance system for ADR reporting at DGMAH.

1.5 OBJECTIVES OF THE STUDY

The objectives of the study were as follows:

- To determine the rate of ADR reporting by HCPs at DGMAH for a 9-month period prior to the interventions

- To assess the quality of completed ADR reports submitted by HCPs at DGMAH for a 9-month period prior to the interventions

- To implement interventions and provide supportive training for HCPs at DGMAH over the study period of 9 months

- To determine the rate of ADR reporting by HCPs at DGMAH for a 9-month period since the implementation of the interventions
Chapter 1: Introduction

- To assess the quality of completed ADR reports submitted by HCPs at DGMAH for a 9-month period since the implementation of the interventions

- To evaluate the implementation of the interventions by comparing i) the ADR reporting rate and ii) the quality of completed ADR reports for the 9-month periods prior to and since the implementation of the interventions

1.6 IMPORTANCE OF THE STUDY

All health care providers (physicians, pharmacists, nurses, dentists and others) should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication (WHO, 2002). However, health care professionals are more likely to identify and report important ADRs if they have confidence in their ability to diagnose, manage and prevent such reactions (WHO, 2002).

The emphasis on adopting methods or interventions to improve PV practices indicates the importance of this study. Under-reporting of ADRs is not only problematic at DGMAH but nationally as well. A study conducted by Joubert and Naidoo (2016) highlighted that a large percentage of their respondents stated low satisfaction with the South African national PV programme.

The pharmacovigilance training of health care professionals which was aimed at providing information on PV principles and concepts as well as the ADR reporting system in South Africa and specifically at DGMAH was evaluated in this study. It aimed to raise awareness and encourage all HCPs to report suspected and unexpected ADRs experienced by patients. The results demonstrated the advantage of implementing interventions to strengthen a PV surveillance system in an academic hospital. The importance of continuous training is emphasised and an adaptation of this study could be used to improve ADR reporting in similar settings.

1.7 OUTLINE OF THE DISSERTATION

Chapter 1 gives an overview of the dissertation. It highlights the rationale for the study and explains its importance. The research question, aim and objectives were addressed.

Chapter 2 discusses the literature related to this study and outlines previous research conducted in this particular field of practice.
Chapter 1: Introduction

Chapter 3 presents the methods used in this study and describes important considerations for the study methodology.

Chapter 4 presents the results of the study which are also discussed in this chapter.

Chapter 5 provides the limitations of the study, recommendations and final conclusion.
CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

This chapter presents a review of literature related to the study. The first section outlines the history of PV. This is followed by a description of the purpose and importance of PV. A detailed discussion of spontaneous reporting of ADRs follows. Challenges in ADR and educational interventions for ADR reporting are discussed. The chapter is concluded with a discussion of the need for quality and completeness of ADR reports.

2.2 HISTORY OF PHARMACOVIGILANCE

Modern medicines have changed the manner in which diseases are managed and controlled globally. However, despite all their benefits, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable cause of illness, disability and even death (WHO, 2004).

The thalidomide disaster in the early sixties is one of the historical drug disasters that led to the systematic attention to ADRs. This tragedy resulted in congenital deformity in neonates born to mothers who used thalidomide to treat morning sickness during pregnancy. The thalidomide case became the modern starting point of a science focused on patient problems caused by the use of medicines (Mishra & Kumar, 2013).

Subsequently, in 1968, the WHO established the Programme for International Drug Monitoring located in Uppsala, Sweden. The Uppsala Monitoring Centre (UMC) has specific procedures for the systematic evaluation and collection of ADRs from various countries, including South Africa (WHO, 2002). An overview of how the various national reporting systems are functioning is regularly published by the UMC (Van Grootheest et al., 2004).

2.3 PURPOSE OF PHARMACOVIGILANCE

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems (WHO, 2002). It has become an integral part of any health system because studies conducted during the animal and clinical testing phase of medicines’ development are inadequate to predict the safety of a particular medicine (Mkele et al.,
2010). This situation is attributed to factors such as the limited number of individuals (100s – 1 000s) exposed to the medicine, more favourable conditions, e.g. in hospital, close surveillance and a narrow population (Montastruc et al., 2006). High risk individuals such as children, the elderly and pregnant women are excluded during clinical trials. Patients with co-morbidities and those subsequently using concomitant medicines are also excluded. These factors make it difficult to detect rare ADRs and those with long latency periods (Molokhia, Tanna & Bell, 2009). Through post-marketing surveillance, PV programmes can detect less common but sometimes very serious ADRs (Montastruc et al., 2006; Mkele et al., 2010).

Specific PV systems to monitor the potential manifestation of both expected and unexpected ADRs to pharmacotherapy are needed to improve the health of the population at large (Molokhia, Tanna & Bell, 2009). In South Africa, PV activities are coordinated by the Medicines Control Council (MCC) which is the national drug regulatory body responsible for ensuring the safety, efficacy and quality of registered medicines used by the South African public (Mkele et al., 2010). The safety of essential medicines in particular is paramount, as they are used by a large percentage of the population (Mehta, 2011). It therefore also becomes the responsibility of the MCC to monitor the performance of these medicines (Mehta, 2011). Doctors, pharmacists, nurses, other HCPs and the pharmaceutical industry are also required to send reports of their suspected ADRs to the NADEMC in Cape Town, which in turn collaborates with the WHO to compile a safety index for most medicines on the market. This process ensures that medicines used by the population have been properly vetted and patients know that the medicines they are consuming are relatively safe (Lopez-Gonzalez, Herdeiro & Figueiras, 2009).

2.4 IMPORTANCE OF PHARMACOVIGILANCE

Pharmacovigilance is important in medicines monitoring, pharmaceutical preparations, ADR reporting and post marketing product surveillance (Mehta, 2011). It is paramount because information on the possible adverse effects of new medicinal products collected during the development phase is usually incomplete on account of a limited number of subjects and the short duration of trials (Rehan, Chopra & Kakkar, 2009). Although pre-marketing investigation of a new medicinal product is carefully performed and critically assessed; it does not always reveal all possible side-effects or adverse reactions or events associated with the product (Zolezzi & Parsotam, 2005). This situation is due to the fact that during these studies, the medicinal products are usually tested only in a subcategory of the general population. Moreover, clinical studies are done in controlled environments for a
short period of time and often exclude certain groups of people like the elderly, children, pregnant women, immuno-compromised patients and patients with co-morbidities (Montastruc et al., 2006). As a result one cannot with confidence conclude that a product is safe for all populations after completion of a trial (Zolezzi & Parsotam, 2005).

According to Striker & Psaty (2004) the limitations of most clinical trials in highlighting a drug's safety are as follows:

- Homogeneous populations.
- Most trials assess relatively healthy patients with only one disease and mostly exclude specific groups such as pregnant women, children and elderly people.
- Sample size - Small sample size (up to 1,000 patients) reduces the chance of finding rare adverse effects.
- Limited duration - Trials of short duration preclude the discovery of long-term consequences such as cancer.
- Inability to predict the real world.
- Drug interactions can be substantial in a population as patients may take drugs concomitantly, a situation that can almost never be predicted from clinical trials.

Pharmacovigilance offers the possibility of gathering further information on the safety and effectiveness of medicines during the post-marketing phase (Montastruc et al., 2006). An observational study conducted in the medical wards of a secondary hospital in the Western Cape estimated that 6.3% of hospitalised patients were admitted as a direct result of an ADR, while a further 6.3% of patients developed a significant ADR while in hospital (Mehta, 2011). ADRs have become a major global public health problem that needs to be addressed at all levels of health care. A reduction in medicine-related problems would ultimately lead to reduced morbidity and mortality rates (Montastruc et al., 2006).

Thus, the introduction of new medicinal products into the market always carries the risks of adverse reactions associated with the product that were not detected during pre-marketing investigation (Zolezzi & Parsotam, 2005). The early identification of medicinal product problems may assist in that correctional measures can be taken before serious harm occurs to a large population. Therefore it is important to monitor and identify ADRs, not only those related to previously known or unknown pharmacological properties, but also those related
to product quality and medication errors (MEs) in prescribing, preparing, administering or taking of medicines. (USAID, 2009)

The aims of PV are to improve public health and safety in the use of medicines by the provision of reliable, balanced information which should result in their more rational use (WHO, 2002). The following are several factors which contribute to the importance and value of PV according to Dikshit (2010):

- The on-going introduction of new medicines.
- Shortcomings of preclinical testing and premarketing clinical trials.
- Simultaneous introduction of new medicines globally.
- The phenomenal growth of “clinical research” that exposes the unsuspecting population to the new or less well-known molecules.

Moreover, ADRs contribute to the overall costs of any health care programme and in some instances lead to hospitalisation and/or prolongation of hospital stay (Mehta et al., 2008). The cost of managing ADRs places a significant burden on health care funds, with some countries spending up to 15-20% of their hospital budget dealing with drug complications (Mehta et al., 2008). It is also important to note that most studies to date have largely concentrated on direct costs, and there are no reliable estimates of the social and indirect costs of ADRs, making it difficult to measure the overall economic burden to the patient and society (Lundkvist & Jonsson, 2004).

2.5 SPONTANEOUS REPORTING OF ADVERSE DRUG REACTIONS

A spontaneous report is an unsolicited communication to a company, regulatory authority or other organization that describes a suspected ADR in a patient given one or more medicines, and does not derive from a study (MCC, 2014). The Medicines and Related Substances Control Act (Act 101 of 1965), as amended, provides for the mandatory reporting of ADRs by the pharmaceutical manufacturing industry. However, this requirement is not the case with health care professionals who have been given leeway when reporting ADRs. Currently spontaneous reporting is the most common method for rapid and easy assembly of data for an effective PV system in any country, which largely hinges on voluntary reporting by HCPs (Kumar et al., 2016). Many serious ADRs occur in hospitals with ADRs accounting for a substantial proportion of hospital admissions (Van Grootheest & de Jong-van den Berg, 2005).
Chapter 2: Literature Review

A spontaneous reporting system has numerous benefits (cover large population, may generate rapid alerts, low set-up/costs) along with some limitations (under-reporting, incomplete data, and bias such as reporting of serious ADRs over non-serious ADRs) (see Table: 2.1).

Table 2.1: Advantages and disadvantages of spontaneous reporting

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<tbody>
<tr>
<td>Include large population, that is not specific to patient groups</td>
<td>Under-reporting</td>
</tr>
<tr>
<td>Include all hospital and out-patient care</td>
<td>Difficult to detect: delayed reactions, reactions with high background incidence.</td>
</tr>
<tr>
<td>May lead to generation of rapid alerts</td>
<td>Number of exposed unknown</td>
</tr>
<tr>
<td>Do not have much influence on prescribing behavior.</td>
<td>Bias such as reporting of serious ADRs over non-serious ADRs</td>
</tr>
<tr>
<td>Low set-up costs</td>
<td>Data collected are incomplete both in terms of quality and quantity</td>
</tr>
<tr>
<td>Provides safety surveillance throughout the marketed life of all medicines</td>
<td>Special studies will need to be set up to obtain accurate information on areas of particular interest such as pregnancy, children and specific events of concern.</td>
</tr>
</tbody>
</table>

Source: Adapted from Kumar et al. (2016)

Implementation of spontaneous reporting systems in resource-limited, developing countries (such as SA) is particularly challenging where other pressing health priorities and infrastructure problems, such as remote location, poor telecommunication services, and low numbers and level of education of health professionals, are commonplace (Sevène et al., 2008). Nevertheless, where spontaneous reporting of suspected ADRs relied traditionally on HCPs, over the years it has been strengthened by broadening the reporter base to include patients (Elakesh & Al-Shariff, 2014). If patients were knowledgeable about their medicines and how to report sub-standard medicines and ADRs, this would go a long way in improving the ADR reporting rate and also the safety, quality and efficacy of medicines (Sevène et al., 2008).

Under-reporting remains the biggest short-fall of spontaneous reporting. It is estimated that only 10% to 14% of ADRs are reported. This low rate of reporting can have a negative impact on public health (Chaplin, 2006). In Africa, PV was previously seen as a relatively new science (Ampadu et al., 2016; Meyer et al., 2017). However, PV being a novelty is not the case as a number of African countries are now part of WHO Programmes for Drug Monitoring, including South Africa (Ampadu et al., 2016). The formation of a national PV Working Group within the MCC of South Africa has facilitated PV activities and has become
dedicated to this (MCC, 2017). There have also been regional initiatives to further improve PV and the reporting of ADRs (Gauteng Province, 2017).

Despite these initiatives, most HCPs in public sector hospitals in South Africa seem unaware of ADR reporting systems, with very few of the professionals stating they had received training on ADR reporting and the majority indicating the need for such training (Terblanche et al., 2017a).

The effectiveness of a post-marketing surveillance programme is directly dependent on the active participation of health professionals (Saleh, Figueras & Fourrier-Réglat, 2016). Health professionals are in the best position to report suspected ADRs observed in their everyday patient care. All HCPs (doctors, pharmacists, nurses, dentists and others) should report ADRs as a part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication (WHO, 2002). Therefore, it is important to increase their awareness about PV to improve spontaneous reporting (Saleh, Figueras & Fourrier-Réglat, 2016).

2.6 CHALLENGES IN ADVERSE DRUG REACTION REPORTING

The WHO set minimum standards that each country can use to set up their PV surveillance systems (WHO, 2002). However, the manner in which countries organise, run and how they expect their HCPs to report ADRs differs. It is therefore essential for HCPs to fully understand how a country’s pharmacovigilance system functions for them to report ADRs adequately (Van Grootheest et al., 2004). When HCPs do not know that such a system exists and how the reporting system is organized, it has a detrimental effect on the number of ADRs that will be reported (John et al., 2012; Terblanche et al., 2017a). Elkalmi et al. (2011) found that HCPs need to be familiar with certain aspects of the PV surveillance system such as the ADR reporting form to report successfully. Lack of knowledge and familiarity of how the reporting process works can have a detrimental impact on reporting (Elkalmi et al., 2011).

Gaps in the PV reporting system could include the unavailability of, or no access to reporting forms, a lack of an address where to send the ADR reports and a lack of guidelines to ensure that continuous awareness is maintained (Elkalmi et al, 2011). In a study conducted in Nigeria, 88% of pharmacists claimed that they did not have access to ADR reporting forms and highlighted this as a vital reason for why they did not report (Oreagba, Ogunleye, & Olayemi, 2010).
Another barrier to spontaneous reporting is if HCPs perceive the reporting process or reporting form to be too complex resulting in a negative effect on their willingness to report ADRs (Elkalmi et al., 2011). An intricate form may be seen as needing more time to complete in an already challenging working environment where time is quite limited (Gupta & Udupa, 2011). If the reporting route is deemed to be complicated by HCPs, the straightforwardness of the ADR reporting form is of little significance (Elkalmi et al., 2011).

The effectiveness of spontaneous reporting systems is compromised by under-reporting, with serious repercussions on public health (Herdeiro et al., 2012). Many factors are associated with under-reporting of ADRs amongst HCPs, which have been broadly classified as personal and professional characteristics of health carers, and their knowledge and attitudes to reporting (Gupta & Udupa, 2011).

The ‘seven deadly sins’ of under-reporting were described by Inman (1996) as the following attitudes relating to professional activities (Gupta & Udupa, 2011):

- Financial incentives: rewards for reporting.
- Legal aspects: fear of litigation or enquiry into prescribing costs: and ambition to compile or publish a personal case series and problems associated with ADR-related knowledge and attitudes.
- Complacency: the belief that very serious ADRs are well documented by the time a drug is marketed.
- Diffidence: the belief that reporting an ADR would only be done if there was certainty that it was related to the use of a particular drug.
- Indifference: the belief that the single case an individual doctor might observe could not contribute to medical knowledge.
- Ignorance: the belief that it is only necessary to report serious or unexpected ADRs.
- Lethargy: the procrastination and disinterest in reporting or lack of time to find a report card and other factors.

Under-reporting has become a serious disadvantage of the spontaneous reporting system for several reasons, most of which were highlighted in different studies namely complacency, insecurity, diffidence, indifference, ignorance, and lack of time (Biagi et al., 2013; Gupta & Udupa, 2011). Similarly, in SA, numbers of reports of ADRs by HCPs are extremely low. One of the few studies conducted in SA on barriers to ADR reporting by
HCPs specified that most HCPs revealed a lack of understanding as to what should be reported, in combination with a lack of sufficient skills and knowledge to identify ADRs (Metha, 2011; Suleman, 2010).

In an interactive workshop on pharmacovigilance at the South African Association of Hospital and Institutional Pharmacists (SAAHIP) 2013 National Conference participants were allowed to determine for themselves whether PV is a vital tool for the pharmacist or a wasted effort (Summers, Dube & Meyer, 2013). It was found that few of the participants practice PV actively although the majority (n=90) rated PV as either important (39%) or very important (58%) in their everyday work (Summers, Dube & Meyer, 2013).

Time constraints and a heavy workload are continually stated as a major challenge to reporting ADRs across different categories of HCPs (Amin et al., 2016). In a resource-constrained environment where public hospitals are under-staffed, other matters such as clinical duties seem to have a higher priority than PV activities. In SA, work and time pressures experienced by HCPs have been stated as serious limiting factors in ADR reporting (Suleman, 2010). Ruud, Srinivas & Toverud (2010) found that a number of pharmacists complained of too much work and that the reporting of ADRs was seen as just additional paperwork piled onto a busy schedule of HCPs.

A lack of clinical knowledge and a lack of understanding of what should be reported were found to have a major impact on ADR reporting amongst health care workers (Suleman, 2010). Thus, HCPs could also fail to identify an ADR if they have little or no knowledge about signals and other trigger tools in particular cases (Ruud, Srinivas & Toverud, 2010).

The provision of pharmaceutical care through a pharmacist’s involvement in the management of hospital in-patients on ARV treatment was advantageous for the identification, management and reporting of ADRs (Ally et al., 2015). Furthermore, even if a suspected ADR is classified as serious or rare, this does not necessarily mean that it will be reported due to HCPs wanting to be sure the causality can be traced back to the suspect drug (Ruud, Srinivas & Toverud, 2010; Elkalmi et al., 2011).

Uncertainty about the legal consequences concerning ADR reporting could possibly have a negative effect on reporting rates (Zolezzi & Parsotam, 2005). Establishing a reporting culture where HCPs feel assured to report ADRs without facing any consequences is essential (Ashcroft, 2006).
Numerous studies (Ruud, Srinivas & Toverud, 2010; Zolezzi & Parsotam, 2005; Elkalmi et al., 2011) identified an important obstacle as lack of feedback provided to HCPs on ADRs. No or minimal feedback to reporters, including confirmation of reports received, discourages the continuous reporting of ADRs (Suleman, 2010; Elkalmi et al., 2011; Ruud et al., 2010). Individualized feedback should be given to HCPs who submit reports and general feedback should be provided based on reporting trends to all HCPs (Elkalmi et al., 2011). Lack of feedback and poor communication were found to be one of the major weaknesses in the current PV systems in a survey done at a national PV stakeholders workshop held in SA in 2012 (Mehta et al., 2013).

2.7 EDUCATIONAL INTERVENTIONS FOR ADR REPORTING

2.7.1 Presentations – Lectures or Meetings

The success of any PV system requires a coordinated multidisciplinary team approach where various HCPs, including pharmacists, play a significant role (Jose et al., 2014).

The use of face-to-face training was investigated in a study conducted in Germany, which reported an initial 148% increase (p=0.001) in the number of ADR reports submitted after the educational intervention. The completeness of ADR reports improved from 80.3% before to 90.7% after the intervention (Tabali et al., 2009). Other interventions reported in the literature include workshops and telephone interviews as means to improve ADR reporting in Portugal (Herdeiro et al., 2012). In a study done by Terblanche et al., (2017b) in a public sector hospital in South Africa, interventions such as supportive training, availability of ADR forms in wards and posters increased the ADR reporting rate significantly from 5 to 69 ADR reports during and after an intervention phase (over an 18-month period).

Continuous education is required to increase the clinical knowledge of HCPs to enable them to identify ADRs and have the confidence to report them (Molokhia, 2009). Pharmacists can play a key role when tasked to help coordinate the reporting process and compensate for any integral flaws and challenges in the PV surveillance system (Sevene et al., 2008). Evidently, the presentations and workshops conducted by a pharmacist at Sebokeng Hospital in South Africa contributed to HCPs gaining significantly in their knowledge about the ADR reporting system (medical practitioners (P<0.0001); pharmacists’ assistants (P=0.0233); nurses (P<0.0001) (Terblanche et al., 2017b).
2.7.2 Posters – Increased awareness

Adverse drug reaction reporting guidelines and information regarding ADRs in the form of booklets, pamphlets and posters were recommended to be easily accessible and placed in key locations throughout health care facilities (Fadare et al. 2011). Sabblah et al. (2014) also showed that educational interventions such as posters acting as visual reminders to report, ADRs and information placards improved awareness of knowledge, attitude, and practice of health-care professionals toward the practice of PV.

2.7.3 Availability of ADR forms – ease of access

According to the literature, lack of knowledge about ADRs, how to report them and who to report them to are usually the cause of under-reporting (Lopez-Gonzalez, Herdeiro & Figueiras, 2009; Gupta & Udupa, 2011). The reporting form used should be as simple as possible to facilitate a more convenient reporting process. The recommendation was made by Elkalmi et al. (2011) that ADR reporting forms should be readily available and always accessible i.e close to HCPs working stations such as consultation rooms and wards. There should be no confusion as to where and to whom the ADR reporting form should be sent to (Elkalmi et al., 2011). Providing a designated PV champion to facilitate the reporting of ADRs will greatly improve the reporting rate (Vinther et al., 2017).

2.7.4 Collection of ADR reports made

Gony et al., 2010 showed that regularly visits to HCPs working stations, improved visibility of an ADR reporting representative and collection of ADR reports made increased the total reporting rate (number of reports/number of beds) in the two case groups, from 3% to 25% and from 11% to 40%. Using periodic educational interventions and frequent collection of reported ADRs increased the proportion of spontaneous ADR reporting from 29.5% to 71.5% in a study conducted in Spain (Cereza et al., 2010).

2.7.5 Using Mobile Technology – EML Clinical Guide Application

Like other countries, SA relied solely on manual reporting using printed forms in the past. However, innovative technology is also being used to empower HCPs to provide quality services. The Standard Treatment Guidelines - Essential Medicines List (STGs-EML) are available as a mobile application, which also allows reporting of ADRs electronically (Meyer et al., 2017). Reports submitted on this application are received by the NDoH Pharmacovigilance Centre for Public Health Programmes and forwarded to the MCC. It is
hoped this innovation will also increase ADR reporting and minimize the bottleneck effect provincially (Gauteng Province, 2017; Meyer et al., 2017).

### 2.8 QUALITY AND COMPLETENESS OF ADR REPORTS

The ADR reporting form is an integral component and a major tool of the PV system of any country; it is used to collect information of ADRs which assists in establishing causality (Bandekar, Anwikar & Kshirsagar, 2010). Although the WHO sets guidelines for these forms, there are still differences among countries. Essentially these reporting forms should include at least four sections, with sufficient information such as patient risk factors that may contribute to signal detection (see Table 2.2) (MCC, 2014; Bandekar, Anwikar & Kshirsagar, 2010).

#### Table 2.2: Minimum requirements for ADR report form

| Patient Information | • Patient identifier  
|                     | • Date of birth/age  
|                     | • Gender  
|                     | • Weight  
| Adverse event or product problem | • Description of event  
|                     | • The date of event  
|                     | • The date of the report  
|                     | • Relevant test done or laboratory data  
|                     | • Patient history  
| Outcome of the event | • Suspected medicine(s)  
|                     | • Name of the medicine(s)  
|                     | • Dose, frequency and route used for all medicines used  
|                     | • Start date of therapy  
|                     | • The diagnosis for use of medicines  
|                     | • The outcome after use of medicine is stopped or dose is reduced  
|                     | • The batch number of medicines used  
|                     | • The expiration date of medicines used  
|                     | • Description if the event reappeared after re-challenge  
|                     | • Concomitant medical products and therapy dates  
| Reporter | • Name, address and telephone number of HCP  
|                     | • HCP occupation and speciality  

Source: Adapted from WHO, 2002

If relevant information regarding ADRs is not entered correctly then it is of no use to the regulatory authority as no conclusion can be drawn from those data (Bandekar, Anwikar & Kshirsagar, 2010). It is therefore important to educate HCPs about the correct manner of completing the forms as failure to do so can result in inappropriate causality assessment of ADRs (Tabali et al., 2009). The MCC has provided guidelines on the minimum information necessary in an ADR report for it to be valid. Moreover, the MCC urges all relevant
information available at the time of the notification be submitted in order to assess the suspected ADR thoroughly (MCC, 2014). A cluster-randomized control trial conducted in Portugal to test an educational intervention’s effect on physician reporting of ADRs, found an improvement in the quality of reports (Figueiras et al., 2006). To further increase access, reporting forms are now available on the EML clinical guide mobile application, which further ensures completeness as smart phones are more convenient than any paper-based system (Meyer et al., 2017).

### 2.9 SUMMARY

Adverse drug reactions are among the leading causes of morbidity and mortality in patients. The effectiveness of post-marketing surveillance is directly dependant on the active participation of HCPs. Previous researchers have reported extensively on the phenomenon of under-reporting of ADRs by various HCPs. However, minimal research has been conducted on using educational interventions to compliment hospital level PV surveillance systems, especially in South Africa. This chapter reviewed the history, purpose and importance of PV. Spontaneous reporting of ADRs and its challenges were discussed. The methods in which educational interventions could be used to improve ADR reporting were explored. The chapter was concluded with a section on the quality and completeness of ADR reports. The next chapter will focus on the methods used to implement this study.
3.1 INTRODUCTION

This chapter presents a detailed account of the methodology used in this study. In the first part of the chapter, the study design which is divided into two phases, the study site, setting (Dr George Mukhari Academic Hospital) and study population are described. Details of the study sample, and types of interventions are then discussed. The data collection process is described in great detail, along with the pilot study, data capture and analysis process. This is followed by an outline of reliability and validity, bias and ethical considerations affecting the study.

3.2 STUDY DESIGN

This was a two-phased, operational, intervention study including the review of ADR reports by DGMAH.

Phase 1 of the study consisted of a retrospective review of ADR report forms submitted prior to the intervention for a period of nine months to determine the number and quality of completed reports.

Phase 2 consisted of two parts. In Part 1 the researcher implemented a number of interventions aimed at improving ADR reporting by HCPs at DGMAH over a period of nine months. Part 2 took place at the same time as Part 1 and involved a monthly retrospective review of ADR reports submitted during the intervention phase to determine the number and quality of completed reports submitted by HCPs. The study process is illustrated in Table 3.1.
Table 3.1: Study process

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time period</strong></td>
<td>One month to review (ADR reports submitted during 9-month period prior to intervention)</td>
<td>Nine months</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>None</td>
<td>Start of, and ongoing interventions</td>
</tr>
<tr>
<td><strong>Specific activities</strong></td>
<td>Retrospective review of ADR reports to determine the number and quality of ADR reports submitted by HCPs for the 9 month period prior to the implementation of the intervention.</td>
<td>Implementation of ongoing interventions over the 9-month period. Examples: • Training sessions for HCPs on PV and ADR-reporting • Posters for the wards, consultation rooms and patient waiting areas • Feedback on ADR reporting to HCPs o Newsletters (printed and electronic) o Meetings e.g. PTC • Making ADR reporting forms and SOPs available in all wards, pharmacy, consultation rooms.</td>
</tr>
</tbody>
</table>

3.3 STUDY SITE AND SETTING

3.3.1 Study site

The study was conducted in the wards, main pharmacy, out-patient departments, satellite clinics and satellite pharmacies of DGMAH, located in Ga-Rankuwa, Pretoria, South Africa. The hospital caters for a catchment population of approximately 1.7 million people in and around the community. The academic hospital affords teaching and training support to Sefako Makgatho Health Sciences University (SMU) and to surrounding district hospitals in the Gauteng Province. At the time of the study, the hospital operated as 28 departments, with 44 wards and 1 650 approved beds.
3.3.2 Operational setting

During a 9-month period in 2017, interventions to strengthen the already existing PV surveillance system at DGMAH were implemented. The researcher placed various aids to encourage PV awareness and provided formal and informal training to HCPs throughout the hospital to improve knowledge about the initiative. The study was incorporated into the weekly practice-based learning, ward inventory management (WIM) activities of BPharm III and IV students. To facilitate WIM activities, each student is allocated a ward to help improve ward inventory activities under the supervision of a pharmacist. In terms of this project, students were trained to engage with HCPs regarding ADR reporting and the interventions implemented to strengthen the PV system at DGMAH.

3.4 STUDY POPULATION AND SAMPLE

The target study population included all ADR reports submitted by HCPs at DGMAH for the 9-month prior to the intervention and for the 9-month period from the implementation of the intervention. No formal sample size calculation or estimation applied for this study as all ADR reports submitted by all HCPs at DGMAH prior to, and since the start of the implementation of the intervention, were included in the study for the purpose of data analysis.

3.5 INTERVENTIONS

During Phase 2 a number of interventions were implemented and coordinated by the researcher over a period of nine months. Assistance with some of the interventions were received from the study supervisors and the BPharm III and BPharm IV students of the School of Pharmacy at Sefako Makgatho Health Sciences University (see Section 3.5.2). The educational interventions were chosen based on those that showed marked improvement in similar settings in various studies (see section 2.7) after careful review of literature.

3.5.1 Supportive training for HCPs

3.5.1.1 Formal training sessions

Supportive training was provided as part of the intervention and was directed towards all medical practitioners, nurses, pharmacists, pharmacist assistants and other HCPs at DGMAH. E-mail requests (Appendix 1) were sent to different departments requesting a training date. The departments which opted to participate were included in this study (Table 3.2). These training sessions were conducted at various forums such as the PTC meetings, nurses’ morning meetings, departmental journal clubs, departmental meetings and weekly pharmacy
staff meetings. The training was done using a PowerPoint™ presentation (Appendix 2) which included the importance of PV and types of ADRs, the role of HCPs in ADR reporting and how ADR-reporting should be done using the paper-based ADR-reporting forms (Appendix 3) and the current electronic ADR reporting platform of the National Department of Health (NDoH). The training sessions also included the interventions implemented by this study to facilitate ADR reporting at DGMAH. During training sessions HCPs were given an opportunity to ask questions as well as make suggestions to improve the PV surveillance system. The number of HCPs involved in the intervention phase was determined by those HCPs who attended the training sessions.

Table 3.2: Training schedule by department

<table>
<thead>
<tr>
<th>Department</th>
<th>Date of training</th>
<th>People trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiology</td>
<td>12 July 2017</td>
<td>8</td>
</tr>
<tr>
<td>Cardio-thoracic surgery</td>
<td>30 August 2017</td>
<td>14</td>
</tr>
<tr>
<td>Clinical psychology</td>
<td>14 June 2017</td>
<td>16</td>
</tr>
<tr>
<td>Diagnostic radiology &amp; imaging</td>
<td>5 July 2017</td>
<td>17</td>
</tr>
<tr>
<td>Family medicine &amp; primary health care</td>
<td>14 November 2017</td>
<td>31</td>
</tr>
<tr>
<td>General and paediatric surgery</td>
<td>13 September 2017</td>
<td>27</td>
</tr>
<tr>
<td>Hand &amp; microsurgery and Orthopaedics</td>
<td>2 August 2017</td>
<td>13</td>
</tr>
<tr>
<td>Intensive care</td>
<td>13 September 2017</td>
<td>13</td>
</tr>
<tr>
<td>Neurology</td>
<td>13 September 2017</td>
<td>15</td>
</tr>
<tr>
<td>Nuclear medicine</td>
<td>22 August 2017</td>
<td>6</td>
</tr>
<tr>
<td>Nursing</td>
<td>1 March 2017</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>7 March 2017</td>
<td>35</td>
</tr>
<tr>
<td>Obstetrics &amp; gynaecology</td>
<td>13 September 2017</td>
<td>17</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>28 June 2017</td>
<td>11</td>
</tr>
<tr>
<td>Otorhinolaryngology</td>
<td>7 July 2017</td>
<td>7</td>
</tr>
<tr>
<td>Paediatrics &amp; child Health</td>
<td>30 October 2017</td>
<td>13</td>
</tr>
<tr>
<td>Plastic &amp; reconstructive surgery</td>
<td>6 October 2017</td>
<td>2</td>
</tr>
<tr>
<td>Pharmacology &amp; therapeutics</td>
<td>28 July 2017</td>
<td>9</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>8 March 2017</td>
<td>26</td>
</tr>
<tr>
<td>Urology</td>
<td>23 August 2017</td>
<td>14</td>
</tr>
<tr>
<td>SMU, School of Pharmacy, academic interns</td>
<td>18 January 2017</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>331</strong></td>
</tr>
</tbody>
</table>

3.5.1.2. Informal training sessions

Informal and interactive on-the-spot training was conducted in the wards if necessary, to ensure that DGMAH HCPs were aware of the interventions. When checking the ADR boxes
for submitted reporting forms, informal trainings were conducted with HCPs and verbal reminders were given. Furthermore, on a weekly basis, BPharm level three and four students who also received the PV training as part of their practice-based WIM activities, would inform the nursing Sister-in-Charge about ADR reporting and the implemented interventions of this study. Because each student was allocated a ward in the hospital, this also ensured broad dissemination of information (see Section 3.5.2).

3.5.2 Posters

Posters containing information about ADRs and ADR-reporting procedures were placed around the hospital targeted at HCPs and patients (Appendices 4 & 5). The posters acted as a visual reminder in the wards and outpatient clinics to report any ADRs. The contact numbers of the researcher and a member of the Pharmacy and Therapeutics Committee (PTC) of DGMAH were clearly visible on the posters. Health care professionals were informed that they could use the contact details should they have any questions regarding ADR reporting or if they had detected an ADR but were too busy with clinical duties to complete the ADR form. The layout, content and design were adapted from a study contacted by Terblanche et al., (2017b).

![Figure 3.1: ADR posters placed in the wards at DGMAH](image)

3.5.3 Availability of ADR forms in the wards and consultation rooms

The unavailability of ADR reporting forms has been cited as one of the main reasons for under-reporting in various studies (Terblanche et al., 2017a; Engler et al., 2016). ADR reporting
forms (Appendix 2) were made readily available to all HCPs in the wards, the pharmacy and in the consultation rooms in the outpatient clinics. Boxes with blank ADR reporting forms were placed at various points in the hospital and HCPs were informed that the forms were there, one no longer needed to go to the main pharmacy. An example of a completed ADR reporting form was pasted onto the reversed side of each box as a point of reference (Appendix 6).

![Figure 3.2: ADR boxes in the wards](image)

3.5.4 Feedback to HCPs on ADR reporting

Feedback on the number of ADR-reports submitted, the types of ADRs reported and the quality of completed ADR reports submitted was provided to HCPs using verbal means of communication. This included feedback at various meetings, e.g. Pharmacy and Therapeutics Committee (PTC), Medical Advisory Committee (MAC), Executive Pharmacy Management Committee, Nursing Managers and Staff Development & Central In-Service Programme. Previous studies have shown that lack of feedback discourages ADR reporting, and that by providing feedback to the individual reporters, ADR reporting was stimulated and fostered an active relationship between the HCP and the pharmacovigilance centre (Oosterhuis et al., 2012).
3.6 QUALITY AND COMPLETENESS OF ADR REPORTS

A checklist was developed to determine the quality and completeness of the ADR reports received pre- and post-intervention (Appendix 7). The checklist consisted of five sections which were further sub-divided into different categories. If information in the different categories were completed on the ADR reporting form a score of “1” was awarded. If the category was not filled in, a score of “0” was given. If the category did not apply such as the case of ADR forms submitted for product quality problems, a score of “2” was given indicating not applicable. A section was considered complete if all the categories received a score of “1”. The sections and categories were adapted from the WHO minimum requirements for information on an ADR report form.

3.7 DATA COLLECTION PROCESS

Data collection and intervention implementation only commenced after ethical clearance for the study was obtained. The actual study was conducted over a period of 10 months in two phases, of which the first phase (retrospective ADR review) occurred over a period of one month (February, 2017), but covered nine months’ retrospective data (June 2016 to February 2017). The second phase was conducted from March 2017 to November 2017 and consisted of implementation of interventions and checking for any ADR reports submitted during this period.

The ADR reporting form of the MCC was the primary data collection source (Appendix 3). All completed ADR reports submitted nine months prior to and during the 9-month implementation phase were retrospectively collected. All ADR reports submitted electronically were requested from the National Pharmacovigilance Centre of the NDoH. Data from these already completed ADR reports were entered onto an Excel™ spreadsheet for analysis.

Furthermore, a data collection sheet was used to record data on the quality of these completed ADR reports. For each report, ADR data in line with NADEMC criteria were recorded and assessed for quality and completeness (i.e. data provided for all obligatory items) (Appendix 7).

3.8 PILOT STUDY

A pilot study was conducted prior to the commencement of data collection following ethical clearance. The data collection instrument (Appendix 7) which was used to determine the completeness and quality of the completed ADR reports was tested for feasibility on 10
previously submitted ADR reports including those submitted from the active surveillance of the transdermal implant Implanon NXT®.

The relevance and feasibility of the training sessions were pilot tested on academic pharmacist interns from SMU to determine the time needed to perform the training as well as for the researcher to familiarise herself with how to conduct the sessions and pre-empt unforeseen circumstances that may arise during training sessions. Following the pilot study, the ADR checklist was amended accordingly. The ADR reports (except those for active surveillance) were not excluded from the actual study as the presentation slides were later amended.

3.9 DATA ENTRY AND ANALYSIS

All collected data from the ADR reports and the quality checklist were captured by the researcher using Microsoft Office Excel™ spreadsheets. All entered information was checked thoroughly for accuracy and completeness and the necessary adjustments were made before any analysis was done.

A statistician was consulted to aid in data analysis. All procedures were performed on SAS® Release 9.4 running under Microsoft Windows®. Data were combined in categories and expressed as numbers and percentages. Frequencies were calculated for the number of ADR reports received pre- and post the intervention. The pre-intervention and post-intervention quality of the reports was assessed in terms of completeness (data provided for all obligatory sections). A comparative analysis of all the data was carried out using the Fischer Exact Test. The statistical level of significance was set at P<0.05.

The ADR reporting rate and the quality of completed ADR reports submitted during the intervention period were compared with the ADR reporting rate and quality of completed ADR reports submitted during the pre-intervention period. The outcomes of this comparison were quantified and assessed to review the impact of the interventions with supportive training for HCPs on ADR reporting at DGMAH.

3.10 RELIABILITY AND VALIDITY

A pilot study was conducted prior to the commencement of the study to test the feasibility of the data collection form and some of the interventions (see Section 3.7). All captured data were cross-checked by a second person to ensure reliability of data entry (see Section 3.8).
Chapter 3: Methodology

All completed ADR reporting forms were placed in sealed boxes that were located in each ward, outpatient consulting rooms and the pharmacy to minimise tampering and ensured that data came from across the whole hospital.

The researcher recognised the fact that this study itself was done over a relatively short period of time which may have had an influence on the possibility to conduct an interrupted time series analysis in future.

3.11 BIAS

Selection bias was avoided by putting forth an open invitation to all HCPs who were willing and available to participate in the training sessions. Volunteer bias which is the concept that people who volunteer to participate in research studies have some different characteristics, privileges and lifestyles from those who do not volunteer, was a high possibility in this study (Study.com, 2015) and was minimised by generating as much interest in the study as possible.

As this was an interventional study, chronology bias may have been a possibility as retrospective data were collected for the nine-month period prior to implementation of interventions. This type of bias was minimised by using as recent as possible historical information and conducting a prospective phase of the study (Pannucci & Wilkins, 2010) which was done in this two phased study.

3.12 ETHICAL CONSIDERATIONS

Ethical clearance for the study was obtained from the Sefako Makgatho Health Sciences University Research and Ethics Committee (SMUREC/H/209/2016:PG) prior to the commencement of the study (Appendix 8). Permission to conduct the study at DGMAH was obtained from the hospital Chief Executive Officer (CEO) (Appendices 9 & 10). Access to and permission to use electronic ADR reports submitted by DGMAH was requested from the National Pharmacovigilance Coordinator, National Department of Health (Appendices 11 & 12). All raw data obtained were accessible only to the researcher and the study supervisors and were handled confidentially.

3.13 SUMMARY

This chapter described at length the methodology used to conduct this two-phase study at DGMAH. The study design was operational and interventional to implement interventions to strengthen the PV system at DGMAH.
Chapter 3: Methodology

In Phase 1, retrospective data were collected on ADR reports submitted nine months prior to the implementation of interventions.

Phase 2 involved implementation of interventions and the collection of prospective data on ADR reports submitted over an intervention period of nine months.

The collected data were captured onto Microsoft Excel® spreadsheets, checked for accuracy and imported into SAS® Release 9.4 for statistical analysis.

Ethical clearance for the study was obtained from the SMUREC and permission to conduct the study obtained from the CEO of the hospital. The results of the data collected in this study are presented and discussed in Chapter 4.
Chapter 4: Results and Discussion

CHAPTER 4
RESULTS AND DISCUSSION

4.1 INTRODUCTION

The results of this study are presented and discussed in this chapter. In the first section the ADR population and frequency of reports are presented. This is followed by the overall completeness of ADR report forms. A review of the completeness of the different sections of the ADR reporting forms submitted pre- and post-intervention is presented and discussed in detail. A summary of the findings concludes this chapter.

4.2 REPORTING OF ADRs

In 2015, Engler et al. (2016) conducted a study at DGMAH which revealed poor knowledge, attitudes and perspectives on ADR reporting by HCPs. The results of their study strongly recommended the need for interventions and training to be conducted at DGMAH to improve PV activities. Similarly, Terblanche et al. (2017a) found the vast majority of their study participants had never reported an ADR, had never received training in PV, but wanted training on ADR reporting in their study conducted at Sebokeng hospital. Recommendations were made to provide trainings to increase HCPs knowledge on ADRs. These two studies served as a baseline assessment for our study. Moreover, Terblanche et al. (2017b) implemented interventions that were very successful in increasing the reporting rate at Sebokeng Hospital. The interventions used in this study were adapted from Terblanche et al. (2017b) into an operational project at DGMAH as they proved successful.

A retrospective review of ADR reports submitted by DGMAH for the period June 2016 and February 2017 showed that only five spontaneous ADR reports were submitted by HCPs at the hospital. Two ADR reports were submitted in the month of June 2016, two in August 2016 and one in November 2016. During the post-intervention phase (March 2017 to November 2017) a total of 14 spontaneous ADR reports were submitted which demonstrated an improvement in the frequency of ADR reporting (180% increase in ADR reporting).

The key finding from this study is that the rate of ADR reporting was increased after the intervention. This finding is comparable to that found in similar settings where an intervention was implemented. A study conducted at Sebokeng Hospital in Gauteng, South Africa, showed an increase in the reporting rate following the implementation of interventions from Six In the 18 months before the intervention to a total of 69 post-intervention (Terblanche et al., 2017).
This improvement of ADR reporting also followed the use of formal trainings using a PowerPoint® presentation, ADR posters placed throughout the hospital, ADR boxes and increased availability of ADR reporting forms. Biagi et al. (2013) observed a 49.2% increase in the number of reports from 63 to 94 in the 12 months post the intervention phase.

The results of this study may not have increased significantly compared to that of Terblanche et al. (2017), this could be due to various factors discussed under section 4.5. However, where there is gross under-reporting of ADRs globally, an increase in PV activities is important.

World Health Organization standards show that the best spontaneous reporting rate is over 200 reports per 1 000 000 populations per year. Should this standard be considered or applied at DGMAH, where a population of 1.7 million people are served, it is expected to have at least 3 400 reports per year. Unfortunately only an average of nine reports per year was recorded for this academic hospital between January 2012 and April 2017 (Gauteng Province, 2017).

A comparative analysis of all the data was carried out using the Fischer Exact Test. The statistical level of significance was set at P<0.05. However, the numbers were too small to produce statistical significant values.

### 4.3 OVERALL COMPLETENESS OF ADR REPORT FORMS

The overall completeness of the different sections of the ADR report forms as determined by the WHO guidelines was evaluated. A quality ADR reporting form is deemed satisfactory if all sections and categories are as complete as possible (WHO, 2002). A section was considered complete if all the categories were filled in.

<table>
<thead>
<tr>
<th>Table 4.1: The completeness of the different sections of the MCC ADR reporting forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section</strong></td>
</tr>
<tr>
<td>1 Patient information</td>
</tr>
<tr>
<td>2 Adverse drug reaction problem/Product quality problem</td>
</tr>
<tr>
<td>3 Adverse reaction outcome</td>
</tr>
<tr>
<td>4 Product quality problem (PQP)</td>
</tr>
<tr>
<td>5 Reporter details</td>
</tr>
</tbody>
</table>

The quality and completeness of the different sections of the submitted ADRs prior to and post the implementation of interventions were evaluated. Although most of the categories in each
As shown in Table 4.1, all categories in the section on reporter details were fully completed in four of five (80.0%) and 12 of 14 (85.7%) ADR reports submitted pre-intervention and post-intervention respectively. The section on ADR/ product quality problem which includes the category with the description of the ADR event was completed on the majority of the forms, both pre-intervention (three of five) and post-intervention (nine of 14). Similar to the quality of ADR report forms in a study in Saudi Arabia, the completeness of the patient information section was inadequate (Alshammari et al., 2015). None of the four ADR report forms that reported a product quality issue had all the categories in the section completed according to the MCC and WHO requirements (MCC, 2014; WHO, 2002).

### 4.4Completeness of Different Categories in Each Section of the ADR Report Form

Table 4.2 illustrates the completeness of the ADR report forms per category according to the minimum requirements for information on an ADR reporting form (WHO, 2002). The completeness of additional categories included on the MCC ADR reporting form were also evaluated and presented with an asterisk (*) in Table 4.2.
## Table 4.2: Completeness of ADR report form submitted by category

<table>
<thead>
<tr>
<th>Categories</th>
<th>Pre-intervention (n=5)</th>
<th>Post-Intervention (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient identifier</td>
<td>4 (80.0%)</td>
<td>10 (71.4%)</td>
</tr>
<tr>
<td>Date of Birth/age</td>
<td>4 (80.0%)</td>
<td>10 (71.4%)</td>
</tr>
<tr>
<td>Gender</td>
<td>4 (80.0%)</td>
<td>8 (57.1%)</td>
</tr>
<tr>
<td>Weight</td>
<td>3 (60.0%)</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>*Height</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Adverse drug reaction or quality problem</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse drug reaction or product quality problem selected</td>
<td>3 (60.0%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>Description of reaction/ problem</td>
<td>4 (80.0%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>Date of onset of reaction</td>
<td>3 (60.0%)</td>
<td>9 (64.3%)</td>
</tr>
<tr>
<td>Report date</td>
<td>5 (100.0%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>*Time of onset</td>
<td>2 (40.0%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td><strong>Outcome of event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected Medicine</td>
<td>4 (80.0%)</td>
<td>10 (71.4%)</td>
</tr>
<tr>
<td>Dose/Route</td>
<td>4 (80.0%)</td>
<td>9 (64.3%)</td>
</tr>
<tr>
<td>Start date of therapy</td>
<td>3 (60.0%)</td>
<td>8 (57.1%)</td>
</tr>
<tr>
<td>Reason for Use</td>
<td>3 (60.0%)</td>
<td>9 (64.3%)</td>
</tr>
<tr>
<td>Resultant outcome of ADR</td>
<td>3 (60.0%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Batch Number</td>
<td>3 (60.0%)</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>Expiry date</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Re-challenge description</td>
<td>1 (20.0%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Concomitant Medicines</td>
<td>2 (40.0%)</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td>*End of therapy date</td>
<td>4 (80.0%)</td>
<td>7 (50.0%)</td>
</tr>
<tr>
<td>*Comments for history, allergies etc.</td>
<td>1 (20.0%)</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td><strong>Reporter details</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>5 (100.0%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>Address</td>
<td>5 (100.0%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>Telephone</td>
<td>4 (80.0%)</td>
<td>12 (85.7%)</td>
</tr>
<tr>
<td>Qualifications</td>
<td>5 (100.0%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>*Signature</td>
<td>5 (100.0%)</td>
<td>14 (100.0%)</td>
</tr>
</tbody>
</table>

*Additional categories included on the MCC ADR report

### 4.4.1 Patient information

The two best completed categories were the patient identifier and the date of birth/age of the patient while the weight was only filled in three of the five pre-intervention ADR reports and five of the 14 post-intervention reports. Patient height as indicated in Table 4.1 with an asterisk (*) is not a requirement of the WHO (2002). However, it is interesting to note that not one ADR report form had the height indicated pre- or post-intervention. The height is essential in determining certain drug doses as well as patient BMI which could be a contributing factor to
an ADR (Alomar, 2014). The patient information which is required for the identification of a patient and to avoid duplicate assessment of the same ADR report (MCC, 2014) was completed on 60% of ADR reports pre-intervention and 21.4% post-intervention. This is similar to the quality of ADR reports analysed in a Saudi Arabian study where the ADR report quality was below specified standards (Alshammari et al., 2015). The other patient information categories, including the date of birth and gender of the patient, were completed on more than 50% of the ADRs pre- and post-intervention. The weights and heights of the patients experiencing an ADR were poorly filled in on both the pre-intervention (60% weights and 0% heights of five ADR reports submitted) and post-intervention (35.7% weights and 0% heights) reports. This result is similar to Alshammari et al. (2015) where the weight was only indicated on 21.1% and the height on 28.3% of the ADR reports.

Not Applicable: ADRs due to product quality problem (PQP)

Figure 4.1: Gender classification of ADR reports

Figure 4.1 shows the gender distribution on the ADRs reported. Only one and three patients who experienced an ADR pre-intervention and post-intervention respectively were male. Three of the five ADRs submitted pre-intervention were experienced by females. Two of the ADR reports post-intervention did not have the gender indicated. The remaining ADR reports were product quality problems, which do not require indication of gender. Demographic details of the participants showed female predominance over males which is in contrast with the report by Malladi (2016).
Chapter 4: Results and Discussion

Figure 4.2: ADRs in different age groups

The distribution of patients by ADR report and age group is shown in Figure 4.2. It is evident that the largest proportion of patients in this study were in the age groups 50-59 and >60 post-intervention and in the age group 40-49 pre-intervention. Pirmohamed and colleagues (2014) found that more older patients experienced an ADR as ADR risk increases with age-related changes in pharmacodynamics and pharmacokinetics (Pirmohamed et al., 2004). This is consistent with the results of this study where the majority of ADR reports were for older patients. The relationship between patients’ age and gender were not investigated. Agu & Oparah (2013) contended that being female increases the risk of general ADRs, contrary to Eluwa, Badru & Akpoigbe (2012) who reported that age and gender were not significantly associated with ADRs.

4.4.2 Adverse drug reaction or product quality problem

The categories in this section were completed almost fully pre- and post-intervention. However, the date (three of five pre-intervention and nine of 14 post-intervention) and time (two of five pre-intervention and six of 14 post-intervention) of the onset of reaction were sections which were entered sparingly compared to other categories in this section. The description of the ADR or product problem was not completed in only one ADR report pre-intervention and was completed in total post-intervention.

As seen in Table 4.2, the time of onset of the ADR, which is not a minimum requirement for the WHO (2002), but is found on the MCC ADR reporting form was poorly completed with less than 50% in both pre-intervention and post-intervention stages. Stating the time of onset of
reaction is clinically important. It helps establish causality of the suspect medicine especially in cases of poly pharmacy (Karimi et al, 2013).

The overall quality of an ADR report form was evaluated based on the completeness of the various sections. If a category was incomplete it influenced the quality of the report. Lindquist (2004) stated that the quality and completeness of an ADR report will improve if a "not applicable (N/A)" or an unknown option is provided for different categories.

The MCC ADR reporting form has a separate section to report a product quality problem which may or may not be related to an ADR. Only one product problem was reported pre-intervention. Of the 14 ADR reports submitted post-intervention, only four involved product quality. Table 4.3 shows the results of the different categories.

**Table 4.3: Product quality problem**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Pre-intervention (n=1)</th>
<th>Post- Intervention (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Batch number</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Registration number</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dosage form and strength</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Expiry date</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Size/type of container</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Product available for evaluation</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

The registration number of the product in question was poorly completed post-intervention. Indication of the registration number is important in order to be able to identify the specific product if resultant in a product recall. None of the reported product quality problems had resulted in an ADR report. Of the four ADR reports submitted post-intervention as a product quality problem, the completeness of the section was compromised by lack of the registration number of the product in question.

Completeness of the product quality problem section including all categories should be encouraged to decrease future ADRs caused by faulty products that were not reported (Juhlin et al., 2015).

### 4.4.3 Outcome of the event

The resultant outcome of the ADR was indicated on three of five and six of 14 of the ADR reports pre-intervention and post-intervention respectively. The batch number of the suspect medicine(s) was only indicated on three of the ADR reports submitted post-intervention. The re-challenge category was inserted on one ADR report pre-intervention. With regards to
Chapter 4: Results and Discussion

Concomitant medicines the patient was on, two of five and four of 14 reports had this category specified pre- and post-intervention.

The MCC ADR reporting form does not make provision for the expiry date although it is a WHO minimum requirement (MCC, 2014). Information about history, allergies, previous exposure, baseline test results/lab data was completed on fewer than 50% of the ADR reports (one pre-intervention and five post-intervention).

With regards to the outcome of event section, the suspect medicine was indicated on 100% of the ADR reports prior to implementation and after the intervention phase. The batch number however, was a category which was sparsely indicated on the ADR reports in the post-intervention phase of the study (less than 30%). This phenomenon could be due to the fact that it is difficult to find the batch number on cut blister packs, repackaged liquids and single ampoules from bulk packs.

Re-administration of the suspect drug to determine causality after complete withdrawal is referred to as re-challenge (Impicciatore & Mucci, 2010). The category on whether a re-challenge was done or not is compulsory on the MCC ADR report form but was only completed on one of five ADR report pre-intervention and six of 14 ADR reports post-intervention (MCC, 2014). Nevertheless, re-challenging an ADR is not always possible such as in the case of antiretroviral therapy and vaccines and therefore completion of this category as optional should be considered (Lindquist, 2004).

4.4.4 Reporter details

The details of the reporter was the most complete section across all the submitted ADR reports, both pre- and post-intervention. The name, address, qualification and signature of the reporter were 100% completed in both phases. The telephone number was not completed on only one ADR report prior to the intervention and two of the ADR reports post-intervention. Reporter demographics by profession were also evaluated in this study. The reporting of ADRs by nurses increased significantly from 0% to 35.7% and that of doctors from 20% to 28.6%. That of pharmacists increased by one report.

Overall, pharmacists seemed to be the most consistent in reporting of ADRs as this largely considered a pharmacist duty (Terblanche, 2017a). Reporting of ADRs by doctors and nurses was poor pre-intervention (one of five and zero of five ADR reports respectively), this is contrary to a study conducted in India where 64.6% of the ADRs are identified and reported by physicians and nurses (Rao, Archana & Jose, 2006).
As all HCPs were invited to participate in this study, Table 4.4 shows the reporter demographics by profession.

Table 4.4: Reporter demographics by profession

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Pre-intervention (n=5)</th>
<th>Post-intervention (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care professionals</td>
<td>Medical practitioner</td>
<td>1 (20%)</td>
</tr>
<tr>
<td></td>
<td>Pharmacist</td>
<td>4 (80.0%)</td>
</tr>
<tr>
<td></td>
<td>Nurse</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

4.4.5 Other characteristics of the ADR reports

The reports due to product quality problems were not included in this category hence the difference in sample size (one of five pre-intervention and four of 14 post-intervention were PQPs hence excluded).

4.4.5.1. Body systems affected by an ADR

Based on the description of the reaction, the body system affected by the ADR was determined (Figure 4.3). Skin was the most commonly involved system amongst the ADRs reported, followed by multi-system involvement in both the pre- and post-intervention ADRs. This is in line with a study conducted in India which showed that skin ADRs affect more than 2% of the hospital admissions and approximately 45% of all the adverse ADRs were manifested in the skin (Nayak & Acharjya, 2008). The respiratory system and the central nervous system were implicated in two ADR reports, both in the post-intervention phase.

Figure 4.3: Body systems affected by ADR
4.4.5.2. **Drug classes implicated in an ADR**

Figure 4.4 illustrates the drug classes implicated in ADRs pre-intervention (Fig 4.4a) and post-intervention (Fig 4.4b). Drugs such as antidiabetics, haematincs and complementary medicine which were classified under “other” were most commonly associated with causation of ADRs in the pre-intervention phase data whilst non-steroidal anti-inflammatory drugs (NSAIDs) and other medicines accounted for the largest proportions of ADRs post-intervention. This finding is similar to previous studies done in the United States of America (USA) and India which also reported the same result (Suh et al., 2000; Malladi, 2016).

**Figure 4.4: Drug classes implicated in an ADR**

4.4.5.3. **Most common route of administration causing an ADR**

The information on the route of administration (Table 4.5) was recorded on all the ADR reports due to an adverse reaction pre- and post-intervention. Most of the ADRs were caused due to drugs administered by the oral route both in the pre-intervention phase and the post-intervention phase, followed by intravenous routes post-intervention. Other routes such as the topical route accounted for one ADR report pre-intervention and post-intervention, as the oral route is the most frequently used route of administration because of its simplicity and convenience. The results illustrated in Table 4.6 are in line with Alomar’s (2014) review article findings conducted in the United Arab Emirates (UAE) which state that the oral route is the most likely to be implicated in ADRs as it is the most convenient and hassle free route of administration.
Table 4.5: Route of administration of drug causing ADR

<table>
<thead>
<tr>
<th>Route</th>
<th>Pre-Intervention (n=4)</th>
<th>Post-Intervention (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other (Topical, inhalations, rectal)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

4.5 OPERATIONAL CHALLENGES

Differences exist between the characteristics of this study compared to Terblanche et al., (2017) that may have contributed to the unimpressive increase in ADR reports. Interventions carried out at Sebokeng hospital were conducted by the pharmacy manager, who worked in the hospital on a daily basis whilst in this study the researcher was a post-graduate student, visiting the hospital on a weekly basis. Biagi et al., (2013) stated that regular updates about ADR reporting by a designated personnel is essential to keep the outcome of the intervention favourable. Similarly Vinther and colleagues cited an increase in ADR reports after the appointment of an adverse drug event manager in the hospital who was introduced to HCPs to facilitate spontaneous reporting (Vinther et al., 2017).

Dr George Mukhari is a much larger hospital compared to Sebokeng Hospital. According to literature, larger settings generally have a low uptake of interventions compared to small more manageable facilities as information dissemination is more difficult (Tabali et al., 2009). Unwillingness by some DGMAH departments to avail themselves for supportive trainings contributed to the low uptake of the implemented interventions. Lack of activity from the PTC PV sub-committee also hindered the success of the study as it was perceived as unsupported by the relevant body therefore deemed unimportant.

Damage to and misuse of ADR boxes placed in the wards to facilitate ADR reporting, bad attitudes and resistance to change routines were some of the challenges experienced during the implementation period of the study. Lack of full support from hospital management with regards to implementation of the interventions also played a role in the outcome of the interventions.

When verbally questioned as to why HCPs did not report ADRs, the usual “lack of knowledge and awareness about PV surveillance system, lethargy, indifference, insecurity, complacency, workload” were the commonly cited factors, despite the extensive interventions implemented throughout DGMAH. This is in line with findings in Dheda et al. (2016) where HCPs also expressed various challenges as reasons for not reporting. Studies conducted in Gauteng
province, South Africa by Engler et al. (2016) and Terblanche et al. (2017a) also cited similar problems. The hurdles experienced during this study could have had a detrimental effect on the impact of the interventions and could be the reasons for such a little increase in ADR reports post-intervention.

4.6 SUMMARY

In this chapter the results collected over a ten-month study period have been summarised and presented. The ADR reporting rate increased from five ADRs pre-intervention to 14 post-intervention. The sections on adverse drug reaction problem/product quality problem and reporter details were completed well, both pre-intervention and post-intervention (more than 60%). The category on weight was the cause of the low completion rate in the patient identifier section. The section on the outcome of events was the most poorly completed section as most of the categories had a score of below 50%. Other characteristics of the ADR reports were analysed namely age, gender, drug class and route of administration of suspect medicine.

In the next chapter a conclusion will be drawn based on the results and recommendations will be offered and the limitations of the study will be detailed.
CHAPTER 5
LIMITATIONS, RECOMMENDATIONS AND CONCLUSIONS

5.1 INTRODUCTION

In this chapter, the limitations of this study are taken into consideration. Recommendations are made based on the results of the study presented in chapter 4. Conclusions are drawn to complete the dissertation.

5.2 LIMITATIONS OF THE STUDY

The reporting rate increased, although the post-intervention frequency was not as high as expected. This study was done in a single centre over a short period of time. The results can therefore not be generalised to all hospitals. As there was no post-intervention assessment, reports submitted could have been submitted by HCPs who did not attend trainings.

The findings would have been more meaningful if the study was carried out in more than one health care institution, and included a qualitative approach (in depth interviews, focus group discussions) in order to obtain a better understanding of HCPs' knowledge about ADR reporting, attitudes towards the implemented interventions, and suggestions to improve future ADR reporting at DGMAH, post the intervention phase.

Another limitation with the provision of training was the willingness of the different departments to undergo training sessions according to the available time slots in their schedules.

5.3 RECOMMENDATIONS

The following key recommendations are proposed based on the results of the study:

- The training interventions conducted in this study should be part of a continuous process and should be done over a longer period for better retention of knowledge. The training should also accentuate the link between improving rational medicine use outcomes, reducing prescribing errors and preventing the occurrence of ADRs (Vinther et al., 2017).
Chapter 5: Limitations, Recommendations and Conclusions

- A basic ADR causality assessment tool that could assist HCPs in identifying possible ADRs and improve confidence amongst HCPs in reporting ADRs (Khan et al., 2013).

- Pharmacovigilance activities should be reinforced by the PV subcommittee of the PTC with enforced quarterly updates from the departments.

- A dedicated staff member for PV who is introduced to all new staff and acquainted with all existing employees should be appointed to help facilitate ADR reporting and raise awareness about ADRs and why it is important to report them. This should be done through education of HCPs and information similar to that described in a study conducted in Denmark (Vinther et al., 2017).

- Standard operating procedures and guidelines specific to DGMAH should be created and implemented to ensure uniformity and understanding of ADR reporting procedures.

- Pharmacovigilance training should be assimilated into the under-graduate programmes for HCPs who will be required to report once they start practising. These PV training sessions could also be made available as Continuing Professional Development (CPD) programmes to emphasise further the importance of ADR reporting and to encourage and equip HCPs to report (Schutte et al., 2017).

- Involvement of the professional bodies of the different health care professions is necessary. There should be activities to improve awareness regarding the detection and reporting of ADRs (Khan et al., 2013).

- A well-known member of the hospital staff should be the point of reference and have continuous involvement in PV activities and promoting ADR reporting in order to increase the reporting rate. This designated person should be the one to receive all ADR reports and can be contacted by HCPs regarding PV in the hospital.

- A qualitative survey of HCPs or clinical heads, chief executive officers etc. is needed to ascertain their knowledge about ADR reporting, attitudes towards the implemented interventions, and suggestions to improve future ADR reporting at DGMAH. A follow-up independent study, through a protocol addendum to this study, will be conducted with focus group discussions and in-depth interviews to supplement the results. This will give a better understanding as to why there is gross under-reporting at the hospital.

- The use of other interventions such as telephone calls, email reminders and newsletters help to improve awareness and should be promoted extensively (Figueiras et al., 2006).
5.4 CONCLUSIONS

The findings of this study contribute to the understanding of the role of HCPs in the public health care system in South Africa and especially at this academic hospital in supporting a spontaneous reporting PV system.

The results of the study suggested that the implemented interventions collectively aided in the increased ADR reporting rate and quality of the different sections of the ADR reporting form, as was evident from the increase in the number of ADRs submitted post-intervention. An evident upsurge in ADR reporting could be explained by creating awareness of and implementing educational interventions to strengthen the PV system at DGMAH. Continuous training of HCPs about PV activities via oral presentations, verbal reminders, advertisement, improved availability of ADR reporting forms, information posters and various other methods were proposed and investigated in various other studies to improve the knowledge and attitudes of HCPs about ADRs and facilitate their reporting.

The quality of an ADR report form is an important parameter in PV and assists in reliable causality assessments and signal detection of ADRs (Bergvall et al., 2014). The completion quality on the MCC ADR reporting form showed that the sections on ADR problem/product quality problem and reporter details were completed well. However, the completeness of the patient information, adverse drug reaction outcomes and product quality problems was generally low. This shows that the incompleteness of one category can affect the overall completeness of the entire section. All compulsory information required on the ADR reporting form is critical and the report needs to be as complete as possible (MCC, 2014).

Unremitting pharmacovigilance training is essential to reduce the negative impact of the barriers associated with under-reporting. These future trainings should be aimed at familiarising HCPs robustly on the different sections of the MCC ADR reporting form and how to complete them. Moreover, they should also concentrate on improving HCPs understanding of which medicine might be responsible for an ADR and establishing causality. This step could lead to less time being wasted trying to identify the suspect medicine, improved reporting rates and better operational and clinical decision making.

Implementing various interventions that add value to an already existing pharmacovigilance system are the key to improving PV activities and the quality of submitted ADR reports at DGMAH and nationally.
5.5 CLOSURE

Strengthening PV systems in the public health sector will go a long way in improving the rational use of medicines, reducing medication errors and increasing patient safety in facilities. Although the results of the study were not as significant as in other studies, an increase in the number of ADR reports submitted post the intervention period was seen. This shows that the methods used in this study can be implemented in other settings to augment PV activities and ultimately improve ADR reporting rates. Furthermore, in-depth interviews and focus group discussion with relevant PV stakeholders are needed to understand better and how to breach the barriers of under-reporting at DGMAH and facilitate PV practices suited to the hospital.
REFERENCES


References


USAID, SPS. 2009. Supporting Pharmacovigilence in Developing Countries, The system Perspective; 2-5.


APPENDICES

Appendix 1: Email request to conduct PV training

Head of ............... Department
Dr George Mukhari Academic Hospital

Dear Dr / Prof ..............

RE: Request to conduct pharmacovigilance training in your department

I am a registered Master’s degree student in the School of Pharmacy at Sefako Makgatho Health Sciences University. As part of the requirements for my degree, I am doing a study entitled;

“Implementation of interventions to strengthen the pharmacovigilance (PV) surveillance system at Dr George Mukhari Academic Hospital (DGMAH), Gauteng Province”.

As part of the planned interventions, all clinical staff will be trained on Adverse drug reactions (ADR) reporting. In addition to the training, interventions will include the following activities:

• Posters in each ward about ADR reporting
• Pharmacist support and contact details
• ADR forms readily available in wards
• Quarterly feedback on ADRs reported at DGMAH

The study has been granted ethical clearance by the Sefako Makgatho Health Sciences University Ethics and Research Committee (SMUREC) and the permissions by the CEO of DGMAH. Please find the supportive documents attached.

I hereby kindly request a 30 minute time slot on a suitable date/s to provide training to clinical staff in your department.
Should you require any further information, please do not hesitate to contact myself or my supervisors.

Yours sincerely,

Kalaba Nkonde, MPharm Candidate
Cell: 0799753266
Supervisors: Prof JC Meyer, Dr M Matlala & Prof RS Summers
Appendices

Appendix 2: PV training slides

Pharmacovigilance and adverse drug reaction (ADR) reporting

Dr George Mukhari Academic Hospital
14 November 2017

Kalaba Nkonde
(MPharm Candidate)

Division: Public Health Pharmacy and Management
School of Pharmacy
Sefako Makgatho Health Sciences University

What is pharmacovigilance?

Detect ADR Prevent ADR
Report ADR Manage ADR

Pharmacovigilance = The science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions and other drug-related problems. (WHO)
What is an adverse drug reaction (ADR)?

- “All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions” Ref: ICH Guidelines 1.1
- ADRs may occur following
  - Single dose
  - Combination of medicines
  - Prolonged administration
- **Adverse event** = Any untoward medical occurrence that may present during treatment with a pharmaceutical product/medication but which does not necessarily have a causal relationship with this treatment

Types of ADRs

- **Type A - Augmented**
  - dose-related, acute, mechanism better understood
  - e.g. hypotension with a beta blocker
- **Type B - Bizarre**
  - (idiiosyncratic - non dose-related, difficult to diagnose)
  - e.g. anaphylaxis after penicillin injection
- **Type C - Continuous (chronic/long term use)**
  - e.g. osteoporosis with oral steroids
- **Type D – Delayed, rare but serious**
  - Long term use ≠ safe
  - e.g. teratogenic effect with anticonvulsants
- **Type E - Ending of use (withdrawal)**
  - e.g. withdrawal syndrome with benzodiazepines
- **Type F - Failure of efficacy (no response)**
  - e.g. resistance to antibiotics
Appendices

Why Report ADRs? (1)

- Institute of Medicine in the United States research over 2 MILLION serious ADRs yearly²
- 100 000 DEATHS yearly due to ADRs
- ADRs = 4th leading cause of death – ahead of
  
Pulmonary disease  Diabetes  AIDS  Pneumonia  Accidents
  
- ADRs - common cause of hospitalisation and an economic burden

Why report ADRs? (2)

- Most medicines that are used in SA are registered based on clinical trials done in other parts of the world
  - SA must be vigilant for ADRs during a medicine’s post-marketing period
- In SA, there is little reporting of ADRs
  - This limits effectiveness of the healthcare system doing post-marketing surveillance of medicines
- HCPs are in best position to report suspected ADRs
  - It is also a moral & professional responsibility of HCPs to report ADRs
Why report ADRs? (3)

- **National Core Standards (NCS) requirement**
- NDoH committed to provision of best quality care and health service delivery
- The significant goal of the core standards is “To assist in improving quality of care in all health establishments.”
- Set standards for quality service through defining and specifying what is expected in terms of quality in the health sector
- Compliance with standards becomes a norm through implementation of a continuous quality improvement process

Why report ADRs? (4)

![Patient Safety Image](PATIENT_SAFETY.png)
Types of ADRs that should be reported

- **All ADRs that are suspected**
  - Serious
  - Minor
  - Known
  - Unexpected beneficial effects or ineffectiveness (e.g. product failure due to resistance)
  - Unusual
  - Suspected pharmaceutical defects
- **ADRs that are *not clearly stated* in the package insert**
- **Observed increases in the frequency of a given reaction**
- **ADRs due to drug use in pregnancy and during lactation**
  - E.g. reactions suspected of causing *birth defects/congenital anomalies*

Types of ADRs that should be reported (2)

- **All ADRs from drugs** that are
  - Established/well-known drugs
  - Newly marketed drugs
  - New drugs added to the EDL
- **All ADRs from reactions suspected of causing**
  - Admission to hospital
  - Prolongation of existing hospitalisation
  - Other serious medical events, such as allergic bronchospasm
  - Persistent or significant disability or incapacity
  - Life-threatening / danger to life
  - Death
Types of ADRs that should be reported (3)

- All suspected ADRs associated with interactions between
  - Drug → Drug
  - Drug → Food
  - Drug → Supplement
- ADRs in special fields of interest e.g. drug abuse
- ADRs occurring from overdose or medication errors
- Lack of efficacy of a medication, or when suspected pharmaceutical defects are observed

Report any ADR considered clinically important

How to complete an ADR form?

You don’t need to be certain, just suspicious!
What to include in a report? (1)

Patient Details
- Name, file number, gender, age, DOB, weight, height.

ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM
(Identities of reporter and patient will remain strictly confidential)

NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE
NADEMC

PATIENT INFORMATION

Name (or initials): ___________________________ Patient Reference Number: ___________________________

Sex: M | F Age: __________ DOB: __/__/____ Weight (kg) __________ Height (cm) __________

Division: Public Health Pharmacy and Management
School of Pharmacy
Sefako Makgatha Health Sciences University
What to include in a report? (2)

- Date and time of onset of reaction
- Description of the ADR/problem
  - Relevant history
  - Allergies
  - Previous exposure
  - Clinical and laboratory data

<table>
<thead>
<tr>
<th>ADVERSE REACTION / PRODUCT QUALITY PROBLEM</th>
<th>(tick appropriate box)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>and/or Product Quality problem</td>
</tr>
<tr>
<td>Time of onset of reaction: __________hour_________min</td>
<td></td>
</tr>
</tbody>
</table>

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

Include as many other details as possible.

What to include in a report? (3)

- Medication history
  - Concomitant medicines
  - Over-the-counter medicine
  - Herbal / Traditional medicine

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

<table>
<thead>
<tr>
<th>Trade Name &amp; Batch No. (An asterisk signifies a product)</th>
<th>Daily Dosage</th>
<th>Route</th>
<th>Date Started</th>
<th>Date Stopped</th>
<th>Reasons for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enap (Enalapril) Batch no: 3326/8</td>
<td>10mg daily</td>
<td>Oral</td>
<td>26/6/17</td>
<td>28/6/17</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Steroid</td>
<td>100mg daily</td>
<td>Oral</td>
<td>27/6/17</td>
<td>28/6/17</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

60
What to include in a report? (4)

Outcome of the reaction

ADVERSE REACTION OUTCOME (Check all that apply)

- death
- disability
- congenital anomaly
- required intervention to prevent permanent impairment/damage
- life threatening hospitalisation
- Other

Reactions stated after stopping medicine:
- T
- X
- N/A

Recovered:
- Y
- N

Sequelae:
- Y
- N

Describe

Event reappeared on rechallenge:
- Y
- N

Rechallenge not done

What to include in a report? (5)

Product quality reports
- Trade name
- Batch & registration number
- Dosage form and strength
- Expiry date
- Size/type of container

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Batch No</th>
<th>Registration No</th>
<th>Dosage form &amp; strength</th>
<th>Expiry Date</th>
<th>Size/Type of container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sparanallerg</td>
<td>332 6/8</td>
<td>3259998</td>
<td>0.9mg/1ml solution</td>
<td>Sep 2019</td>
<td>10ml</td>
</tr>
</tbody>
</table>

Product available for evaluation?:
- Y
- N
What to include in a report? (6)

Details of reporter
- name
- qualifications
- contact details
- institution

Reporting Healthcare Professional:
K. Nkonde
12 BMS Dr. Ga-rankuwa

012 123 4567

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

OUTCOMES OF REPORTS

Regulatory or drug marketing authorities may:
- Propose appropriate measures for risk prevention e.g. dose reduction, avoid in certain conditions etc.
- Propose studies to further investigate the hazard and frequency of its occurrence.
- Withdraw the product from the market.
How can we Improve ADR reporting at DGMAH?

The process of reporting at DGMAH

1. Observe or suspect an ADR (in the ward/during dispensing)
2. Complete the yellow form
3. Submit to the drug controller in the main pharmacy
4. Fax a copy to the NADEMC & MCC
5. Report to the local PTC & Provincial PTC
Appendices

Provision of ADR reporting forms

- Can be found in the ward and at the main pharmacy

ADR reporting boxes

- Once completed ADR forms can be placed in coloured boxes found in the ward for collection
**ADR posters**

- Look out for posters in the wards with contact details if help required

---

**EML clinical guide app**

- Used to submit online ADR report through your smartphone

---
Feedback about ADRs

- Proposed newsletter will be printed and distributed throughout the hospital and emailed

ADR REPORTING NEWS
Adverse drug reaction (ADR) reporting Newsletter
July 6, 2017

Importance of ADR reporting
Most medicines that are used in South Africa are not approved or licensed by the South African Medicines Control Council (SA-MCC), but they are being used. Therefore, the hospital needs to comply and improve patient safety.

Drug Safety Update
Latest advice for medicines users
The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Contents

References

1. ICH Guidelines 1.1
2. Institute of Medicine, National Academy Press, 2000
3. NDoH, Guideline use of database, National Core Standards for Health Care Establishments, 2011
Thank you for your attention

School of Pharmacy

Contact Details:
Kalaba Nkonde Cell: 079 975 3266
Email: kaynkonde@gmail.com

Dr Moliehi Matlala Cell: 082 569 7954
Email: moliehi.matlala@smu.ac.za

MPharm: Public Health Pharmacy
and Management
# Appendix 3: Adverse Drug Reaction Report Form

## ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM

(Identities of reporter and patient will remain strictly confidential)

### NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE

NADEMC

The Registrar of Medicines
Private Bag X 828
Pretoria, 0001

Fax: (021) 448-6181
Tel: (021) 447-1618

In collaboration with the WHO International Drug Monitoring Programme

### PATIENT INFORMATION

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

### ADVERSE REACTION / PRODUCT QUALITY PROBLEM

(tick appropriate box)

Adverse reaction  and/or Product Quality problem  
Date of onset of reaction: ............./............../..............

Time of onset of reaction: ..............hour.............min

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

1. **M EDICINES / VACCINES / DEVICES (include all concomitant medicines)**

<table>
<thead>
<tr>
<th>Trade Name &amp; Batch No.</th>
<th>Daily Dosage</th>
<th>Route</th>
<th>Date Started</th>
<th>Date Stopped</th>
<th>Reasons for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Asterisk Suspected Product)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ADVERSE REACTION OUTCOME (Check all that apply)

<table>
<thead>
<tr>
<th>Death</th>
<th>Life-threatening hospitalisation</th>
<th>Required intervention to prevent permanent impairment/damage</th>
<th>Reaction abated after stopping medicine:</th>
<th>Recovered:</th>
<th>Sequelae:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event reappeared on rechallenge:</th>
<th>Sequelea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y  N</td>
<td>Rechallenge not done</td>
</tr>
</tbody>
</table>

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

### 2. PRODUCT QUALITY PROBLEM:

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Batch No</th>
<th>Registration No</th>
<th>Dosage form &amp; strength</th>
<th>Expiry Date</th>
<th>Size/Type of container</th>
</tr>
</thead>
</table>

Product available for evaluation?:  
Y  N

### REPORTING HEALTHCARE PROFESSIONAL:

NAME: ..........................................................
QUALIFICATIONS: ..........................................................
ADDRESS: ..........................................................
Postal Code: .............. TEL: (..................) Signature .............. Date

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

Appendix 4: ADR poster 1

REPORT
ADVERSE DRUG REACTIONS

An Adverse Drug Reaction (ADR) is any unexpected, unintended or harmful reaction caused by the administration of a drug. Onset of the ADR may be sudden or develop over time. May occur following a single dose or prolonged administration as a result from combination therapy.

- All healthcare professionals should report suspected ADRs
- Report adverse experiences with
  - medication, vaccines and biologicals
  - medical devices (including in-vitro diagnostics)
  - complementary / alternative medicines (including traditional, herbal remedies, etc.)
- Report even if
  - you are not certain the product caused the event
  - you do not have all the details
- Reporting forms are available in the wards and at the pharmacy

ADRs reported will contribute to the improvement of medicine safety and therapy in South Africa

Contact Details:
Kalaba Nkonde
Cell: 079 9753 266

Moliehi Maela
Cell: 082 5697 954
Appendices

Appendix 5: ADR poster 2

ADVERSE DRUG REACTION
Would you recognise it?

Is your patient experiencing an **UNEXPECTED** effect from a medication?

Is your patient experiencing **SIDE-EFFECTS** from one of their medications?

Is your patient experiencing an **UNDESIRABLE EFFECT** from drug therapy?

Are you giving your patient one medication because of the **SIDE-EFFECTS** from another medication?

Has your patient developed a new **DRUG ALLERGY**?

Have you had to administer a reversal agent or **PRN ANTIDOTE**?

If you answered **YES** to any of the above questions, then your patient may be experiencing an **ADVERSE DRUG REACTION** that needs to be reported!

Please fill out an ADR report form!

Contact Details:
Kalaba Nkonde
Cell: 079 9753 266

Molelehi Matlala
Cell: 062 5697 954
Appendix 6: Example of completed ADR form

- **Name (or initials):** M. Nkoyane
- **Patient reference Number:** G1000000091
- **Sex:** M
- **Age:** 24
- **DOB:** 24/08/92
- **Weight (kg):** 90
- **Height (cm):** 167

**ADVERSE REACTION/PRODUCT QUALITY PROBLEM**
- **Date of onset of reaction:** 01/03/17
- **Time of onset of reaction:** 18 hour 30 min
- **Description:** Rash all over skin of upper body

**1. MEDICINES/VACCINES/DEVICES**
- **Trade name & Batch No.** (Asterisk suspected product)
  - Flagnyl 100mg 10's
  - Purbide 40mg 10's

**ADVERSE REACTION OUTCOME**
- **Death:** N
- **Disability:** N
- **Congenital anomaly:** N
- **Required intervention:** N
- **Recovery:** Y
- **Sequels:** N
- **Describe:** Rash lead to skin shedding off and burn-like wounds
- **Rechallenge:** N

**COMMENTS:** No previous exposure to medicine

**2. PRODUCT QUALITY PROBLEM**
- **Trade Name:** Turbac D.S.
- **Batch No.:** 43267/5
- **Registration No.:** 27/27/0138
- **Dosage form & strength:** Tablets
- **Expiry date:** 03/2019

**REPORTING HEALTHCARE PROFESSIONAL:**
- **Name:** Smith
- **Qualifications:** BPharm
- **Address:** No. 301 BMS
- **Signature:** B

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

Appendix 7: ADR Checklist

Checklist for the evaluation of the quality and completeness of submitted ADR reports. Criteria are based on the MCC ADR report form.

Study ID: _______________  Date: __________

DEMOGRAPHIC INFORMATION

Health Care Professional:  Nurse☐ Pharmacist☐ Registrar ☐ Clinical Specialist☐ Other ☐ (specify) . . . . . . . . . . . . . . . . . . .

Years of experience:  < 2 years☐ 2-5 years☐ 6-10 years☐ >10 years☐

Unit/Ward:  Pharmacy☐ ICU☐ Burns unit☐ Internal Medicine☐ Paediatrics☐ Obs & Gynae☐ Surgical☐ Renal☐ Spinal☐ Other ☐ (specify). . . . . . . . . . . . . . . . . . .

ADR CHECKLIST

1 = Yes; 0 = No; 2 = N/A (not applicable)

<table>
<thead>
<tr>
<th>Content</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient information</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initials/Reference number</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/Date of Birth</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse drug reaction problem/Product quality problem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Quality problem</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Date of onset of reaction</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of Onset of reaction</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description of reaction or problem</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medicines/vaccines/devices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trade name</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Batch number</strong></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Daily dosage</strong></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Date started</strong></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Date stopped</strong></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Reasons for Use</strong></td>
<td>1</td>
<td>0</td>
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**Adverse reaction outcome**

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**Product Quality Problem**

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**Reporter**

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Appendices

Appendix 8: SMUREC clearance certificate

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

Molotlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/3698 | fax: (012) 521 3749
Email: lorato.phiri@smu.ac.za
P.O. Box 163 Medunsa 0204

APPROVAL NOTICE - NEW APPLICATION

01 September 2016

Ms K Nkonde
Department of Pharmacy
P.O Box 218
Medunsa, 0204

MEETING: 07/2016
SMUREC Ethics Reference Number: SMUREC/H/209/2016: PG

The New Application received on 19 August 2016, was reviewed by members of Sefako Makgatho University Research Ethics Committee 01 September 2016 and was approved on 01 September 2016.

Title: Implementation of interventions to strengthen the pharmacovigilance surveillance system at Dr George Mukhari Academic Hospital, Gauteng Province

Researcher: Ms K Nkonde
Supervisor: Prof JC Meyer
Co-supervisor: Dr M Mafela

Department: Pharmacy
School: Health Care Sciences
Degree: Master of Pharmacy

Please note the following information about your approved research protocol:

Protocol Approval Period: 01 September 2016 – 01 September 2017

Please remember to use your protocol number (SMUREC/H/209/2016: PG) on any documents or correspondence with the REC concerning your research protocol.

Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

International Organisation (IORG0008691), Institutional Review Board (IRB000010386) Expiry date: 09 December 2018, Federal Wide Assurance (FWA000023943) Expiry date: 31 August 2017 and NHREC No: REC 21/04/03

Sincerely

DR C BAKER
DEPUTY CHAIRPERSON SMUREC

Date:
Chief Executive Officer  
Dr George Mukhari Academic Hospital

Dear Sir

RE: Request to conduct a study at Dr George Mukhari Hospital

I am a Master of Pharmacy student and academic intern at Sefako Makgatho Health Sciences University. As part of my post-graduate degree, I am required to conduct a research project. The title of my study is “Implementation of interventions to strengthen the pharmacovigilance surveillance system at Dr George Mukhari Academic Hospital”. The study will only be conducted after ethical approval by the Sefako Makgatho Health Sciences University Research Ethics Committee.

I hereby kindly request your permission to conduct the study at Dr George Mukhari Academic Hospital.

Attached please find a copy of my research protocol for your information. Please do not hesitate to contact me or my supervisors should you require further information.

Thank you for your consideration.

Yours in anticipation

Kalaba Nkonde (Miss)  
0799753266  
29 July 2016

cc: Prof JC Meyer (Supervisor); Tel: (012) 521 4567
Appendices

Appendix 10: DGMAH permission to conduct research

Dr. George Mukhari Academic Hospital

Office of the Director Clinical Services
Enquiries: Dr. PMT. Mabusela
Tel: (012) 529 3880
Fax: (012) 560 0099
Email: philly.mabusela@gauteng.gov.za
kelitumetsa.mongale@gauteng.gov.za

To Ms K Nkonde
Department of Pharmacy
University of Sefako Makgatho Health Sciences
P.O Box 218
MEDUNSA
0204

Date: 09 February 2017

PERMISSION TO CONDUCT RESEARCH

The Dr. George Mukhari Academic Hospital hereby grants you permission to conduct research on "Implementation of interventions to strengthen the pharmacovigilance surveillance system at Dr. George Mukhari Academic Hospital."

This permission is granted subject to the following conditions:

☐ That you obtain Ethical Clearance from the Human Research Ethics Committee of the relevant University
☐ That the Hospital incurs no cost in the course of your research
☐ That access to the staff and patients at the Dr George Mukhari Hospital will not interrupt the daily provision of services.
☐ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.

Yours sincerely

DR. PMT. MABUSELA
DIRECTOR CLINICAL SERVICES
Appendix 11: Letter to National Pharmacovigilance Coordinator

Mr Mukesh Dheda
National Pharmacovigilance Coordinator
National Department of Health

Dear Mr Dheda

RE: Request to have access to electronically submitted adverse drug reaction (ADR) reports

I am a Master of Pharmacy student and academic intern at Sefako Makgatho Health Sciences University. As part of my post-graduate degree, I am required to conduct a research project. The title of my study is “Implementation of interventions to strengthen the pharmacovigilance surveillance system at Dr George Mukhari Academic Hospital”. The study will only be conducted after ethical approval by the Sefako Makgatho University Research Ethics Committee.

As part of the study, I am going to review all ADR reports submitted by health care professionals from Dr George Mukhari Academic Hospital. This will include all paper-based ADR reports, which will be accessed at the hospital, as well as electronically submitted ADR reports. I kindly request your permission to have access to these ADR reports submitted in electronic format by health care professionals from Dr George Mukhari Academic Hospital for the period of the study. All information will be kept confidential and the results of the study will be made available to you with recommendations for future interventions as appropriate.

Attached please find a copy of my research protocol for your information. Please do not hesitate to contact me or my supervisors should you require further information.

Thank you for your consideration.

Yours faithfully

Kalaba Nkonde (Miss)
0799753266
29 July 2016

cc: Prof JC Meyer (Supervisor); Tel: (012) 521 4567
Appendices

Appendix 12: NDoH data user’s agreement

NATIONAL DEPARTMENT OF HEALTH

DATA USER’S AGREEMENT

The National Department of Health, South Africa encourages all interested users to request for Data Sets/Data on projects conducted by or for the Department. Users are however required to read and sign the User’s Agreement for Information, which stipulates the conditions for use of the Data/Data Sets before the requested Data/Data Sets is made available.

Please read the following agreement. All users of all the Data Sets agree to the following conditions listed below. If you accept these conditions, fill in the required information and sign at the appropriate place.

1. The User agrees that the South African Government is the owner of the Data Set(s).
2. The use of these Data Sets in research communication, scholarly papers, journals and the like is encouraged, but the authors of these communications and documents are required to acknowledge/cite the National Department of Health as the source of the Data.
3. The User will be required to provide sufficient detail for which the data will be used for e.g. research proposal, protocol, evaluation methodology etc.
4. The User agrees that he/she will not provide/publish any reports/statements without prior discussion with and permission of the Chief Director for Health Information Management, Monitoring and Evaluation.
5. A copy of any document produced from the Data Set for publication or other forms of circulation should be submitted to the Chief Director for Health Information Management, Monitoring and Evaluation.
6. The User agrees that any use of the Data or reliance by the User or any of the Data is at the User’s own risk and that the National Department of Health shall not be liable for any loss or damage howsoever arising as a result of such use.

7. The User agrees that he/she will not attempt to link nor permit others to attempt to link the records of persons in these Data Sets with personally identifiable records from any other source.

8. The User agrees that he/she will not attempt to use nor permit others to use the Data Sets to establish the identity of any person included in any set.

9. The User agrees that he/she will make no statement nor permit others to make statements indicating or suggesting that interpretations drawn are those of the National Department of Health.

10. PENALTY CLAUSE: The user agrees that non-adherence to the above statements may result in the National Department of Health not making available any datasets to the user in future.
The User agrees that his/her signature indicates his/her agreement to comply with the above-stated requirements (Points 1-9)

**Please complete this form**

<table>
<thead>
<tr>
<th>Data/Set/s for which Agreement is signed (Provide detail list):</th>
<th>Adverse drug reaction reports submitted from Dr George Makhari academic hospital and Sefako Makgatho Health Sciences University for the period 2016-2017 via the app and manually.</th>
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</thead>
<tbody>
<tr>
<td>Name (Print or Type):</td>
<td>Kalaba Nkonde</td>
</tr>
<tr>
<td>Organisation/Department:</td>
<td>School of Pharmacy, Sefako Makgatho Health Sciences University</td>
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<tr>
<td>Position:</td>
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<td>Purpose for which the data will be used (List attachment):</td>
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<tr>
<td>Title (Mr/Mrs/Ms/Dr/Prof):</td>
<td>Ms</td>
</tr>
<tr>
<td>Address:</td>
<td>0109 New Pharmacy Building Sefako Makgatho Health Sciences University</td>
</tr>
<tr>
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<tr>
<td>Fax:</td>
<td>012 521 3992</td>
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<tr>
<td>E-mail:</td>
<td><a href="mailto:kaynkonde@gmail.com">kaynkonde@gmail.com</a></td>
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**For Department of Health use only:**

| Approval by DOH Representative*: | |
| Date: | |

* The Data User’s Agreement must be signed by the Chief Director for Health Information Management, Monitoring and Evaluation.

3/3