KNOWLEDGE, ATTITUDES AND PRACTICES OF COMMUNITY PHARMACISTS IN HARARE REGARDING THE REPORTING OF ADVERSE DRUG REACTIONS

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BY

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DECLARATION

In fulfilment of the requirements of the degree of Master of Pharmacy in the Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Tafadzwa Christine Mafundikwa, declare that:

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ii. This dissertation has not been submitted for any degree or examination at any other university.

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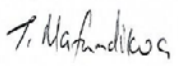
Student Signature: 

Date: 23 November 2017

DEDICATION

This dissertation would not have been completed if it was not for the grace and will of God. This dissertation is dedicated to my husband, Tafadzwa, thank you for your unwavering love and support. To my daughter Kudiwanashe, thank you for your patient and understanding heart. To my parents, thank you for the encouragement and wise counsel and to my sisters, thank you for your belief in me. To my friend Rachel, thank you for walking this journey with me.

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ACRONYMS AND ABBREVIATIONS

ADE – Adverse drug event

ADR - Adverse drug reaction

ARV - Antiretroviral

ASHP - American Society of Health-System Pharmacists

AU - African Union

DPS - Directorate of Pharmacy Services

FDA - Food and Drug Administration (United States of America)

FIP - International Pharmaceutical Federation

GFATM - Global Fund to Fight AIDS, Tuberculosis and Malaria

LMICs - Low- and middle-income countries

MCAZ - Medicines Control Authority of Zimbabwe

MoHCC - Ministry of Health and Child Care

NEPAD - New Partnership for Africa's Development

NMRA - National medicines regulatory authority

PCV - Pharmacovigilance

SADC - Southern African Development Community

SARPAM - Southern African Regional Programme on Access to Medicines and Diagnostics

UMC - Uppsula Monitoring Centre

UN - United Nations

UNICEF - United Nations Children's Fund

WHO - World Health Organization

LIST OF FIGURES

LIST OF TABLES

Table of Contents

ABSTRACT

Background: Adverse drug reactions (ADRs) cause considerable morbidity which contributes significantly to health expenditure. Worldwide, there is under-reporting of ADRs by healthcare workers and Zimbabwe is no exception. In Zimbabwe, ADRs are mainly detected by use of a spontaneous reporting system. There is a greater need for enhanced pharmacovigilance (PCV) in Africa, where weak health systems are likely to contribute to medicine-related harm.

Study Aim: The aim of the study was to contribute to the safe use of medicines by strengthening reporting of adverse drug reactions by pharmacists in Harare, by identifying knowledge, attitudes and practices that hinder their involvement at present. The objectives of the study are to determine if pharmacists practicing in private community pharmacies in Harare, Zimbabwe, know how to identify and when to report ADRs and whether they are reporting ADRs to the relevant authorities. In addition, the study seeks to determine their attitudes towards identification and reporting of ADRs and finally, to make recommendations for interventions to improve the knowledge, attitudes and practices of pharmacists in relation to the identification and reporting of ADRs.

Study Design: The study was designed as an observational, cross-sectional, analytical study. This design was used since it offered a cost-effective way of gathering information from many people in a relatively short period.

Study Population and sampling: The study took place in Harare, Zimbabwe, where over 44% of the country's private community pharmacies are located. A census approach was used as little is known about the subject locally.

Methods: A self-administered questionnaire was designed to establish the socio-demographics of the respondents, their knowledge on ADR reporting and their attitudes and practices regarding ADR reporting. The questionnaires were distributed via electronic mail and at a continuing professional development session to a combined total of 129 community pharmacists. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 16 and Microsoft Excel 2007.

Results: The respondents displayed poor knowledge of ADR reporting and hence there is under-reporting of ADRs. Factors such as post-graduate training and years of experience post- graduation have no bearing on the knowledge possessed by the respondents regarding ADR reporting. Although the respondents showed an appreciation of the importance of ADR reporting, there are barriers such as lack of knowledge and fear of legal liability that prevent pharmacists from reporting ADRs.

Discussion: Lack of knowledge is the main barrier to reporting of ADRs by community pharmacist in Zimbabwe. To address this gap, interventions such as education for community pharmacists are required for both undergraduate pharmacist students and qualified pharmacists.

Conclusion: There is a low level of knowledge and poor attitudes and practices amongst Zimbabwean pharmacists with respect to ADR reporting. Multi-sectoral interventions are required to overcome the barriers that community pharmacists encounter in reporting ADRs.

CHAPTER 1: INTRODUCTION

1.1 Introduction

This chapter serves to introduce the concept of pharmacovigilance, show how the concept has been developed globally, and then provide background material on the organisation of the health system in Zimbabwe. Finally, it introduces the problem addressed by this study and lists the aims and specific objectives.

1.2 Background

For all medicines, there is a fine balance between the anticipated benefits and potential harm. Besides their intended pharmacological effects, medicines produce unwanted, side effects which are defined as any unintended effects of a pharmaceutical product occurring at normal dosage which is related to the pharmacological effect of the drug (World Health Organization, 2015). Such side effects are also termed adverse drug reactions (ADRs). Depending upon the severity, ADRs can cause hospitalization or death. In developing countries, most ADRs go undetected. It was estimated that they are the fourth to sixth leading cause of death in the United States in 1994 (Lazarou *et al*., 1998).

ADRs also cause considerable morbidity and, in Europe, it is estimated that approximately 5% of all hospital admissions are due to ADRs. A survey conducted in South Africa approximates 1 in 12 hospital admissions, which is about 8%, are because of an ADR (Mouton *et al*., 2016). In addition, 5% of hospitalised patients will experience an ADR during their stay in hospital and 197 000 deaths can be attributed to an ADR (Bouvy and DeBruin, 2015). In 2000, in the United States of America, it was estimated that $177.4 billion in healthcare expenditure could be attributed to ADRs (Ernst and Grizzle, 2001).

Whenever new medicines have been introduced into the market or there is a change in prescribing practices, this has resulted in an increased need for post-marketing safety surveillance studies and related activities, also known collectively as pharmacovigilance (PCV).

There are many benefits in conducting post-marketing surveillance of the effects of medicines once they are utilised clinically and at scale, compared to during clinical trials. These benefits include the determination of ADR incidence in real-world settings, and measuring the economic impact of ADR prevention as seen through reduced hospitalisation, optimal and economical medicines use (American Society of Health System Pharmacists, 1995). Put another way, the “PCV system safeguards the public through efficient and timely identification, collection, and assessment of medicine-related adverse events and by communicating risks and benefits to support decision making about medicines at various levels of the health care system” (Mobile Health Without Borders, nd).

Researchers (Lopez-Gonzalez *et al*., 2015) have cited various reasons for the under-reporting of ADRs in various settings, and these mostly reflect the level of knowledge, attitudes and practices of medical

practitioners in particular, although other health professionals are also implicated. Examples of such reasons include:

- lack of financial incentives;
- fear of legal proceedings;
- lack of knowledge with regard to the guidelines/regulations on ADR reporting.

In Africa, it has been reported that insufficient and inadequate resources to monitor the safety of medicines; the unreliable supply of quality, safe, and effective medicines; the lack of trained health workers; and the weak state of the health systems are more likely to contribute to significant medicines-related harm (Mobile Health Without Borders, nd). There is therefore in Africa, a greater need for PCV, because most medicines are produced in developed countries and their safety profiles may not be applicable to African or other settings. With the high disease burden evident in Africa, and with vulnerable populations receiving antiretrovirals (ARVs) for instance, it is important to scale up PCV activities to prevent unnecessary morbidity and mortality.

Other than morbidity and mortality, there are also economic consequences of ADRs, which constitute significant costs to the health system. These include the impact of ADRs on patient adherence to treatment regimes, drug resistance, and treatment outcomes, including loss of confidence in the health system. All of these consequences will impact negatively on the efficiency and effectiveness of resource–constrained health systems in particular.

1.3 Concept of Pharmacovigilance

Pharmacovigilance, ‘’the science of activities relating to the detection, assessment, understanding, and prevention of adverse drug reactions or any other drug-related problems’’ evolved in the mid-1900s (WHO, 2002). The most important part of PCV is to collect extensive data related to a medicine's actions throughout the product life cycle, both pre-market (prior to marketing authorisation, reflecting clinical trial experience) and post-market (after marketing authorisation is granted, and the medicine is used both for its labelled and for off-label indications and in a wider variety of patients and settings).

Fainzang (2010) notes that "PCV covers all activities aimed at detecting, evaluating, quantifying, preventing the harmful effects of drugs, and at optimizing the benefit-risk ratio through adapted, individual or collective decisions: to prescribe a drug or not, to adapt or to interrupt a treatment, to modify the indications of the drug or the information given to doctors or patients, or even to withdraw the drug from the market’’. This definition clearly shows that medicines safety needs to engage both health care professionals and patients.

Medicines are highly regulated products in many countries and medicine regulation promotes and protects public health by ensuring that medicines are of the required quality, safety and efficacy. A new medicine must therefore pass three hurdles before receiving approval from the national medicines regulatory authority (NMRA). These are: there must be enough evidence to prove the new medicine is safe for the purposes it is proposed, effective for the proposed indication, and of good quality (World Health Organization, 2015).

Before a new medicine is registered (or receives marketing authorisation), it undergoes a series of clinical trials to determine its safety and efficacy. It is during all three phases (1, 2 and 3) of clinical trials in human subjects that adverse effects are identified. The United States Food and Drug Administration (FDA) considers a medicine to be safe for use when the benefits outweigh the known risks (Food and Drug Administration, 2015). Clinical trials are limited in terms of time, number and type of patients involved. However, after successful completion of pivotal phase 3 trials, the medicine may be approved for marketing and therefore enter phase 4, the post-marketing phase. During this last phase, there should be monitoring of the effectiveness of the medicine in the general population and of the adverse effects that emerge with widespread use over a prolonged period of time, particularly in patient populations that may have been excluded from clinical trials. These groups may include the young, the elderly, pregnant and lactating women, those with co-morbid conditions, and those also taking other medicines that may interact with the medicine in question. Despite all the studies carried out before a medicine is marketed, no medicine is ever 100 percent safe. The risks of suffering an adverse drug reaction can be exacerbated by interpersonal physiological differences such as genetic makeup, body size and concomitant use of other medicines. As a result, a medicine might cause someone to suffer a side effect that someone else taking the same medicine would not have experienced.

The WHO is currently pursuing harmonisation of activities related to medicines regulation. This has been necessitated by the increase in the global trade of pharmaceutical products and the rise in complexity of technical regulations related to medicines safety and quality. In Africa, scarcity of regulatory resources has prompted the creation of the African Medicines Regulatory Harmonisation (AMHR) programme, which aims to strengthen capacity building efforts and harmonisation of regulatory requirements. In the Southern African Development Community (SADC) region, harmonisation efforts are coordinated by Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM). Notable achievements of SARPAM include the development of a SADC Medicines Regulatory Strategic Framework. Within this initiative, the ZAZIBONA process was initiated in 2013. This was initially a process of collaboration between the national medicines regulatory authorities (NMRAs) in Zambia, Zimbabwe, Botswana and Namibia (hence the acronym, based on the first two letters of each country's name) to facilitate the provision of good quality medicines through work sharing of regulatory processes (Luthuli and Robles, 2017). Membership of the initiative has been broadened to include South Africa, requiring a renaming as Zazibona (not an acronym, *per se*), but retaining the work-sharing approach. Meetings are held to jointly assess dossiers submitted for marketing authorisation, but the ultimate registration decision remains with each NMRA.

In an effort to further consolidate harmonisation across the African content, the African Union, (AU) in January 2016 endorsed the AU Model Law on Medical Products Regulation (United Nations Development Programme, 2017). This law was developed as a result of a partnership between AU, New Partnership for Africa's Development (NEPAD) and other key partners. There are plans to create an African Medicines Agency, which will have a co-ordination role rather than being a supranational MRA along European lines. For the foreseeable future, NMRAs will remain key institutions in each country, ensuring the safety of the public in relation to the use of medicines.

In Zimbabwe, the Medicines Control Authority of Zimbabwe (MCAZ) is the local NMRA. The Authority regulates medicines through evaluation and registration of all medicines that are marketed in the country, licensing of all premises and personnel who handle medicines, and enforcing compliance, authorising and overseeing clinical trials, conducting and promoting PCV and conducting analytical work on medicines (Medicines Control Authority of Zimbabwe, 2016). No medicine can be used legally in Zimbabwe until the MCAZ issues a marketing authorisation for its use.

1.4 Establishment of ADR reporting systems in countries

A brief review of unfortunate events associated with medicines in the past will highlight the importance of PCV. In 1937, Elixir Sulfanilamide reportedly caused the death of over 100 patients across 15 American states. Sulfanilamide had been shown to be very effective in treating streptococcal infections and had been used safely in tablet and powder form. The demand for a liquid formulation of the drug resulted in it being made using diethylene glycol, a chemical used as antifreeze, as it resulted in a product that had good texture, taste and fragrance. No toxicity studies where done on the new formulation as it was not a legal requirement at that time. Soon after the elixir was first distributed, reports of deaths after using the formulation were received. Diethylene glycol was isolated as the toxic ingredient and the FDA, which had been in place from 1908, but with a focus on product purity (quality) not safety, immediately recalled the product from the market. Intriguingly, the basis for the recall was actually the lack of alcohol in the formulation, which rendered the “elixir” name misleading. This episode accelerated the final enactment of the Federal Food, Drug, and Cosmetics Act 1938, and an extension of the remit of the FDA to include safety issues (Ballentine, 1981). However, marketers of medicines were still not required to provide evidence of efficacy prior to marketing.

In the 1950s, thalidomide was marketed as a safe sedative, and included in a number of fixed-dose combination preparations for varying indications. It was also discovered that it alleviated the symptoms of morning sickness in pregnant women and this off-label use was recommended to many pregnant women worldwide. In 1961, it was discovered that the drug led to severe birth defects in children, and in particular the unique adverse effect of phocomelia, which resulted in shortened, absent or flipper-like limbs. In this major drug disaster, approximately 10 000 children were affected across a number of countries (Asberg, 2011). This event became known as the thalidomide disaster or tragedy and it resulted in the first international efforts to address drug safety issues (Bara *et al*., 2009). The thalidomide tragedy is one on the greatest of all adverse drug reaction disasters to date. It resulted in the Harris-Kefauver amendments to US legislation, extending the remit of the FDA to include consideration of efficacy data prior to marketing authorisation. This development was also the spur for similar legislative reforms in many developed and developing countries, and the establishment of the 3-fold hurdle of quality, safety and efficacy (QSE), which need to be satisfied before a medicine can be released onto the market.

After the thalidomide disaster, a project was started with six countries to convey spontaneous ADR reports to the World Health Organization (WHO). Today, the centre for the WHO’s international database is situated in Uppsala, Sweden. Currently, the database contains almost eight million such spontaneous reports and over 100 countries are reporting ADRs to the Uppsala Monitoring Centre (UMC) (WHO-UMC, 2015).

Despite regulatory advances, safety problems have continued to emerge. In Australia in 1960, for example, phenytoin toxicity was enhanced when during production, lactose was used as the excipient in place of calcium sulphate. Phenytoin had been previously used with success in the past as an anticonvulsant when it was made using calcium sulphate as an excipient. It was believed then that the change in excipients would not cause any challenge since they are not active ingredients. However, the substitution resulted in an increase in the bioavailabilty of phenytoin and thus increased toxicity (Ramanujam, 1997).

Zimbabwe, which is the reference country of this study, became a member of the WHO International Drug Monitoring programme in 1998, through the MCAZ. The MCAZ also serves as the country's PCV centre and the operations are based on WHO guidelines for running a national PCV centre. The MCAZ has in the past reported issues of under-reporting of ADRs by practitioners and has been trying to increase awareness and promote reporting (Medicines Control Authority of Zimbabwe, 2016).

In spite of the many studies carried out in many countries, there is lack of adequate information on the knowledge, attitudes and practices (KAP) of pharmacists in Zimbabwe with regard to ADR reporting. This study was thereforedesigned to evaluate the KAP of Zimbabwean pharmacists with regard to ADR reporting.

1.5 Global Response to the challenge of Pharmacovigilance

In 1997, the Erice Declaration was drawn up by all stakeholders in the medicine safety fraternity (Hugman, 2005). The Declaration concluded that all the primary goals of public safety in medicine use could be achieved through open, transparent, effective and ethical communication of medicine safety issues. It seeks to promote confidence and trust among all levels of society in issues of medicine safety. In addition, it also encourages the provision of education in the appropriate use of medicines and emphasises how to correctly interpret information on safety for the public and healthcare providers.

The Declaration states that patients have a right of access to high quality, up-to-date information pertaining to the benefits, risks and effectiveness of medicines. This information should clearly distinguish between facts, hypotheses and conclusions and areas of uncertainty should be clearly defined. In light of this, the participants at Erice agreed that it is essential for every country to have an adequately financed system with independent expertise to ensure that medicine safety information is adequately collected and disseminated to the public. There should also be exchange of data and evaluations at international level.

The Uppsala Monitoring Centre (UMC), which is an independent WHO Collaborating Centre, was established to screen and analyse international adverse reaction data. Their aim is to detect, as early as possible, potential issues of importance for patients and public health in relation to the use and safety of medicines. The Centre also provides education and training on the operation of national PCV programmes and supports effective communication of the most focussed, up-to-date scientific information. The UMC has ensured that PCV is now based on sound scientific principles and is integral to effective clinical practice (WHO-UMC, 2015).

The WHO (2002) notes that spontaneous reporting of ADRs remains a cornerstone of PCV and is indispensable for signal detection. It also states that in daily practice, medical practitioners report very few adverse effects which are caused by medicines, with only 5% of health practitioners estimated to participate in PCV activities. The spontaneous reporting system relies on vigilant physicians and other healthcare professionals who not only generate a suspicion of an ADR, but also report it.Reporting of ADRs is crucial as it assists in detecting unexpected and unusual reactions that were missed in the initial phases of drug development (such as during clinical trials in human subjects) and the process provides a way to continuously assess the benefit-risk ratio of medicines during real-time use (Elkami and Hassali, 2013).

The PCV systems in many low- and middle-income countries (LMICs) are weak and fragmented and not in a position to protect public health (Systems for Improved Access to Pharmaceuticals and Services (SIAPS), nd). The weak regulatory system results in substandard and falsified medicines penetrating the supply chain, which have the potential to compromise human health. Olsson *et al*. (2015) noted that few LMICs have fully functional PCV systems and therefore reliable, scientific data on medicine-related harm and the preventability of such harm is largely missing in such settings. Under-reporting of ADRs has been reported in LMICs because healthcare professionals are few and the patient burden is high. This leaves little or no time to report ADRs. In addition, distribution and returning of completed ADR forms can be expensive and in many LMICs, postal services and electronic networks are not reliable.

Olsson *et al*. (2015) also highlighted that very few LMICs have the capacity to collect relevant and sufficient local safety information to inform and the capacity to carry out independent benefit/harm assessments. It is because of this observation that they suggest that LMICs focus primarily on detecting high- burden preventable ADRs instead of attempting to find problems that are completely new. That said, some medicines (such as those for malaria or neglected tropical diseases) may only be used in LMIC settings, so spontaneous reports from such settings may be the only way in which such data can be generated, and novel signals detected.

In Europe, however, PCV activities are synchronised and collaborated between the European Medicines Agency (EMA), the European Commission and medicines regulatory authorities of member states of the European Economic Area (EEA). The PCV system is driven by the member states which maintain the inspectorates, ensuring that medicines manufactured and marketed in the European Union (EU) are of the desired quality, and the PCV systems of the industry. Such systems are functioning at a high level, if not entirely faultlessly. The European Commission and the EMA cooperate and coordinate with other international regulators in an effort to standardise approaches and requirements. In line with the Erice Declaration, there is transparency and effective dissemination of accurate safety information to the EU public (European Commission, 2016).

1.6 Responsibilities of various actors

The European Union (EU) has clearly defined the role of the patient and the healthcare provider in the PCV system. The patient's role in reporting ADRs is crucial to building a better PCV system. It has been shown that

reports from the patient are as valuable as those from healthcare professionals and they can be better, in the sense that they may provide details in depth (European Patients Forum, 2012).

The healthcare professional's role is to identify and report all cases of suspected ADRs to the authorities. In addition, the healthcare provider should seek to build a patient- healthcare professional relationship based on trust and mutual respect. Such a relationship will encourage the patient to have the confidence to discuss and report the effects their medicines are having on him/her (European Patients Forum, 2012).

The manufacturer is suitably placed to contribute to medicines safety monitoring from the beginning of the development of the new medicine and throughout its lifetime (World Health Organization, 2016). It is the role of the manufacturer to actively seek and collect information on adverse effects and report these to the monitoring centres (Association of British Pharmaceutical Industry, 2005). There is an increasing requirement for post-approval monitoring that is being set by NMRAs and there is need for continuous communication and information exchange between regulatory authorities and the industry (World Health Organization, 2016).

1.7 Healthcare in Zimbabwe

The Zimbabwe healthcare system is somewhat fragmented, and can be described as comprising a public sector, not-for-profit groups, church organisations, private sector company-operated clinics, and for-profit organisations. In addition, a traditional medicine sector also exists in parallel with the formal health sector, and provides traditional African treatment for different ailments. The majority of Zimbabweans, however, are catered for by the public health sector. The Financial Gazette (2016) reported that about 1.3 million people in Zimbabwe, or 8.7% of the population, have healthcare insurance. This figure is mainly comprised of people who work in the formal sector, including their beneficiaries. Most medical insurance holders access healthcare services in the private sector, although a few are accepted in the public sector,

The Ministry of Health and Child Care (MoHCC) provides guidance for policy and administration, system-related decision-making, human resources planning, surveillance, monitoring and evaluation, regulation and co-ordinating responses to national health issues such as disease outbreaks. Health service delivery in the country has been severely weakened as a result of the country's economic meltdown (World Bank, 1998). The health care system is still recovering from the effects of the economic challenges and continues to face serious difficulties such as reduced budget allocations and emigration of healthcare personnel (Osika*et al*., 2010). In 2016, the MoHCC was allocated 8.3% of the national budget. This allocation is below the Abuja-stipulated target of 15%, to which African Health Ministers have committed themselves, and also below the sub-Saharan average of 11.3% (United Nations Children's Fund, 2016). The same report from United Nations Children's Fund (UNICEF) stated that a 30% staff vacancy rate was reported in 2016 across public health institutions because of the skills flight that the country has been experiencing in recent years, in light of the prevailing economic challenges.

Health delivery services in the public sector are decentralised, with primary, secondary, tertiary and quaternary levels. The primary level provides basic curative and preventative services, and maternity health care, and is the first port of call for patients, especially those in the rural areas. It consists of small clinics

which work with the support of village health workers (VHWs) and community-based distributors. In many countries, community pharmacies are also considered to be part of the primary care level. In Zimbabwe, there is a skewed pattern in the distribution of community pharmacists, with the majority of community pharmacists based in urban areas.

The secondary level represents about 3.6% of all health facilities in the health care system (Osika*et al*., 2010) and consists of district hospitals and some mission hospitals. These hospitals receive referrals from the primary care facilities. District hospitals also provide primary health care in the communities they serve.

Seven provincial hospitals make up the tertiary level. Hospitals in this level treat referrals from lower health facilities and they have specialists on their staff complement to deal with complicated medical issues. Due to skills flight, junior doctors now man most of the tertiary institutions and attend to serious cases that really should be managed by specialists.

Lastly, there are six central hospitals in the country, which make up the quaternary level of care. This is the highest level of service provision. The central hospitals have the highest number of specialists and clinicians, and have the most advanced equipment and access to the most advanced pharmaceuticals.

In addition, there are private hospitals and clinics, which are beyond the financial reach of most Zimbabweans. In total, they account for less than 1% of all health facilities in Zimbabwe.

The distribution chain for medicines in the private sector is independent and different from that in the public sector. In the private sector, as represented by community pharmacies, private hospitals/clinics and dispensing practitioners, medicines are procured from local wholesalers or directly from local manufacturers or suppliers (importers of finished pharmaceutical products). Such medicines will all be authorised by the MCAZ prior to being put on the market. In the public sector, the procurement of medicines is both centralised and decentralised. The central medical stores, referred to as National Pharmaceuticals (NatPharm), procures for the public sector, using funds allocated to them from the fiscus (DPS, MoHCC, 2011). Such medicines are all registered by MCAZ and procured from local manufacturers or suppliers that are licensed to operate in the country. However, the nation has increasingly become reliant on donor funds and there are medicines that are imported into Zimbabwe by partners such asThe Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) andThe United Nations Children's Fund (UNICEF) for use predominantly in the public sector, but also by non-governmental organisations (NGOs). In an effort to facilitate access to key medicines such as ARVs, the WHO provides United Nations (UN) agencies with advice on the safety and quality of medicines in principle for procurement, a process known as prequalification. Donor-provided medicines may therefore not be registered by MCAZ. WHO prequalification does not necessarily mean WHO-approved and as such, it remains the responsibility of the NMRAs to ascertain efficacy and most importantly, safety of medicines that enter the local market as donations. PCV remains, therefore, very important to assess the quality, safety and efficacy of the medicines on the local market.

1.8 Problem statement

The insufficient and inadequate resources to monitor safety of medicines, the unreliable supply of quality, safe, and effective medicines, the lack of trained health workers; and the weak state of the health systems in many parts of Africa, create a greater need to promote and monitor the safety and effectiveness of medicines. In addition, the high disease burden has resulted in increased availability of new essential medicines such as artemisinin-based combination therapy (ACT) for malaria and ARVs for HIV. Achieving the full benefits of these new medicines may be hindered by the burden of adverse events from poor product quality, ADRs and medication errors.

In a bid to promote and monitor the safety and effectiveness of current and new medicines, a number of studies have been undertaken to establish the knowledge, attitudes and practices of healthcare professionals in various settings when it comes to ADRs and their reporting (Khoza *et al*., 2004; Khalili *et al*., 2012). Most of these studies indicate that there is under-reporting of the incidence of ADRs. However, few seem to have been conducted with community pharmacists only, despite the fact that such pharmacists are normally the last point of contact with a patient in the healthcare system, and are in a position to be the first to receive reports of ADRs.

Nonetheless, a study conducted in the United Kingdom, concluded that community pharmacists and their staff would be unlikely to report adverse drug reactions if they witnessed them occurring in patients served in that setting (Ashcroft, 2006).

The research question is therefore: **"**What do pharmacists in private community pharmacies in Zimbabwe know regarding ADRs and what are the attitudes, beliefs and practices of pharmacists regarding the reporting of ADRs?".

1.9 Purpose of the research

An assessment of knowledge, attitudes, and practices will help identify areas where education and information efforts are required.

1.10 Aims and objectives

The broad aim and specific objectives of this study were therefore as follows:

Aim:

The aim of the study is to contribute to the safe use of medicines by strengthening the reporting of adverse drug reactions by pharmacists in Harare, Zimbabwe, by identifying knowledge, attitudes and practices that hinder their involvement at present.

Specific objectives

1. To determine if pharmacists practising in the private community pharmacy sector in Harare, Zimbabwe, know how to identify and when to report an adverse drug reaction.
2. To determine the attitudes of pharmacists practising in the private community pharmacy sector in Harare, Zimbabwe, towards the identification and reporting of adverse drug reactions.
3. To determine whether pharmacists practising in the private community pharmacy sector in Harare, Zimbabwe, are currently reporting adverse drug reactions to the relevant authorities.
4. To make recommendations for interventions targeted at improving the knowledge, attitudes and practices of Zimbabwean private community pharmacists in relation to the identification and reporting of adverse drug reactions.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter presents the review of literature which has informed the design and implementation of this study. It illustrates the conceptual framework and provides definitions of the terms used, including adverse drug reaction (ADR), knowledge, attitudes and practices.

2.2 Impact of pharmacovigilance

Although the importance of pharmacovigilance (PCV) has been clearly established, assessment of the impact of PCV activities/programmes is less commonly undertaken. The European Medicines Agency (2016) states that there are two principle reasons why it is prudent to measure the impact of PCV activities. Firstly, the information can be used to inform the review of the benefit-risk profile of individual medicines that have been undergoing risk minimisation efforts, and secondly, this information will contribute to the development of proactive PCV systems by informing regulators about the activities that are successful and those that are not effective in generating positive health and economic impacts. Proactive approaches would allow for early detection and risk minimisation of ADRs throughout a medicine's lifecycle (McNaughton *et al*., 2014).

Several medicines have been withdrawn from the market for safety reasons after receiving initial marketing authorisation. The most high-profile incident involved rofecoxib (most commonly marketed as Vioxx®), an anti-inflammatory medicine, which was withdrawn from the US market in 2004 following findings that it may cause an increased risk of cardiac events such as stroke (FDA, 2004). Other countries and NMRAs quickly followed suit and withdrew marketing authorisation in their jurisdictions.

2.3 Definition of Adverse Drug Reactions

An adverse drug reaction (ADR), also referred to as an adverse medicine reaction, is a "reaction to a medicinal substance that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (World Health Organization, 2015). In common parlance, ADRs are also referred to as "side effects", signifying that these are effects that are incidental to, and different from, the intended therapeutic effects of the medicine. In the written materials provided both to professionals and patients, adverse drug reactions are listed, and these also inform and shape the warnings and special precautions that are listed for all patients and for particular sub-populations (e.g. the very young, elderly, pregnant and lactating women, those with specific organ dysfunction, those taking other medicines).

An ADR is therefore a negative patient outcome that can be attributed to the therapy. Lack of effect from therapy is also considered an ADR. Side effects are not all negative and can have positive effects, such as the reduction of testosterone accompanying use of oral contraceptives which may result in a reduction in acne symptoms (Ebede *et al*., 2009). Such effects are referred to as pleiotropic.

By contrast, an adverse drug event (ADE) is defined by the UMC (2017) as any negative or harmful occurrence that presents during treatment that may, or may not be associated with a medicine. The difference lies in the certainty of causality. In other words, all ADRs are ADEs, but not all ADEs are ADRs.

ADEs can also result from medication errors, which in turn can be a result of errors in prescribing, dispensing, counselling, distribution and use of the medicine. A medication error is any preventable event that occurs while the medication is in the control of the patient or a healthcare professional, which may lead to the inappropriate use of the medication or harm to the patient (National Research Council [NRC], 2007). Importantly, medication errors are all potentially preventable. Not all ADEs (or ADRs) are preventable. Toxicity that results from an overdose (whether resulting from a prescribing error, dispensing error, administration error or patient error) is a preventable medication error, but not an ADR. By contrast, toxicity that results from exposure to the correct or normal dose would be considered an ADE, and if causally related to the medicine in question, an ADR. The assessment of causality is a non-trivial task that forms a key component of PCV practice.

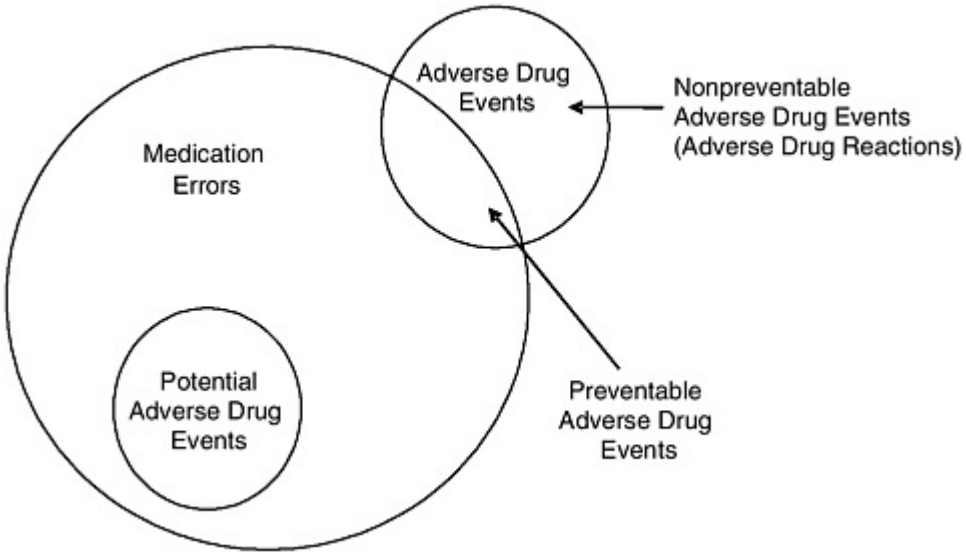

Figure 2.1: Relationship between adverse drug events and medication errors (NRC, 2007)

2.4 Classification of Adverse Drug Reactions

Classification of ADRs is important because it assists with describing and quantifying data, identifying causative agents to determine trends, identifying those medicines that tend to cause severe reactions, and allowing for remedial activities to be prioritised. Classification also assists with the regulation of medicines, as pre-licensing studies can reveal certain types of reactions that are amendable to remedial action, such as the recommendation of doses that can be titrated to levels that are safer for humans. Classification of ADRs is

done to by the UMC as part of processing of ADR reports from the member states of the WHO Programme for International Drug Monitoring (Hugman, 2005). However, some countries like the United Kingdom have well established PCV systems that can classify the reported ADRs themselves.

2.4.1 Pharmacological Classification

The pharmacological classification initially proposed by Rawlings and Thompson classifies ADRs on the basis of two characteristics: dose-dependency and predictability (Palaian *et al.,* 2006).

Type A reactions are dose-dependent and predictable from what is already known pharmacologically about the drug. Type A reactions are normally reversible if use of the medicine is reduced or stopped. Examples of Type A reactions include constipation due to opioid use and dry mouth associated with the use of tricyclic antidepressants and other medicines with anticholinergic effects.

By contrast, Type B reactions are relatively uncommon, unpredictable and not dose-dependent. An example of a Type B reaction is an anaphylactic reaction to penicillin.

Aronson and Ferner (2003) have highlighted some limitations with the Rawlings and Thompson pharmacological classification system. For example, there are certain types of reactions that are comfortably classified by the system, such as asthma associated with the use of β-adrenoceptor antagonists, which do not occur in all patients even at the same dose. In addition, all reactions that cannot be classified as Type A are classified as Type B. This makes the reactions in Type B group highly varied, with almost nothing in common. As a result, the above classification has been further extended to cater for all types of reactions.

2.4.2 Expanded Classification

ADRs can also be classified into nine types, using the Wills and Brown classification method (Angeline and Prerumaloo, 2015). The nine types are:

- Type A (Augmented) - these are relatively common, are pharmacologically predictable, are dose related and improve if medicine is withdrawn. An example of a type A reaction is hypoglycaemia resulting from the use of sulfonylureas.
- Type B (Bizarre) - these are pharmacologically predictable, involve interaction with a microorganism and improve if the medicine is withdrawn. Resistance due to overuse of a particular antibiotic is an example.
- Type C (Chemical,) - these are related to the concentration of the medicine and an irritant reaction is observed, such as thrombophlebitis after intravenous infusion of amphotericin B.
- Type D (Delivery) – these are caused by the method of administration or the nature of the formulation; they improve if the medicine is withdrawn or if there is a change in the method of delivery for instance inflammation or infection around a sub-dermal implant.
- Type E (Exit) - these are pharmacologically predictable, but begin when the dose is reduced or the medicine is stopped, and thus improve if the medicine is reintroduced. Withdrawal symptoms from opioids and benzodiazepines are examples of type E reactions.

- Type F (Familial) – these occur only in the genetically predisposed population such as haemolytic anaemia associated with the use of primaquine in a patient with glucose-6-phosphate dehydrogenase deficiency.
- Type G (Genotoxicity) - these are reactions which result in irreversible genetic damage. Genotoxic substances are potentially mutagenic and carcinogenic, such as the alkylating agents.
- Type H (Hypersensitivity) – these reactions require activation of the immune system, and improve when the medicine is withdrawn. Hypersensitivity reactions to the sulfonamides can be classified this way.
- Type U (Unclassified) - these are ADRs for which the mechanism is not understood e.g. taste disturbances whilst on treatment with simvastatin.

The Wills and Brown classification attempts to differentiate adverse reactions that would have been classified as Type B by the Rawlins and Brown classification. The Wills and Brown classification therefore attempts to classify ADRs into homogenous groups, rather than to combine many different types into a single category (Type B). The classification is therefore more informative, but more challenging to apply and requires greater insight into the mechanism of the adverse reaction, even though an “unclassified” option remains.

2.5 Assessing the Causality of Adverse Drug Reactions

In the event of an adverse drug reaction having occurred, it is imperative to establish and ascertain the causality of the ADR to avoid ambiguity of data, improve scientific evaluation and to ensure consistency of reporting. Causality assessments are nonetheless applied retrospectively, and can therefore not distinguish with absolute certainty between valid and invalid cases or prove a causal relationship between a medicine and an event. They remain a value judgment, informed by evidence. Several causality methods have been used to assess the relationship between an adverse event and a medicine to ascertain the distinction between and ADE and ADR. These include;

- WHO-UMC Probability Scale
- Naranjo’s ADR scale (algorithmic)
- The Shumock and Thornton Criteria for determining predictability of an ADR (Padmavathi *et al*., 2013)

No method is used universally, but the WHO-UMC Probability Scale and the Naranjo scale are more widely used. The scales are each provided as an Annex (Annexes 1, 2 and 3).

2.5.1 The WHO-UMC Probability Scale

The WHO-UMC assessment tool was developed in consultation with National Centres which are part of the Program for International Drug Monitoring. The tool takes into consideration the clinical-pharmacological aspects of the case history and the quality of the observation documentation. Criteria for causality are categorised into certain, probable, possible, unlikely, unclassified, and unclassifiable. The WHO-UMC scale is considered simple and easy to use (Belhekar *et al*., 2014). This method is, however, likely to be prejudiced by subjectivity, which will in turn affect reproducibility.

2.5.2 The Naranjo Scale

In an effort to address the issue of lack of standardisation of causality, Naranjo developed an assessment tool popularly known as The Naranjo Scale or Algorithm. The scale is categorised into definite, probable, possible and unlikely. In comparison to other causality algorithms, the Naranjo scale is considered to be brief and simple. It is used by the PCV centres of several countries. However, this scale is not without disadvantages, and in particular it has been shown not to be easily reproducible (Kahn *et al*., 2016).

2.5.3 The Shumock and Thornton Criteria

The Shumock and Thornton scale classifies preventability of ADRs into definitely preventable, probably preventable and unpreventable. The classification is done using a tool that was developed by Shumock and Thornton with a set of questions to determine to which criteria the ADR belongs.

2.6 Assessing the Severity of Adverse Drug Reactions

In addition, to the causality assessments, ADRs can be assessed in terms of severity. Severity can be classified as mild, moderate, severe and lethal. The minor ADRs do not require a change in therapy or administration of an antidote or other medicine to manage the adverse reaction, and do not result in increased or extended hospitalisation.

Moderate ADRs require a change in therapy, an antidote or symptomatic treatment, and might require additional hospitalisation by at least one day.

Adverse drug reactions that are considered to be severe are potentially life-threatening, require intensive medical care and have the potential to cause permanent harm to the patient.

Lastly, there are lethal ADRs, which result in the death of a patient.

Scales that have been used to assess severity include the Karch and Lasagna assessment scale and the ADR Severity Assessment (Hartwig and Siegel) scale.

The ADR Severity Assessment scale is depicted in Annex 4. In Zimbabwe, expert causality assessments of reported cases are carried out at the MCAZ by the Pharmacovigilance and Clinical Trials Committee (PVCT).

2.7 Predisposing Factors to Adverse Drug Reactions

There are many factors that affect the incidence of ADRs in different individuals. A review article by Alomar (2013) indicated that pharmacological, immunological and genetic variables are involved in the pathogenesis of ADRs. Drug interactions, pharmacodynamic and/or pharmacokinetic abnormalities, medicines formulation differences, and dosing variances may induce pharmacological ADRs. An example of such an ADR is hypoglycemia associated with the use of the sulfonylureas, at the normal doses prescribed to patients with type 2 diabetes mellitus.

Genetic variables such as ethnicity have also been found to play a role in induction of ADRs, although this is still under debate. For example, black patients have been reported to be three times more likely to suffer from angio-oedema whilst taking angiotensin converting enzyme inhibitor (ACE-I) antihypertensives as compared to non-blacks (McDowell *et al*., 2006). The same systematic reviewalso showed that East Asian patients were three times more likely to suffer a cough from ACE-I antihypertensives as compared to whites. Another study found Caucasians to be at higher risk of suffering for abacavir hypersensitivity reactions as compared to any other race, a difference which relates to the differential incidence of a specific genetic variability (Alomar, 2013).

Physiological factors such as age, gender, weight, pre-exisiting comorbidities and concomitant medicinesuse also alter a patient's susceptibility to ADRs. In the review by Alomar (2013), females where reported to be at a higher risk of developing hepatotoxicity in hepatic drug reactions. This is possibly due to women having higher levels and activity of the enzyme CYP 3A4 in comparison to men.

Angeline and Prerumaloo (2015) have noted that the elderly and the young aged between one to four years are more susceptible to ADRs because clinical trials do not focus on them. The difference here is not just physiological, but due to the increased risk associated with medicines use in the absence of evidence. However, in addition, the young have an immature physiological system, still under development, and the elderly have reduced liver and renal function making them particularly prone to Type A ADRs.

During pregnancy, there are changes to the pharmacokinetic and pharmacodynamic profiles of medicines that might affect the mother and the foetus. The mother's gastric tone, acidity and motility are reduced during pregnancy and this in turn affects the absorption, distribution, metabolism and excretion (ADME) of medicines.

The use of many medicines at the same time, also known as polypharmacy, increases the likelihood of an ADR. The risk of drug interactions increases with the number of medicines been taken concurrently. For instance, the use of anti-depressants together with antihistamines and antiepileptics may cause severe drowsiness (Tanzania Food and Drug Authority, 2006).

2.8 Reporting of Adverse Drug Reactions

According to WHO, it is the professional responsibility of all healthcare professionals to report ADRs as they are in the best position to detect and report on these events (World Health Organization, 2002). ADR reporting is done by two basic methods, namely spontaneous reporting and intensive reporting. Spontaneous reporting is a system whereby reports of suspected ADR cases are voluntarily submitted to the national PCV centre by healthcare professionals, either directly or via pharmaceutical companies, or by the public (patients or carers). Spontaneous reports are now also known as Individual Case Safety Reports (ICSRs). Intensive reporting, also known as cohort event monitoring, involves prospective studies done on patients who have taken or are taking the medicine of interest. All or specific adverse events in these patients are recorded over time in a planned manner (WHO-UMC, 2006).

Generally, studies carried out across the world show that reporting of ADRs by healthcare professionals is poor, regardless of the setting. This is particularly the case, though, in developing country settings. In a cross-sectional study by Gurmesa and Dedefom (2016), conducted in Nekemte Town in Ethiopia, only 48% of the healthcare professionals responded correctly to the knowledge-related assessment questions, 42% to the attitude-related questions and 9,8% to the practice-related assessment questions. Gurmesa and Dedefom further stated that only 5% of the ADRs that were encountered in Ethiopia were reported to the national Drug Administration and Control Authority. A study conducted on healthcare workers by Fadare and Enwere (2011) in Kano, Nigeria, revealed that there was low spontaneous ADR reporting, with only 42.7% of the respondents having ever reported an ADR.

Khoza *et al*., (2004) conducted a study of ADR reporting by health workers at a referral hospital in Zimbabwe. Only 52,8% of the respondents knew how to report an ADR in Zimbabwe and 47.1% were unaware of the existence of a formal PCV centre in the country. Of the study participants, only 20% had ever reported an ADR. These Zimbabwean results are consistent with the other two African studies cited above, and with other studies conducted in different countries. The MCAZ has continuously been looking for funding to strengthen activities by, for example, implementing cohort monitoring of ARVs and improving ADR reporting (Ministry of Health and Child Care, 2011).

2.8.1 Reporting systems

Most developed countries have an established spontaneous reporting system. In the United Kingdom (UK), for instance, spontaneous reporting is undertaken using the Yellow Card Scheme which was introduced in 1964. The Yellow Card is currently both an electronic and a paper-based system. The manual Yellow Cards are found in the British National Formulary (BNF), which is the UK's premier medicines information resources, and is distributed on a regular basis to all prescribers and pharmacists. The electronic Yellow Card, which was introduced in 2002, is web-based and allows the reporter to insert the relevant information about the ADR directly onto the website, without having to complete a paper submission (Yellowcard, 2017).

In Canada, the Canada Vigilance Program also has both paper-based and electronic ADR reporting platforms. In addition, those reporting can call the centre to log in a case. Initially, in both the UK and Canada, only doctors and dentists where allowed to report under the schemes but it is now open to include pharmacists, nurses, coroners and patients (Anon,2004). In South Africa, the national ADR form has been included in the SA Medicines Formulary for many years, but has now also been included with the national public sector Standard Treatment Guidelines/Essential Medicines List (STG/EML) on a cellular telephone application (app).

The Zimbabwean PCV system currently relies on a paper-based system in the form of an official standardised form, which, like in the UK, is found in the country's EML, at the MCAZ offices and on the MCAZ website. In addition, the MCAZ recently introduced an online ADR reporting link on the MCAZ website. The MCAZ has in the past indicated that there was a backlog in submission of ADR reports to the WHO collaborating centre and funding is required to enable the Authority to conduct more pharmacovigilance activities (Ministry of Health and Child Care, 2011). MCAZ aims to disseminate information to all its stakeholders i.e. industry, academia, research local and international bodies through newsletters, journals, editorials, reports and project reports (MCAZ, 2017). The MCAZ, however, does not report publicly on the number of individual case report forms (ICSRs) received over time. Access to the Uppsala Monitoring Centre's Vigilyze database is restricted. Where data on ICSRs have been placed in the public domain, in the form of the UMC's VigiAccess web site (http://www.vigiaccess.org/), the data show the total number of ICSRs submitted per medicine per region (i,e. from Africa, the Americas, Asia, Europe and Oceania), but not individual countries. The data also show the total number of ICSRs for that medicine submitted per year but are not disaggregated by region or country.2.8.2. Role of the Pharmacist in ADR Reporting

The American Society of Health-System Pharmacists (ASHP) has noted that it is the pharmacist's responsibility and professional obligation to report any suspected ADR (American Society of Health-System Pharmacists, 1995).The International Pharmaceutical Federation (FIP) also recognises the pharmacist as a vital tool in the post-approval environment, as s/he can provide early detection of ADRs (FIP, 2006).The FIP (2006) also recognises that pharmacists have expertise in the safety profiling of medicines to meet a patient's needs, and that they are a useful source of both information and critical evaluation of drug information. The FIP further states that; "Governments and medicines control agencies authorised by governments:

- should recognise the pivotal role of pharmacists in pharmacovigilance and ensure that the necessary resources and incentives are appropriately directed to achieve maximum benefit from their involvement;
- provide a method for reporting that is concise, electronic and compatible with pharmacypractice;
- promote a greater awareness about ADRs and other drug-related problems withemphasis on their significance, recognition, management and prevention as an important instruction to promote rational and safe prescription practices;
- assign the primary responsibility for the collection of pharmacovigilance to thepharmacist along with the necessary tools and compensation.'' (FIP, 2006).

Despite these international calls, the role of a pharmacist in PCV activities varies by country and has evolved over time. About a decade ago, pharmacists in some countries were not in a position to participate in PCV activities. This has however changed and nowadays, in countries such as the UK, USA and Zimbabwe, pharmacists are independently allowed to report ADRs. In a review article on ADR reporting, Bushra *et al*. (2015) highlighted that pharmacists play a crucial role in the management of ADRs as they have the

knowledge and skills to discover and deal with ADRs. A pharmacist's involvement produces a reporting rate with higher calibre (Bushra *el al*., 2015). Team work between pharmacists and physicians is important in reporting of ADRs and to avoid health and economic crises. However, van Grooteest *et al.* (2004), in their study on pharmacists' role in reporting ADRs in an international perspective, indicated that in countries wherepharmacists are allowed to report, they do not fully embrace the opportunity to do so.In the same study, it was nonetheless noted that pharmacists' ADR reports are greatly appreciated in countries that receive many reports from pharmacists. It was also concluded that, if the contribution pharmacists make to the quantity and quality of ADR reports was to be fully exploited, there would be a significant improvement of the international ADR reporting system.

In Zimbabwe, all healthcare professionals and patients are requested to report all suspected ADRs to the MCAZ PCV programme. The role of the pharmacist in handling of ADRs is clearly defined in Zimbabwe. Pharmacists in the country should:

- "Carry out assessments of ADRs by examining the cause and analyse trends, frequency and outcomes.
- implement prevention strategies, monitor interventions and make necessary amendments. This is especially true if the ADR is due to medication error and protocols can be developed to prevent reoccurrence.
- Communicate with other healthcare workers the end result of the ADRs, to train and to encourage them to report ADRs to the MCAZ" (Medicines Control Authority of Zimbabwe, 2016).

The MCAZ acknowledges that the pharmacist is better placed in the healthcare system to identify and deal with ADRs. Community pharmacists deal with a wide array of medicines, including herbal products and over the counter (OTC) medicines. As such, they can detect ADRs due to interactions and can assist in the management and reporting of such ADRs.

2.9 Factors Affecting Reporting of Adverse Drug Reactions

Under-reporting of ADRs is a global trend affecting both developed and developing countries. Researchers have been looking for solutions globally to help better understand factors that affect reporting of ADRs. Having an appreciation of these factors will inform strategies that need to be implemented to increase the number and quality of ADR reports.

Knowledge, attitude and practice (KAP) studies have been carried out in several countries in an attempt to assess issues of ADR reporting. Factors that determine whether healthcare professionals (HCPs) report ADRs are determined by the attitudes the HCP has towards ADR reporting. In a number of studies, for example Belton *et al.* (1995) and Kalaiselvan *et al.* (2014), most HCPs pointed out that the following reasons hinder them from reporting ADRs: lack of adequate training (knowledge), lack of time, lack of feedback, fear of not being taken seriously, lack of financial incentives, fear of legal proceedings and lethargy. These reasons affect both developing and developed countries to a similar extent.

Lack of adequate knowledge on ADR takes many forms. It can be a failure to understand what to report, who to report to or how the reporting tool works or even the existence of a PCV centre or ADR reporting program. In Iran, Vessel and Mardani (2008), assessed pharmacists' knowledge, attitudes and practices (KAP) with respect to the reporting of ADRs, and reported that 25% of the pharmacists who had witnessed an ADR reported it. Furthermore, 30% of the pharmacists in Iran were not aware of an ADR reporting program in the country, and 43% of community pharmacists indicated that the reason they did not report ADRs was because they were uncertain of the association between the drug and the reaction. A study conducted in the United Kingdom by Belton *et al*. (1995) on ADR reporting by medical practitioners reported that only 63% of the medical practitioners that responded to the questionnaire (only 57% of those polled) had ever reported an ADR to either the manufacturing pharmaceutical company or to the Committee on the Safety of Medicines (CSM). The study revealed that there was under-reporting due to the misconception that the practitioner had to be absolutely sure about the diagnosis of the ADR, as well as the lack of time and lack of report forms. Lack of understanding of the Yellow Card reporting scheme which is used in the UK also significantly contributed to the high under-reporting rates in that country. In a study by Khalili *et al*.(2012), to evaluate clinical pharmacists' interventions aimed at improving KAP of healthcare workers about ADRs in a teaching hospital in Iran, it was reported that 91.5% of hospital workers where the study was carried out had never reported an ADR and 49% were not aware of the existence of a national PCV centre. In Iran, pharmacists were reported to be more aware of PCV compared to other healthcare professionals.

Some studies (Ahmad *et al*., 2013; Eniojukan *et al*., 2015) have shown that healthcare professionals with advanced qualifications tend to report ADRs more than do their colleagues with lower qualifications, or with less familiarity with medicines. Doctors and pharmacists could be expected to report more ADRs than other HCPs, due to a greater understanding pharmacology and of the impact ADRs have on the healthcare system. In a study that was carried out in Northern Cyprus by Toklu *et al*. (2016) to determine the knowledge, and attitudes of healthcare professionals in their country towards PCV, doctors and pharmacists in the study claimed to have reported more ADRs than did nurses.

There are other factors that potentially affect reporting, but that are unique to a particular setting. In Africa and most developing nations for example, health systems are weak. There is lack of trained health personnel and there are insufficient and inadequate resources for PCV. All these factors are likely to contribute to both a significant increase in the incidence of ADRs and to low rates of reporting. Oreagba *et al.* (2011) have reported that Nigeria, and Africa as a whole, still has a long way to go when it comes to issues of PCV. Twenty percent of pharmacists in Nigeria reported ADRs despite 40% of them receiving reports of ADRs from patients on a monthly basis. Pharmacists in the country were seen to have poor KAP when it comes to ADR reporting. Reasons for poor reporting, like in the other studies mentioned above, included lack of awareness about PCV and lack of incentives for reporting. In addition, there is also a high workload which is a result of the loss of healthcare professionals due to emigration. This is the case with Zimbabwe where, in 2004, the doctor: patient ratio was reported to be 1: 6000, specifically as a result of losses to emigration (Chibango, 2013). Such a high workload will negatively impact on PCV activities,

Legislative requirements are also a factor that affects ADR reporting and these differ between countries. A systematic review carried out by Hazell and Shakir (2006) of ADR studies carried out in twelve countries (in the UK, Germany, France, Spain, Norway, Demark, Sweden, Canada, Hong Kong, US, Netherlands and Italy) showed that ADR under-reporting ranged from 6% to 100%, with a median rate of 94% across all included studies. The wide range was related to the different methodologies that were employed in the studies that were reviewed. In some countries like Sweden, pharmacists were not allowed at the time to report ADRs to the national program (Zolezzi and Parsotam, 2005) and this might mean that some ADRs were completely missed.

2.10 Interventions to improve Adverse Drug Reaction Reporting

Several interventions have been employed by researchers in different settings to determine if they can improve ADR reporting by HCPs (Gurmesa and Dedefom 2016; Lopez-Gonzalez *et al*., 2015). These interventions include:

- educational activities such as continuing professional development (CPD) sessions;
- reminders such as letters, emails or posters;
- modification of the ADE reporting form (simplification of reporting);
- modification of reporting procedures (reporting by telephone or electronically);
- incentives;
- assistance from another professional including regular visits by Clinical Research Assistants to hospitals;
- enhancing availability of reporting forms; and
- providing continuous motivation through feedback provision.

2.10.1 Educational activities

Many studies (Desai *et al*., 2011; Khan *et al*., 2013; Ruud *et al*., 2010) have attributed lack of knowledge as a hindering factor in reporting of ADRs. As such, one solution is to address this by educating healthcare professionals and increasing awareness of PCV. Lopez-Gonzalez *et al.* (2015) conducted a study in Spain to determine if educational interventions will improve ADR reporting among physicians, using two complementary approaches, one active and one passive. The active group had group sessions and the passive group had educational material sent to them. The study showed that ADR reporting in the intervention group increased by 65.4% during the period of follow-up. In Iran, Hanafi *et al*. (2014) employed a pharmacologist and a pharmacist who where specialised in PCV to give a lecture to nurses on the importance of PCV and ADR reporting. In the lecture, the nurses where also taught how to fill in the Iranian Yellow Card when reporting an ADR. The study determined that an educational intervention increases ADR reporting amongst nurses and that it also has a positive impact on their knowledge, attitudes and practices towards the reporting of ADRs. However, this was a one-off intervention and the sustainability of the change was not assessed. It would appear to be imperative that continuing awareness programmes, which can be in the form of Continuing Professional Development (CPD) encounters, are instituted to address grey areas and to repeatedly and continually emphasise the importance of ADR reporting.

2.10.2 Electronic reporting

Some healthcare professionals have suggested that the introduction of electronic reporting systems will improve their ADR reporting. Lynn*et al.* (2010) studied the use of electronic reporting to aid ADR reporting in children, and found that there was an 80% response rate with electronic reporting compared to 83% with the paper-based cards. Nonetheless, the respondents, who comprised of paediatricians and pharmacists, indicated that they prefered to use the electronic method for reporting.Nonetheless, although the introduction of an electronic reporting system may improve accessibility to the reporting tool and save time, it alone does

not significantly improve ADR reporting. Other factors, such as limited knowledge and a lack of incentives, also need to be addressed.

2.10.3 Provision of incentives

In many studies, healthcare professionals have cited a lack of incentives as an obstacle to reporting ADRs. Incentives can be in the form of educational credits, notepads, coffee mugs or financial payments. In Sweden, Backstrom and Mjorndal (2006) evaluated the effect of incentives on ADR reporting. Two counties in Sweden were studied, one as the control and one as the intervention site. The intervention county received an incentive in the form of two lottery tickets for every ADR reported in each period of six months. The intervention group reported 59% more ADRs compared to the previous year, and 40% of these were assessed to be serious ADRs. The control group only had a slight increase in the first three months, with the number of reports decreasing at the end of the study. The study concluded that economic inducements can increase the number of ADR reports. The British Medical Association (BMA) (2006) noted that at least 30% of Green Cards which were issued in Southampton for Prescription Event Monitoring (PEM) were not returned by general practitioners (GPs), citing a lack of financial incentives.

It should be noted. however. that some incentives, especially financial, if paid directly to health care practitioners, may create a perverse incentive to report ADRs. This will inadvertently result in an increase of reported ADRs, some of which may be supported by tenous evidence. In addition, prescribers might be inclined to prescribe newer medicines which are likely to have more adverse effects in order to gain more incentives (Berniker, 2004).

2.11 Conceptual Framework

A conceptual framework is a combination of assumptions, principles and rules that govern the ideas of a broad concept. For an HCP to report ADRs, s/he must first have the requisite knowledge on how and what to report. This knowledge might affect her/his attitude, which in turn will also determine if she/he will actually submit a report. There are other factors that can affect if one reports or not but according to Cabana *et al*. (1999), behaviour change due to an influence on knowledge and attitude is more sustainable. The present study has therefore relied broadly on the Health Belief Model (HBM) as the theoretical framework (Jones *et al*., 2015).

2.11.1 Definitions of key terms

The following definitions have been provided for the components of knowledge, attitudes and practices (KAP) (Gumuchio, 2011;Rav-Marathe *et al*., 2016):

- ‘’Knowledge is one’s way of perceiving and understanding of the subject matter. It is acquisition, retention and use of inormation or skills. The degree of knowledge assessment will help identify areas where education and information efforts remain to be exerted. Knowledge can be influenced by things like training and years of experience.
- Attitude is a way of being and tendencies. It is a psychological tendency that is expressed by evaluating a particular entity with some degree of favor or disfavor. Attitudes are not directly

observable and it is imperative to assess them. It explains why one subject chooses a certain practice as opposed to another if submitted to a stimulus. Complexity of a research instrument or a task can determine one's attitude towards the task.

- Practice is the observable response to a stimulus.It is the application of of knowledge. It deals with actions. A KAP survey can identify key knowledge, social skills and know-how shared by a particular group about particular issue. Practices can be affected by time constraints, fear of legal liability, workload and lack of access to reporting forms''.
- Feasibility is the degree to which something is easily or conveniently done. Factors that can affect feasibility include time contraints and the complexity of the task.
- Self efficacy is one's belief in the ability to succeed in specific situations or to accomplish certain tasks. This is how one feels when sufficiently acquainted with the specific requirements and procedures for a task, such as ADR reporting.
- Challenge to autonomy is when one feels not completely free from external control or influence.

2.11.2 The Health Belief Model

The HBM suggests that an individual takes action on a health-related problem based on four things: perceived susceptibility, perceived benefits, perceived severity and perceived consequences (Jha *et al*., 2013). The rational action model, also known as the KAP mode, relies on the HBM, as it is based on the assumption that improving one's knowledge will result in a change in attitude, which will in turn result in a change in behaviour. In this model, education strategies which are targeted at individuals or group of individuals are implemented to promote positive health behaviour choices and prevent negative choices. The weakness of the rational model is that knowledge alone is not sufficient in changing individual or collective behavior (World Health Organization, 2012).

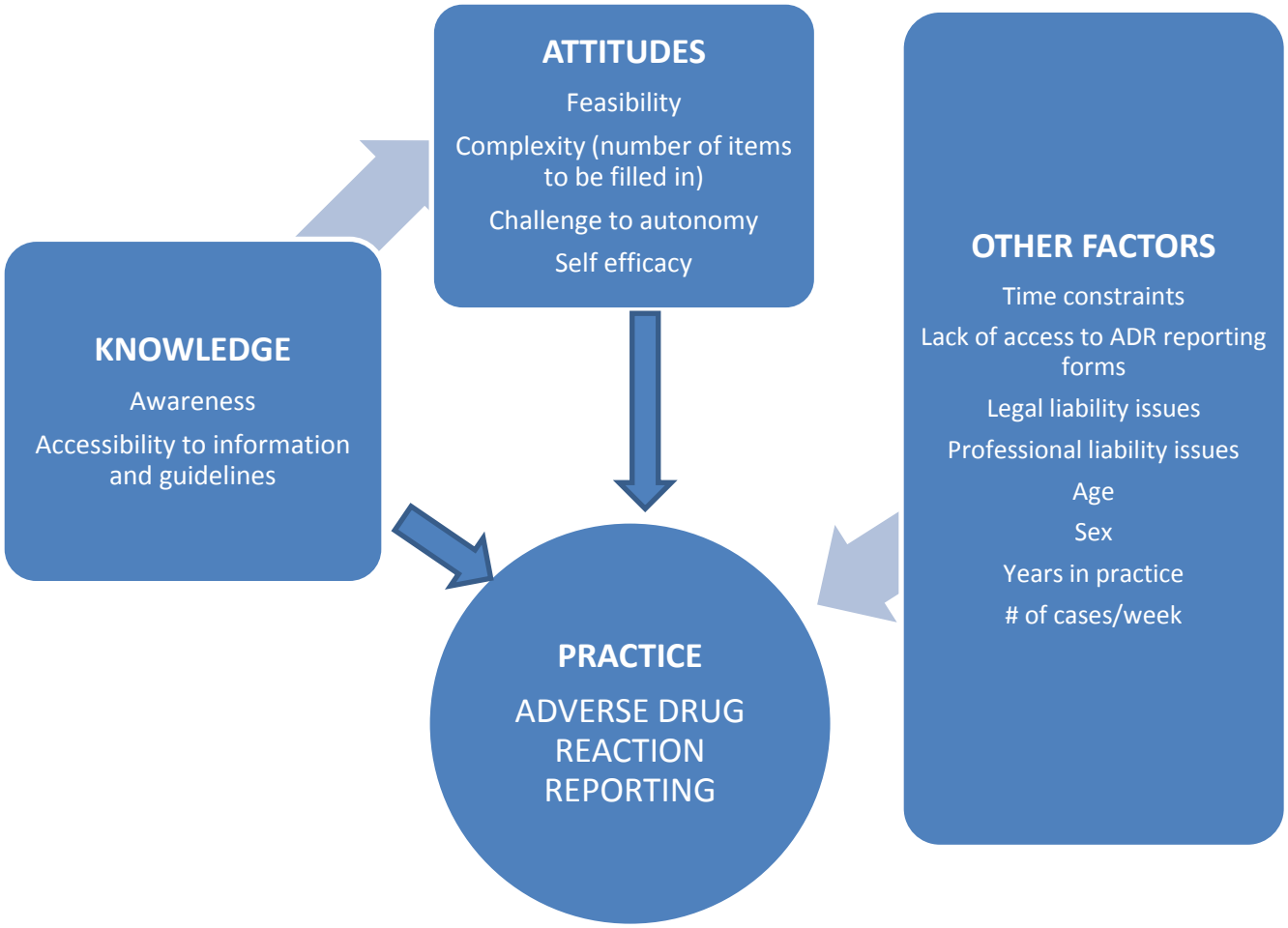

Figure 2.2: Conceptual framework diagram and perceived barriers (Adapted from Cabana *et al*., 1999)

CHAPTER 3: METHODS

3.1 Introduction

This chapter sets out to describe the approach which was used to determine the knowledge, attitudes and practices of pharmacists on ADR reporting. It includes a description of the study design, sampling, data collection, statistical analysis, potential biases and limitations.

3.2 Study Method and Design

The study was designed as an observational, cross-sectional, analytical study. This design was used since it offered a cost-effective way of gathering information from many people in a relatively short period. The study design also provided a high degree of standardisation coupled with reliability that is useful for comparability of data (Joubert and Ehrlich, 1998). In order to quantify knowledge, attitudes and practices of pharmacists in reporting ADRs, a quantitative approach was considered to be ideal. Although a purely qualitative approach would have provided room for greater in-depth exploration, it was not used as it would not have allowed for the measurement of knowledge, attitudes and practices. A range of stakeholders (the medicines regulatory body (MCAZ), the statutory council for pharmacists (Pharmacists' Council of Zimbabwe, PCZ), the voluntary professional association (Pharmaceutical Society of Zimbabwe, PSZ), and pharmacists themselves) were involved in the research from the conceptualisation phase to designing of the data collection tools.

3.3 Setting

The study took place in Harare, Zimbabwe, where over 44% (MCAZ, 2016) of the country's private community pharmacies are located. Harare is the capital of Zimbabwe and it is situated in the north-east part of the country.

3.4 Research population

Pharmacists who are practising in the private, community pharmacy sector in Harare, Zimbabwe, constituted the research population. The population was selected as it was convenient for the researcher.

3.5 Sampling

Harare is a large city with a number of private community pharmacies. A census approach was usedas little is known about the subject locally and an accurate sample size estimation could not be performed. In addition, in a randomised clinical trial carried out by Kongzved *et al*.(2007)on response rates in Internet versus pencil-based questionnaires, the results indicated that Internet questionnaire had a low response rate of 17.9%. The census approach was therefore used in an effort to maximise the response and enhance the generalizability of the study. This also helped minimise costs as it allowed the use of electronic communication with participants. According to Polit and Beck (2012), a census is a survey that covers the entire population.

The inclusion criteria were as follows:

- willingness to provide informed consent; and
- pharmacists practising in private community pharmacies in Harare.

The exclusion criteria were:

- pharmacists practising in other sectors, outside of community pharmacies;
- community pharmacists from other towns and cities outside Harare; and
- refusal to participate in the study.

3.6 Data collection

The data collection tool used was a self-administered questionnaire (Annexure 6), which was adapted from a similar study by Desai *et al*. (2011). Prior to the study, the questionnaire was piloted with five (5) pharmacists to ascertain acceptability and validity and to determine appropriateness and quality of the data collection tool. The questionnaire had a total of sixteen (16) questions, subdivided into three sections. Section A consisted of three (3) questions covering socio-demographic issues. Section B had five (5) questions covering the knowledge of ADR reporting. Lastly, Section C had eight (8) questions that consisted of questions on attitudes and practices regards ADR reporting. During the pilot period, it was identified that the possible options provided for Question 12 were not appropriate, and these were amended before the actual study was commenced. The questionnaires were distributed by email for those with readily available addresses sourced from the Pharmacists' Council of Zimbabwe (PCZ) and the Pharmaceutical Society of Zimbabwe (PSZ). Two reminders where sent via the same email addresses for those that had not responded. The first reminder was sent a week after the initial email and the second reminder was sent 2 weeks after the second reminder. The questionnaire was also distributed physically to pharmacists present at acontinuing professional development (CPD) session in Harare. Those who had already participated in the survey where excluded from the exercise at the CPD session.

3.6.1 Variables measured by the instrument

The instrument measured independent variables, which were the demographics of the respondents (such as age and gender). The dependent variables that were measured were knowledge, attitudes and practicesrelated to thereporting of ADRs.

3.7 Study Limitations

There were a number of possible sources of bias in the study. Although it was expected that the participants would respond with honesty and integrity, there was the possibility that some pharmacists might have researched the correct answers before submitting their questionnaires.This might be considered an example of social desirability bias. Likewise, the possibility of recall bias could not be eliminated. Both of these potential

biases were addressed in the information provided to potential participants prior to eliciting informed consent. In addition, the low response rate could have affected the interpretation of the results, by limiting generalisability.

3.8 Ethical considerations

The following ethical considerations (Annexure 5) were observed during the process of conducting this study:

(i) Ethical clearance was obtained from the University of KwaZulu Natal Humanities and Social Sciences Research Ethics Committee (HSSREC) and the Pharmacists Council of Zimbabwe to do the research.

(ii) A signed informed consent form was obtained from the respondents after providing them withinformation on the purpose of the study and their rights with regard to participation in the research as well as the right to withdraw consent at any point.

(iii) Anonymity and confidentiality was ensured by using a questionnaire that did not require respondents to divulge their identity. No respondent identifiers were recorded and all analyses were anonymised.

3.9 Data Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 16) and Microsoft Excel 2007 were used for data analysis.Descriptive statistics were prepared in the form of means, medians and appropriate measures of distrubition about those measures of central tendency. Chi square tests and Fisher's exact test were conducted to establish relationships between categorical variables, as appropriate. A chi squared test was done to establish the relationship between practice experience and reporting of ADRs. In addition, Fisher's exact test was performed to determine the possibility of a relationship between reporting of ADRs and formal post-graduate training and also ADR reporting by sex.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter presents the results of the analysis of the data collected from respondents through the use of a questionnaire. The findings are reported according to the objectives and research questions of this study.

4.2 Response rate

In total, 129 questionnaires were distributed via both email and at a CPD session held in Harare. A total of forty-four (44) questionnaires were returned, yielding a response rate of 34.1%.

4.3 Socio-demographic characteristics of the respondents

This section presents the descriptive statistics pertaining to the demographic characteristics of the respondents, namely: age, sex, years of experience after registration and level of education.

Responses were received from a total of 44 pharmacists, of whom 28 (63.6%) were male. The median age was 30 years (interquartile range 27.25 to 33 years). The demographic details of the respondents are provided in Table 4.1.

The median years of experience after registration was 7 years. The reported duration of work experience, after registration, ranged from 1 to 18 years.

The distribution of years of experience, post-registration, for male and female respondents, is shown in Figures 4.1. The males had a median of 7.5 years of experience, post-registration, and the females had a median of 5.5 years of experience, post-registration. Both histograms were skewed to the left.

Table 4.1: Summary of respondent demographics

Parameter	Minimum	Maximum	Median	Interquartile range
Age	25	40	30.0	27.25 – 33.0
Age (male; n=28)	25	40	30.5	28.0 - 32.75
Age (female'; n=16)	25	38	29.0	26.25 - 33.0
Years of experience, after registration	1	18	7.0	4.0 – 9.0
Years of experience (male)	2	18	7.5	4.0 – 9.0
Years of experience (female)	1	14	5.5	5-3 – 9.0

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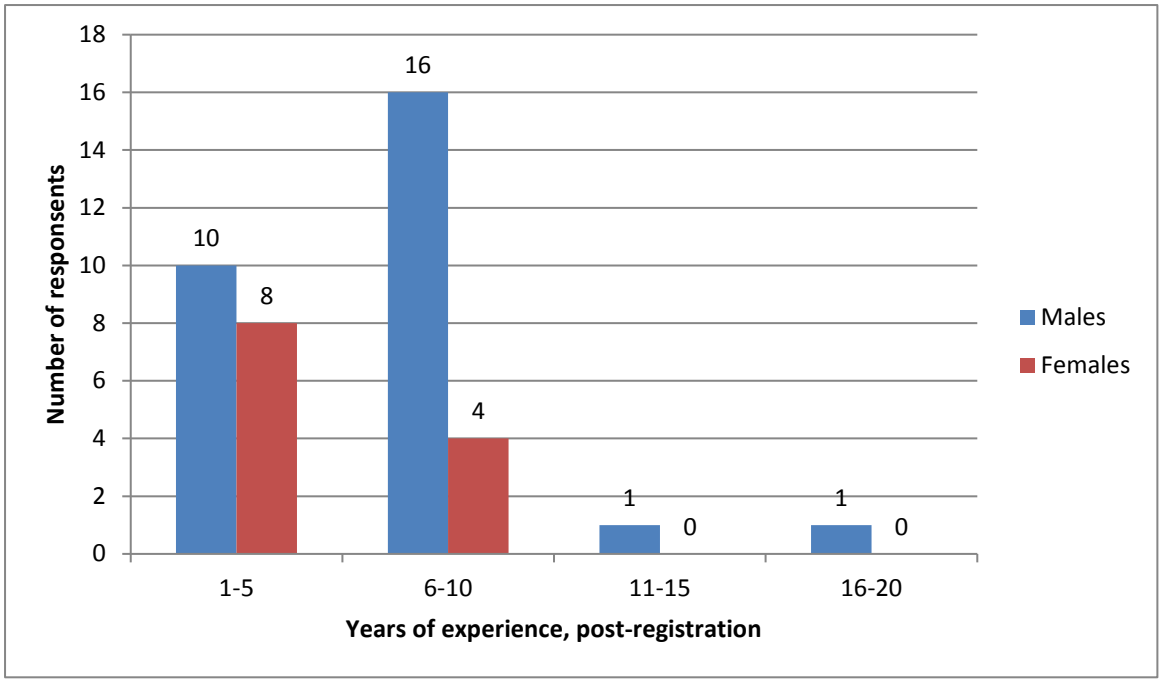

Figure 4.1: Histogram showing the distribution of years of experience, post-registration, for males and females

A total of 32 respondents (72.7%) reported having completed post-graduate training with more men (78.6%, n=22) than women (62.5%, n=10) reporting as such. Only 18.75% (n=6) of those with postgraduate training undertook a medically-related course (such as a Master of Public Health or a Master of Health Informatics qualification). Examples of other post-graduate training courses were Master of Business Administration, Master of Business Leadership, Diploma in Purchasing and Supply, and Diploma in Marketing. Table 4.2 below shows the distribution of post-graduate training courses amongst the respondents.

Table 4.2: Distribution of respondents with a formal post-graduate qualification by type

Postgraduate qualification	Master of Business Administration	Master of Business Leadership	Master of Public Health	Master of Health Informatics	Diploma in Marketing	Diploma in Purchasing and Supply
Number of respondents	12	3	4	2	5	6

4.4 Knowledge of Reporting of Adverse Drug Reactions

This section reports on responses to Section B of the questionnaire, dealing with knowledge.

All 44 (100%) respondents said that they encountered an average of 0-5 ADRs per week, which suggests that there might have been limited knowledge of ADRs by the respondents. None of the respondents selected the other, more prevalent options (6-10 per week; more than 10 per week).

The most common ADRs encountered, and the medicines that were perceived to cause them, are listed in Table 4.3 below. The most common ADR cited was rash caused by cotrimoxazole, which was reported to have been encountered by 38 (86.4%) of the respondents.

Table 4.3: List of common ADRs encountered and the medicines that cause them

Medicine	ADR	Number of respondents who cited the ADR
Cotrimoxazole	Rash	38
Tenofovir, Emtricabine, Efavirenz (fixed-dose combination)	Severe headache	30
Promethazine	Drowsiness	29
Nevirapine	Stevens-Johnson Syndrome	23
Penicillins	Hypersensitivity reaction	16
Amlodipine	Headache	12
Stavudine	Nephropathy	7
Codeine-containing analgesics	Constipation	7
Secnidazole	Diarrhoea	4
Amoxycillin	Abdominal pain and diarrhoea	3
Azithromycin	Gastrointestinal disturbances and vomiting	2
Sildenafil	Headache and blocked nose	1
Doxylamine succinate	Localised reaction	1

Thirty-five (79.5%) of the respondents indicated that they were aware of a medicine having been removed from the market (banned) due to the emergence of an ADR. Table 4.4 below listed the medicines that were provided as examples, and the ADRs for which they were responsible.

Table 4.4: Medicines banned and ADRs they caused

Name of medicine	ADR caused
Thalidomide	Phocomelia
Astemizole	Cardiac arrhythmias
Tetrazepam	Serious cutaneous reactions
Rofecoxib	Heart failure
Dextropropoxyphene	Cardiotoxicity

No statistically significant relationship was found between being able to identify a medicine that had been withdrawn from the market (banned) as a result of the emergence of an ADR and having completed post-graduate training of any sort (Fisher's exact test; $p = 1.000$), as depicted in Table 4.5.

Table 4.5: Relationship between awareness of any medicine ban and formal post-graduate training

Awareness of any medicine ban due to ADR	Formal post-graduate training		
	Yes (%)	No (%)	Total (%)
Yes	25 (71.4)	10 (28.6)	35 (100)
No	7 (77.8)	2 (22.2)	9 (100)
Total	32 (72.7)	12 (27.3)	44 (100)

Likewise, no statistically significant relationship could be detected between the duration of practice experience, post-registration, and knowledge of any medicine ban (Pearson's chi-square (χ^2) = 1.217, df =3, p =0.745), as shown in Table 4.6

Table 4.6: Relationship between awareness of any medicine ban and years of practice experience

Awareness of any medicine ban due to ADR	Years of experience, post-registration				
	1-5 years n (%)	6-10years n (%)	11-15years n (%)	16-20years n (%)	Total n (%)
Yes	13 (37.1)	17 (48.6)	4 (5.6)	1 (2.9)	35 (79.5)
No	5 (55.6)	3 (33.3)	1 (11.1)	0 (0.0)	9 (20.5)
Total	18 (40.9)	20 (45.5)	5 (11.4)	1 (2.3)	44 (100)

All 44 respondents (100%) were of the opinion that the reporting of ADRs is "very important", as opposed to "important" or "not very important". Based on a Likert scale of 1-4, where 1 was described as "least important" and 4 as "very important", the respondents ranked a series of statements justifying the reporting of ADRs, as shown in Table 4.7.

Table 4.7: Results of Likert scale responses on the importance of reporting ADRs

Statements justifying the importance of ADR reporting	Likert scores				
	1 (least important)	2 (quite important)	3 (important)	4 (very important)	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
To identify and detect new ADRs	4 (9.1)	4 (9.1)	32 (72.7)	4 (9.1)	44 (100)
To improve safety	0 (0.1)	2 (4.5)	2 (4.5)	40 (90.9)	44 (100)
To share information	5 (11.4)	37 (84.1)	2 (4.5)	0 (0.0)	44 (100)
To measure incidence	35 (79.5)	1 (2.3)	8 (18.2)	0 (0.0)	44 (100)

While 72.7% (n=32) of respondents felt that the identification and detection of new ADRs was “important”, even more (90.9%, n= 40) were of the opinion that reporting ADRs was “very important” in order to improve safety. Respondents were less sure about the importance of measuring incidence, with 79.5% (n= 35) reporting this to be “least important”. However, 84.1% (n=37) were of the opinion that sharing information was a “quite important” reason to report ADRs.

4.5Attitudes and Practices on reporting ADRs

The responses to section C of the questionnaire, dealing with attitudes and practices, are summarised here.

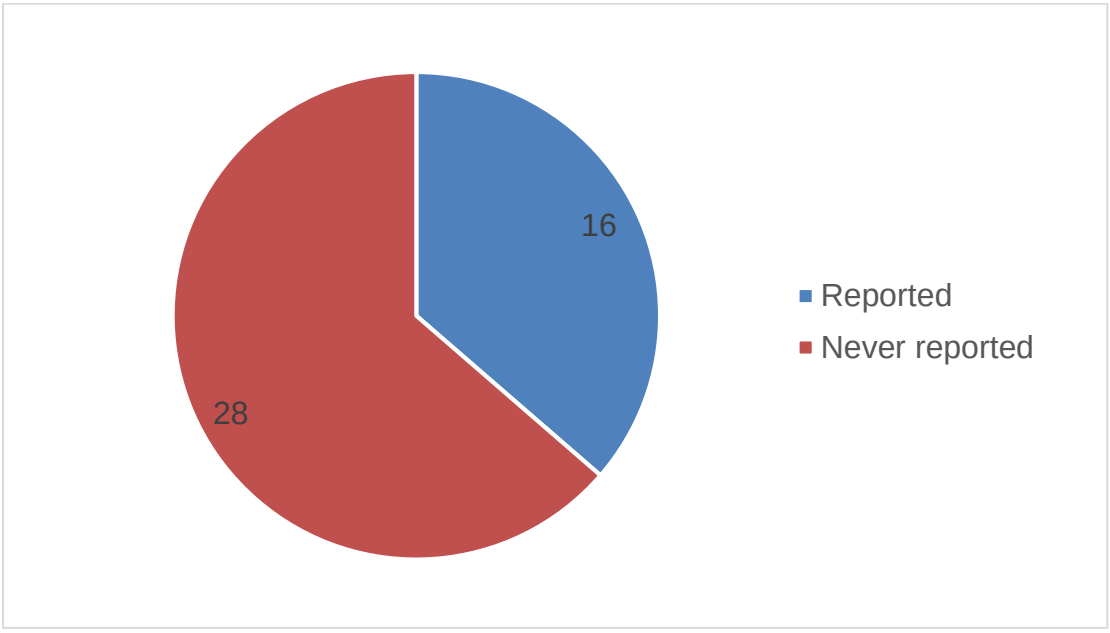

Figure 4.2: Pie chart showing those who have ever reported an ADR

Of the respondents, 16 (36.3%) reported ever reporting an ADR to the authorities. All reports were made to the MCAZ. The maximum number of ADRs reported by an individual from the respondents was 16. The mean of number ADRs reported was 0.98 with a standard deviation of 2.6.

Statistical tests were conducted to determine if there was a relationship between the demographics and ADR reporting practices in the respondents. A Chi square test was. The results of a chi squared test done to establish the relationship between practice experience and reporting of ADRs indicated that there is no significant relationship between the two parameters. In addition, Fisher's exact test was performed to determine the possibility of a relationship between reporting of ADRs (p= 0.487) and formal post-graduate training and also ADR reporting by sex (p= 0.333). Both results indicate that no statistically significant relationships could be established.

Opinion was sought from the respondents on factors they considered or would consider before making a report of an ADR.

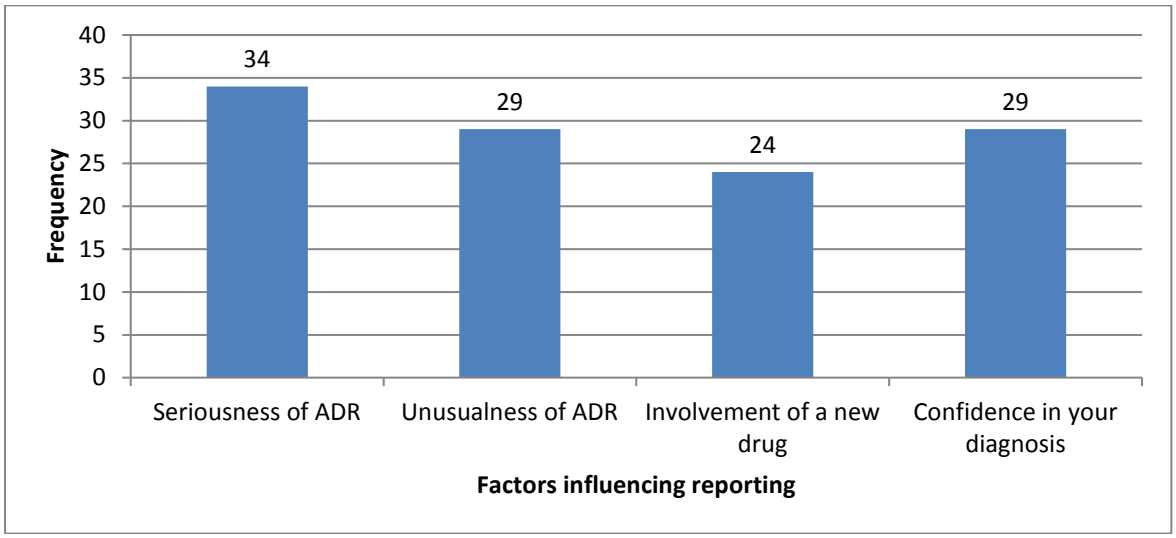

Figure 4.3: Bar graph showing factors that influence reporting of ADRs

As depicted in Figure 4.4 above, 34 respondents (77.3%) felt they should report an ADR depending on its seriousness. However, 29 respondents (65.9%) felt that the "usualness" of the ADR and one's confidence in the diagnosis of the ADR are factors that should be considered when reporting an ADR. Twenty-four (54.5%) felt the involvement of a new drug makes reporting of an ADR important.

The survey participants were also questioned on factors that discourage them from reporting ADRs.

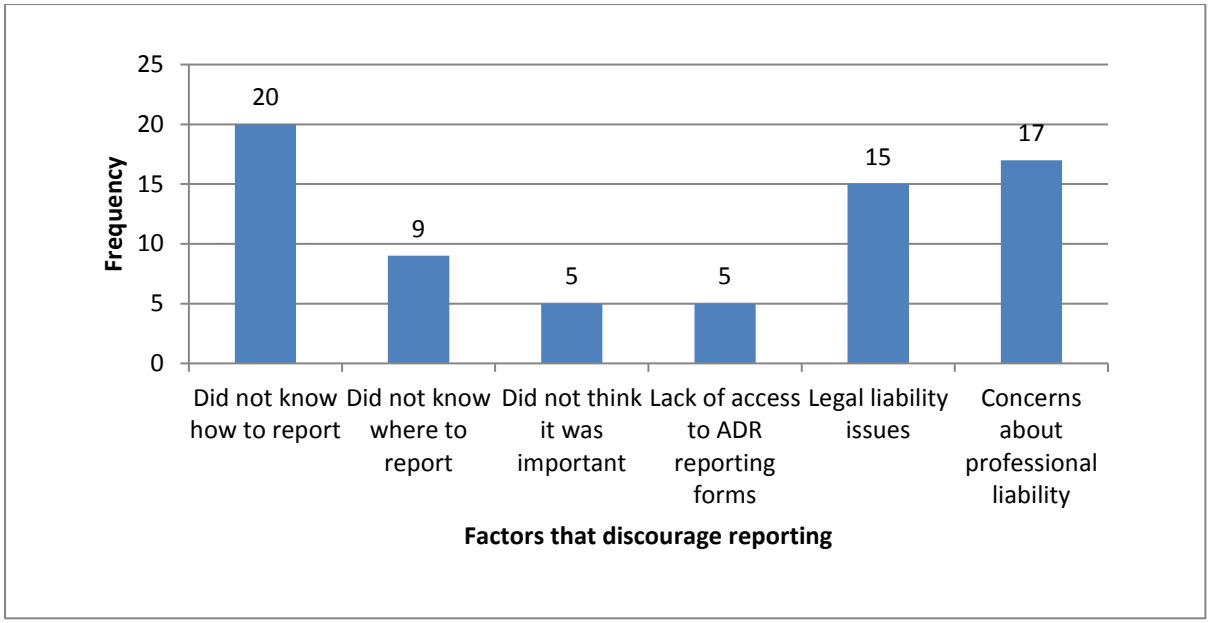

Figure 4.5: Bar graph showing factors that discourage reporting of ADRs

As depicted in Figure 4.5, above, 20 respondents (45.5%) did not know how to report an ADR. Seventeen (38.6%) indicated that they had concerns about professional liability. Legal liability issues where noted by 15 (34.1%) and 9 (20.5%) highlighted that they did not know where to report. Lack of access to ADR reporting forms was noted by 5 (11.3%) and an equal number did not think the ADR they observed was important. Other factors that were specified by the respondents was lack of feedback from the regulatory authority on ADRs reported, lack of incentives, limited time and no action taken by the authorities.

Nonetheless, 42 (95.5%) of the respondents answered correctly that all ADRs should be reported. The other 2 (4.5%) answered incorrectly that only serious ADRs should be reported. All respondents correctly identified MCAZ as the centre to reports ADRs in Zimbabwe.

Seminars or conferences were identified as the most popular sources of information on ADRs, with 77.3% of respondents (n=34). Medical representatives were cited as a source by 20.5% of respondents (n= 9). It was evident from the responses that most respondents relied on several sources of information on ADRs. The Internet was reported to be used by only 22.7% (n=10) of the respondents (see Figure 4.6).

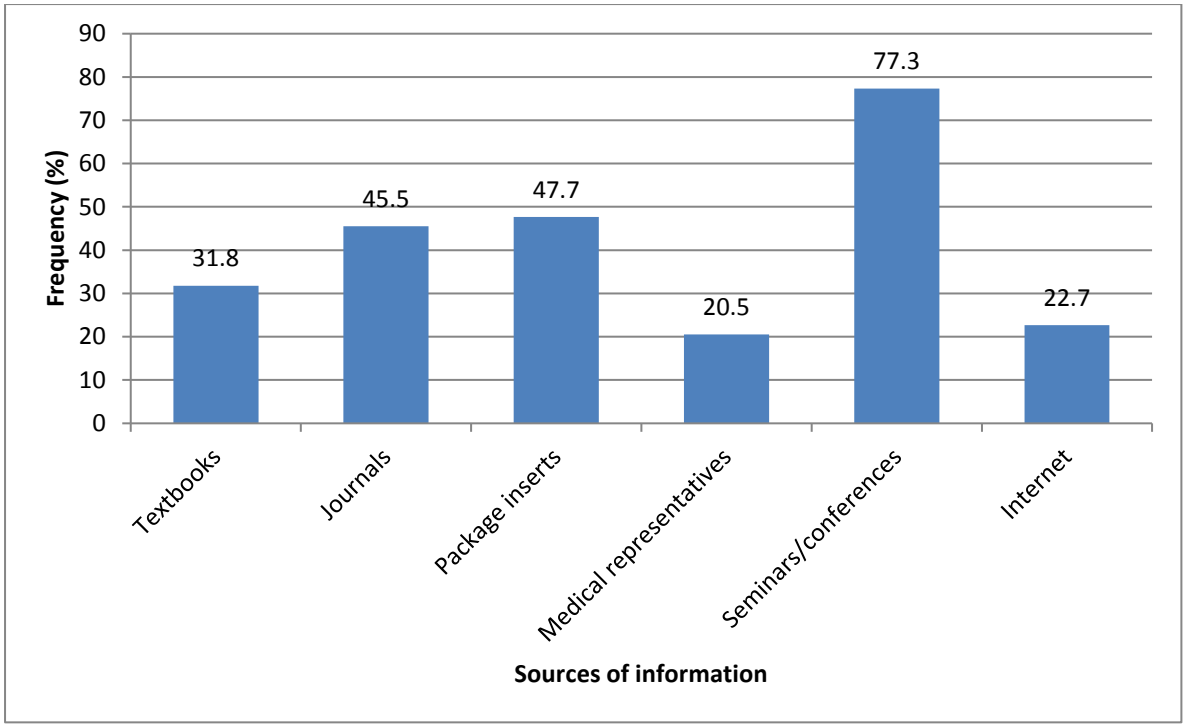

Figure 4.6: Histogram of sources of information used

Opinion was sought from the respondents on their preferred method of ADR reporting. Electronic mail or use of a dedicated website was the most preferred method, with 72.7% (n=32) of the respondents. This was followed by direct contact, with 20.5% (n=9) of the respondents. Returning a report by post was preferred by only 6.8% (3) and the least preferred method was telephone. The results are depicted in Table 4.8.

Table 4.8: Preferred ADR reporting method

Reporting method	Count	Percentage
Email/ on website	32	72.7
Direct contact (going in person to the relevant authority)	9	20.5
Post	3	6.8
Telephone	0	0
Other	0	0
Total	44	100

4.5 Conclusion

This chapter has presented the results obtained from a questionnaire distributed to all 129 community pharmacists currently practising within the Zimbabwean capital city, Harare. The results represent the data provided by the 44 respondents to this questionnaire. The following chapter has placed these results in the context of the available literature and explored their meaning and implications for pharmacovigilance practice in Zimbabwe.

CHAPTER 5: DISCUSSION

5.1. Introduction

This chapter discusses the findings of this study in relation to the available published literature and the objectives of the study.The objectives of the study were to determine if pharmacists practising in the private community pharmacy sector in Harare, Zimbabwe, know how to identify and when to report an adverse drug reaction; to determine their attitudes towards the identification and reporting of adverse drug reaction; and to determine whether they are currently reporting adverse drug reactions to the relevant authorities.

5.2 Background and context for the study

ADRs cause an estimated 5% of all hospital admissions in Europe and in Africa. Where health systems are weak and under-resourced, there is an increased likelihood of significant medicine-related harm (Olsson *et al.*, 2015). An assessment of knowledge, attitudes, and practices would therefore be expected to help identify areas where interventions such as education and information efforts are required. Identifying factors that hinder ADR reporting among health care workers and implementing strategies to improve reporting rates would be expected to contribute to the safe use of medicines, and ultimately to improved patient outcomes and avoidance of the wastage of scarce resources.

As was described in Chapter 1, Zimbabwe's health system operates under considerable resource constraints. These constraints apply to both the public and private sectors, and apply equally to pharmacists in community practice. In the context of significant financial pressures, with access to imported and locally-produced medicines under pressure, the need to avoid wasteful expenditure and maximise the likelihood of positive patient outcomes is even more acute. Zimbabwean healthcare professionals also have to contend with less than optimal access to telecommunications infrastructure. That said, there is a widely-respected national medicines regulatory authority operating in Zimbabwe (the MCAZ), effective regulation of health professionals, local Schools of Pharmacy, and a sustainable professional association (the PSZ).

5.3 Questionnaire research

Any study which relies on responses to a questionnaire will need to confront the challenges of poor response rates. The present study achieved a response rate of 34.1% (44 respondents out of an expected 129), which was somewhat lower than that achieved in other similar studies. For example, similar studies in the United Kingdom (Ashcroft *et al.*, 2006) and Iran (Vessal *et al.*, 2009) achieved response rates of 79% and 55%, respectively. A number of reasons for the poor response may be identified. It could be that private community pharmacists in Zimbabwe have not fully grasped the importance of participating in surveys and find them time-consuming and tedious. In addition, the busy schedules of the respondents, the demanding nature of the pharmacist's job, the high level of respondent apathy owing to the lack of incentives, as well as confidentiality

fears, despite assurance from the researcher, could have contributed to the poor response rate. Although studies with lower response rates are very common, they are difficult to generalize, especially for large populations (Gray, 2015). Saunders *et al*. (2015) have suggested that response rates must be at least 75% or more in order to ensure validity and reliability of the findings. That target, though justifiable, may not always be attainable.

5.4 Unpacking the findings

5.4.1 The respondents

The mean age of the respondents was 30.1 years, with a narrow range from 25 to 40 years. If typical of the entire community pharmacist workforce, this would indicate a relatively young group of community pharmacists. The most experienced respondent (a male pharmacist) had been qualified for 18 years, whereas the most recent graduate (a female pharmacist) had only one year of post-qualification experience. Most strikingly, a high proportion of respondents (72.7%) reported having completed a formal post-graduate qualification. The mean age is, nonetheless, reflective of the demographics of the working class in general in Zimbabwe (ZimStat, 2016). Many pharmacists, like many Zimbabweans in general, emigrated between 2001 and 2004 (FIP, 2006). This flight into the diaspora has left a relatively younger workforce to manage and operate community pharmacies on behalf of an older group of existing pharmacy owners.

In other ways, the respondents may also have been somewhat different from what might be expected in a typical community pharmacy setting. Contrary to global trends towards a female-dominated profession, 63.6% of the respondents were male. A similar study conducted in South Africa, a neighboring country, had more female than male respondents (Joubert and Naidoo, 2016). The International Pharmaceutical Federation (FIP) (2006) also states that there is a higher percentage of female pharmacists, especially in Africa, Europe and Eastern Mediterranean region. It is possible that continued male dominance in the profession in Zimbabwe is characteristic of more patriarchal societies, such as are found in many African countries. In such countries, economic and business activities may be deemed to be more suitable for men. Fewer women in such countries may be able to access tertiary education, and an even lower portion may be able to study in science-related fields. Male dominance has also been demonstrated in similar studies conducted in India (Prakasam *et al*., 2012; Ahmad *et al*., 2013). This is consistent with the overall trend in India, where 70% of the pharmacist workforce has been reported to be male (FIP, 2006). That said, the survey did obtain responses from a number of women community pharmacists (36.4% of respondents), which does show some degree of gender mainstreaming and gender equality, and the integration of women in mainstream economic activities which were previously reserved for men. However, no significant relationship could be found between sex and attitudes and practices when it came to ADR reporting. Women are expected to be more likely to seek healthcare than men and one might have expected, on the basis of first principles, that female pharmacists would be more likely to report ADRs than male pharmacists. However, no date to support this contention is accessible from this study. The chances are that a lack of knowledge nonetheless played a major role in affecting the attitudes and practices of both sexes, as implied by the Health Belief Model.

5.4.2 Factors determining the extent of ADR reporting

Apart from highly directed, prospective cohort studies or pregnancy registries, ADR reporting is, by its very nature, a spontaneous act by a healthcare professional or patient, and requires a deliberate decision to report in the middle of a busy clinical practice. That such a decision may be delayed, or even avoided, is understandable, especially where healthcare professionals, such as community pharmacists, are operating under time pressure and with various resource constraints. The decision relies not only on the ability to identify an ADR as such, and then to consider it worthy of reporting, but also on experience of, facility with, and easy access to a reporting mechanism. Each of those prerequisites could be expected to determine the extent and efficiency of ADR reporting in a given setting.

The first prerequisite would be to be able to identify an ADR as being drug-related, and worthy of reporting. Experience of ADRs is therefore important, and would be expected to be related to the prevalent disease burden and prescribing patterns in the study setting. In the present study, one of the most common ADRs encountered was skin rash caused by cotrimoxazole, reported to have been encountered by 86.4% of the respondents. Respondents were able to identify the causative agents of high-profile ADRs (such as thalidomide, astemizole, tetrazepam, rofecoxib) as well as the ADRs with which they are associated (such as phocomelia, cardiac arrhythmias, serious cutaneous reactions, heart failure). In addition, 79.5% of the study participants were aware of a medicine that had been removed from the Zimbabwean market as a result of an ADR. In addition to the globally-renowned cases of thalidomide and rofecoxib, respondents were able to identify a more recent local example (dextropropoxyphene). These findings also reinforce the position held by the MCAZ (2016), which has acknowledged that pharmacists are well placed to deal with ADRs. In addition to possessing the necessary knowledge about prescription medicines, they also deal with a wide array of medicines, including herbal products and non-prescription medicines (also referred to as “over-the-counter” (OTC) medicines). Bushra *et al*. (2015) have concluded that pharmacists can play a crucial role in the management of ADRs, as they have the knowledge and skills to discover and deal with such events. However, there has also been an acknowledgment of the limitations of spontaneous ADR reporting, and the MCAZ has actively pursued support from development partners and global financing mechanisms to strengthen PCV activities, for example by implementing cohort monitoring of antiretroviral medicines (ARVs) (Ministry of Health and Child Care, 2011). It is not known whether any of the respondent to this survey have been involved in the cohort monitoring effort or have received specific training in this regard.

Knowledge of the existence of an ADR is not sufficient – the pharmacist has to decide that an identified event is worthy of reporting. Only 36.3% of the respondents had ever reported an ADR to the authorities, with a mean of just less than one such report per respondent to that date (mean number of ADRs reported 0.98; standard deviation 2.6). The highest number of ADR reports submitted was recorded as 16. Under-reporting of ADRs by pharmacists, in particular, is not unique to Zimbabwe. In Nigeria, only 42.7% of pharmacists had ever submitted a spontaneous ADR (Fadare and Enwere, 2011). In New Zealand, Zolezzi and Parsotam (2005) showed that only 5.7% of the ADR reports received between January and June 2004 were from pharmacists. In Cyprus, the reporting rate by pharmacists was found to be 10.3% in a study by Toklu *et al*. (2016). This low rate of ADR reporting amongst the pharmacists was also suggested by Khalili *et al*. (2012),

who stated that 91.5% of Indian hospital workers had never reported an ADR. In a similar survey by Elkalmi *et al*. (2014) in Malaysia, more than half of the responding pharmacists emphasized the importance of ADR reporting but only 12.9% of these claimed to have ever reported an ADR to the relevant authority.

Ampadu *et al*. (2016) showed that the number of independent case safety reports (ICSRs) received from Africa was very low, when compared to the rest of the world. Cumulatively, Africa had submitted 0.88% of the reports in the Uppsala Monitoring Centre's global database (VigiBase) as at 30 September 2015.This can be attributed to the fact that the first African countries to join the Programme for International Drug Monitoring (PDIM) joined in 1992, 24 years after initiation of the programme. Suggested reasons for low rates of reporting in Africa include weak health infrastructure and systems, a lack of understanding of PCV and low interest by healthcare workers (World Health Organization, 2017). Although reporting of ADRs is better in high-income countries, the report rates are still far from satisfactory, as highlighted in the review by Hazell and Shakir (2006) where the median rate of under-reporting was estimated to be 94% in 12 developed countries.

Given that Zimbabwe has a high HIV burden, with an estimated adult HIV prevalence of 13.4% (Avert, 2017), it is perhaps not surprising that the most commonly reported ADRs were those associated with cotrimoxazole, which is used routinely to prevent opportunistic infections in those living with HIV. This finding is typical of most African nations, which bear a significant proportion of the world's infectious disease burden, as illustrated in the study conducted by Ampadu *et al.* (2016). They reported that 2.98% of all ADRs submitted to VigiBase by African nations were due to cotrimoxazole and 23.4% to ARVs. In contrast, the main causative agents for ADRs in the rest of the world were tumour necrosis factor-α (TNF-α) inhibitors and topical non-steroidal anti-inflammatory preparations. Other medicines for which large numbers of ADRs were reported were antibiotics (other than cotrimoxazole), analgesics and certain antihypertensive medicines. Each of these represents medicines that are heavily used in both acute and chronic care.

The respondents in the present study indicated that very few ADRs were encountered on a weekly basis (reporting between 0 and 5 ADRs per week). However, in a setting in which under-resourced pharmacists are not able to comprehensively counsel every patient who fills a prescription, whether for the first time or when collecting a repeat prescription, potential ADRs may be missed, and therefore not be reported. The ability to report depends not only on the knowledge to be able to identify, and the willingness to take the trouble to submit a report, but also on the opportunity to elicit a careful history from a patient and therefore to be presented with the data on which the necessary clinical decision can be made. Time constraints related to workload pressures may limit the ability to elicit such a careful history and therefore identify actual ADRs.

The decision to submit a report is also affected by the knowledge and attitudes of pharmacists to the need for and reasons for spontaneous reporting of ADRs. Despite the majority of respondents correctly pointing out the need to improve patient safety, it was clear that, of those who actually encountered patients with ADRs, very few eventually reporting them. In the present study, respondents were asked to rate the reasons for ADR reporting on a 4-point Likert scale (1 being least important, 2 quite important, 3 important and 4 very important). Improving patients' safety was rated "very important" by 90.9% of respondents. The identification

and detection of new ADRs was felt to be “important” by 72.7% of respondents, whereas 84.1% rated sharing information as “quite important”. The majority (79.5%) rated measuring the incidence of ADRs as “least important”. This appears, at face value, to be a highly defensible rating, indicating the requisite insights into the place of spontaneous reporting in clinical practice. By contrast, Gurmesa and Dedefom (2016) showed that only 48% of Ethiopian healthcare professionals correctly answered the knowledge aspect of the KAP questions, displaying poor knowledge of the importance of ADR reporting. In a study carried out by in Shiraz, Iran, 60% of the respondents wrongly believed that spontaneous reporting was intended to measure the incidence of ADRs (Vessal *et al*., 2009). Although pharmacists exhibit a positive attitude towards ADR reporting, they rarely take the trouble to report them.

An understanding of the need for and importance of spontaneous reporting is also linked to knowing which ADRs need reporting. In the present study, 95.5% of the respondents indicated that all ADRs should be reported. Nevertheless, there seemed to be uncertainty as to which characteristics of an ADR warranted it worthy of reporting. Most of the respondents (77.3%) were influenced to report by the seriousness of the ADR. This finding is in agreement with the available literature. In South India for instance, Prakasham *et al*. (2012) reported that 64.3% of the pharmacists they surveyed did not report ADRs that they felt were non-serious and simple. Pharmacists seemed to feel that authorities only wanted serious ADRs to be reported, as reporting minor ADRs would not contribute to improving medicine safety. In spite of this, there is evidence from other studies which have indicated that even serious and fatal ADRs are under-reported, with as high as 95% under-reporting rate (Hazell and Shakir, 2006; Backstrom *et al.,* 2004). There is however evidence from Zimbabwe to support the view that reporting seemingly non-serious ADRs will have an impact and significantly improve patient safety. In 2006, the MCAZ reclassified combination analgesics containing meprobamate, codeine and paracetamol from prescription-only to controlled medicine status, specifically as a result of reported side effects of drowsiness which led to misuse and abuse of these medicines (MCAZ, 2006).

In other countries such as Australia, healthcare workers are only required to submit expedited reports of serious expected on unexpected ADRs to the relevant authorities. For non- serious ADRs, they are required to only keep records which should be availed to the authorities as and when required (Yadav, 2008). In light of the challenges being experienced by pharmacists in Zimbabwe with some citing workload as a barrier to reporting ADRs, adopting a system like that is South Africa, where one is not required to report non-serious, expected ADRs would be more feasible and also decrease the burden on the PCV centre (Medicines Control Council, 2016)

The second most important factors cited (in both cases by 65.9% of respondents) were the unusualness of the ADR and one’s confidence in the diagnosis of an ADR. Globally, pharmacists tend to find difficulties in confidently diagnosing an ADR (Desai *et al*., 2011; Vessal *et al*., 2009), and this could be because their training lacks an emphasis on diagnosis. In the United Kingdom, 22.6% of pharmacists in a survey by Green *et al.,* (2001) had failed to report an ADR because they had filled in a Yellow Card for a doctor to sign. This clearly shows the low level of confidence pharmacists have in terms of the identification of ADRs, regardless of the place of practice. Furthermore, polypharmacy, could be a contributory factor in causing doubt about

causality as it becomes increasingly difficult to ascertain which medicine would be responsible for an ADR. However, pharmacists are trained to promote safe and rational use of medicines which will ultimately reduce the incidence of ADRs. The use of causality assessment tools such as the Naranjo algorithm and the WHO Assessment tool can help to overcome this barrier to some extent.

Lastly only 54.4% felt that ADR reporting is important if a new drug is involved. During clinical trials, medicines are tested in a controlled environment with relatively few study participants, usually excluding the elderly, pregnant women and children. Post-approval, these controls fall away and the chances of identifying previously undetected problems rise markedly (Zolezzi and Parsotam, 2005). Thus it is crucial to observe and report any ADRs occurring from new medicines as there are strong chances that these ADRs were missed in the clinical trial process. Reporting of ADRs for new medicines also assists in the risk-benefit profiling of the medicine to establish if it should be kept on the market or be withdrawn altogether. Pharmacists in the United Kingdom and Canada seem to appreciate the importance of reporting ADRs from new drugs and ADR reporting is said to significantly improve if there is involvement of a new agent (Green *et al*., 2001; Rawson, 2015). This could be because pharmaceutical companies in the developed world are proactive and aggressive in ensuring medicine safety, and communicate the need for reporting, as well as consistently conveying reports they receive to the necessary authorities. The extent to which firms operating in low- and middle-income countries comply with such reporting requirements is not known with any accuracy.

In South Africa, the recently-issued General Regulations to the Medicines and Related Substances Act, 1965 places an obligation on all holders of a certificate of registration to report all “new or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to adverse drug reactions”, as well as on their “risk management activities” in relation to such concerns (Minister of Health, 2017). In Zimbabwe, marketing authorization holders and applicants are under an obligation to report any ADRs (MCAZ, 2013). As there is limited enforcement and awareness of PCV, and a lack of emphasis on industry to maintain good PCV practice in LMICs (WHO, 2017), it is yet to be seen if making ADR reporting mandatory will yield better ADR reporting rates, with clinically sound information that could support a confident assessment of causality.

The extent to which pharmacists have the requisite knowledge to identify ADRs might be expected to be correlated with additional or post-graduate training. As mentioned above, a surprisingly high proportion of the respondents (72.7%) reported having completed a formal post-graduate qualification. Perhaps because of this very high proportion, it was not possible to demonstrate a statistically significant relationship between possessing such a qualification and knowledge of ADRs. In contrast, Argarwal *et al*. (2013) demonstrated a positive correlation between possession of a post-graduate degree and higher knowledge of ADRs. However, a study conducted in India also failed to show that possession of a post-graduate qualification had any bearing on knowledge of ADR reporting (Khan *et al*., 2013). It is possible that a relationship might not exist between knowledge and post-graduate training, where such qualifications are not in a medical field (e.g. in business management), as only 18.75% (n=6) of the respondents were in possession of a medically-related post-graduate qualification. It may also be possible that post-graduate qualification in the medical field do not

specifically provide emphasis on PCV and its importance. It is therefore imperative that PCV is covered in detail in the undergraduate pharmacy curriculum, and is also covered repeatedly and in detail in continuing professional development (CPD) programmes, in order to ensure continuous sensitisation to this crucial topic. Exposure to such CPD events should be correlated with duration of practice post-qualification. However, the present study showed that practice experience had no bearing on the attitude and practice of reporting ADRs by pharmacists. This finding was similar to that of Khan *et al*. (2013), who showed that Indian doctors' years of practice experience had no bearing on their attitudes towards ADR reporting.

In the present study, 79.5% of the study participants were aware of a medicine that was banned due to the ADR it caused. No significant relationship could be found between awareness of a ban and formal post-graduate training. As discussed above, the reason behind this lack of a relationship could be that of the type of post-graduate qualifications that the pharmacists who participated in this study had did not emphasise PCV. In addition, no relationship between years of experience post registration and respondents' knowledge of a medicine ban was demonstrated. This was an unexpected result as one would assume that knowledge increases with practice experience. Similarly, no statistically significant relationship was found between being able to identify a medicine that had been withdrawn from the market (banned) as a result of the emergence of an ADR and having completed post-graduate training of any sort. These findings suggest that greater effort should be made to include PCV in CPD programmes.

5.4.3 Addressing the systems issues

A previous study showed that only 52.8% of Zimbabwean health workers knew how to report an ADR (Khoza *et al*., 2004). Likewise, in a survey of community pharmacists in Lagos state, south west Nigeria**,** the most important reason cited by most pharmacists (44.6%) for failing to report ADRs was lack of knowledge on how to report (Oreagba *et al*., 2011). Although all the respondents in the present study correctly identified the MCAZ as the place to which ADR reports should be directed, almost half (45.5%) indicated that they did not know how to report an ADR. Similarly, only 29% is respondents in a survey conducted in Shiraz, Iran, were not aware of the existence of the national PCV centre (Vessal *et al*., 2009). In contrast, 97% of pharmacists in the United Kingdom knew they could participate in the Yellow Card scheme (Green *et al*.,2001). The issue here is not one of knowledge or attitudes, but of practice that is shaped by systems design and the barriers inherent in that system.

Other barriers identified by respondents in the present study were concerns about professional liability, lack of feedback from the authority on reported ADRs, and the lack of access to reporting forms. Previous research has acknowledged that feedback is essential in facilitating ADR reporting. These findings are no different from those in studies in other low-income countries as well as in high-income countries, In Canada, for instance, Rawson (2015) suggested that Canadians did not report ADRs because they believe that only safe medicines are approved for marketing, that they are ignorant about the reporting requirements, and that they feared litigation. Desai *et al*. (2011) emphasised that continuous feedback provides awareness of the initiatives of the PCV centre and further enlightens reporters on the causality of ADRs reported. In Zimbabwe, the MCAZ, through its online Drug Information Bulletin, provides feedback to stakeholders on statistics, progress and action on reported ADRs. However, the Bulletin is not published consistently with a gap of as

long as a year between issues of the publication. Further studies of the preferred form of feedback required (e.g. individual letters, drug bulletins, in CPD session) would be important for the regulator to conduct, so that they can improve in their attempts to increase the quality and quantity of spontaneous ADR reports.

Surprisingly, the respondents in the present study also indicated that they failed to report because of lack of access to reporting forms. The MCAZ has made great efforts to make ADR forms (Annex 9) easily and readily accessible to anyone who would require one. The form is available in the Essential Drug List of Zimbabwe (EDLIZ), from the MCAZ offices and on their website. In addition, they have also introduced electronic reporting by means of the MCAZ website. Completed ADR forms can be faxed, hand-delivered, emailed or posted to the MCAZ. This barrier is however not unique to Zimbabwe. In India, Ahmad *et al.* (2013) reported that 62.5% of pharmacists surveyed indicated that they lacked access to the ADR reporting forms. The question of accessibility also has to do with attitudes though. In a study conducted in South Africa by Ruud *et al*. (2010), it was reported that most South African pharmacists perceive ADR reporting as additional paperwork being added onto an already busy schedule. The Zimbabwean pharmacists also indicated that time constraints attributed to poor ADR reporting. This could be because of a heavy workload, but is also indicative of the weakened state of the healthcare system is Zimbabwe, which has been characterised by an exodus of healthcare professionals, including pharmacists. As a result, the few remaining pharmacists have a high patient load and reporting of ADRs may receive less priority as a result. Interestingly though, lack of time is an obstacle even in developed countries, where the pharmacist-patient ratio may be expected to approach the ideal (Green *et al.*, 2001; van Grootheest *et al*., 2002). The little emphasis given to PCV during initial under-graduate training could be the reason why it is not a priority for pharmacists the world over. However, in a setting where telephone and fax lines might not always be operative, the ability to capture and then forward a report later, such as by electronic mail or by means of a dedicated website, is critical. These were the most preferred methods of reporting an ADR identified in the present study. These findings are in concurrence with those of the United Kingdom Yellow Card (2017), where it has been stated that electronic, web-based reporting means are advantageous as they allow the reporter to insert the relevant information about the ADR without having to complete a paper submission. Direct contact was the second most preferred option, followed by post and telephone.

Some pharmacists in the present study pointed out that they were poorly motivated to report ADRs because there were no incentives to report. Incentives can be financial or non-monetary, such as CPD points, awards and journal subscriptions. The provision of non-financial incentives would be a more practical solution in a resource-constrained country like Zimbabwe. However, the provision of incentives might also result in an increase in minor ADR reporting with no impact on patient safety. Therefore, any incentive should be appropriately weighted to provide enough motivation for pharmacists to report without compromising on the quality of reports received.

Information sources are an important systems element. In a country with limited Internet access, direct attendance of face-to-face seminars or conferences was the preferred source of information on ADRs reporting (cited by 77.3% of the respondents). A likely reason for this is that attendance at a conference or

seminar contributes significantly to the CPD points that are required in order to maintain registration as a pharmacist. Only 22.7% of the respondents reported using the Internet to access information on PCV. Other sources of information cited were package inserts, journals and textbooks. While some may be current, the risk exists that such sources can rapidly become out of date. It was evident, however, from the responses that the pharmacists did not rely on only one source of information but would use different sources, as available.

5.5 Study Limitations

In this section, the limitations of the study are discussed, as well as remedial steps that must be taken by future researchers. The major limitations faced in this study were the poor response rate, high respondent apathy, the lack of spontaneous reports of ADR data as well as the lack of adequate resources for the study. Each of these limitations is discussed below, highlighting the necessary remedial strategies.

5.5.1 Poor response rate

One of the major limitations in the present study was the poor response rate. Even though a census approach was used and no sampling was performed, the questionnaire response rate was only 34.1%. This was significantly low and could affect the validity, reliability and generalizability of the findings of the study. Poor generalizability means that the findings will not be able to be applied to other pharmacists in Zimbabwe. To deal with the limitation of the poor response rate, the researcher recommends the use of strategies to enhance respondent interest in the study, such as enhancing respondent anonymity, putting in place incentives to enhance participation in the study, as well as the triangulation of research instruments. Particularly, triangulation would allow a researcher to take advantage of the strengths of other instruments so as to make up for the weaknesses of the questionnaire component. Questionnaires can be difficult to understand, require an appreciable level of education to ensure reading and writing eligibility, can be lost once dispatched and can be damaged in the filling process. Making use of other instruments like interviews and focus group discussions can enhance the response rate and hence the validity, reliability and generalizability of the findings.

5.5.2 Respondent concerns

The issue of respondent concerns was another limitation in this study. The researcher established that some of the respondents were afraid to participate in the study owing to various misconceptions, such as that the researcher was an undercover employee from the MCAZ, had political intentions and sought to expose bad pharmacists to their management. These misconceptions affected the study despite efforts by the researcher, such as distributing introductory letters from her university. It is suggested that to deal with such concerns, which negatively affects the response rate to the study, researchers must make use of an organization's managers in providing detailed information on the aims and objectives of the study as well as on how the data from the study will be used. Respondent reservations can also be managed by engaging educated respondents who have a history or experience of participating in academic surveys and using them to promote engagement with the study. A suitable organization can be a voluntary professional association, such as the Pharmaceutical Society.

5.5.3 Lack of ADR data

The lack of data on actual spontaneous ADR reporting in Zimbabwe was also a limiting factor in the present study. Even though empirical literature from studies done on the subject in other countries was readily available, data on the issue of ADR reporting in the Zimbabwean pharmaceutical context was scarce. In particular, the researcher found that there were hardly are any records of the ADR practices of the pharmacists in the country, as well as on the strategies used to deal with ADR reporting. The MCAZ has inadequate data available, which were not sufficient to be used in the data analysis processes in the present study and the researcher resorted to making use of primary data gathered from the research questionnaires. More academic studies are recommended on the issue of ADR reporting in Zimbabwe's pharmaceutical sector. Furthermore, researchers are encouraged to not only do the studies but to also make sure that they publish their findings in university presses and in academic journals to enhance data availability for other scholars in the discipline or field of study.

5.5.4 Design of the questionnaire

Any questionnaire design has to balance the desire to cover all possible issues and yet remain easily and quickly completed by the respondents. The questionnaire as applied in this study did not cover all of the potential barriers to reporting that have been identified in the literature. Specifically, it is acknowledged that questions relating to perceived challenges to autonomy and self-efficacy were not adequately covered. Likewise, no questions were specifically posed that explored workload issues, access to training or the extent to which feedback had been received from the MCAZ when making previous spontaneous reports.

Specifically, the options in question 12 of the questionnaire (which elicited which ADRs should in the opinion of the respondent, be reported) was constrained to a single option, when multiple options might have been possible. In question 16, the "direct contact" option was not explained, and was not identified as problematic during piloting, but could have been misinterpreted.

Lastly, although the respondents were asked which reporting method for ADRs would be preferred, and an "other" option allowed for free text entries, there was not a specific question eliciting opinions or thoughts on how the system would be strengthened. The interpretation of what might be done is therefore based on the available literature, experiences in other settings, and the views of the researcher alone, rather than the expressed views of the respondents to the study.

5.5.5 Resources for the study

The researcher also found resources to be a limiting factor in the course of the study. High costs were encountered in respect of the stationery needed for the study as well as in the gathering of secondary data for the literature review. In addition, the respondents had to scan their completed questionnaires if they responded via email. This proved difficult for most as scanners are not readily available in their places of practice and it is expensive to get documents scanned by a service provider. This could have negatively affected the response rate.

5.6 Conclusion

In this chapter, the discussion of the findings of the study was presented. The chapter reflected on the study objectives, and then placed the findings in the context of the literature. In the next chapter, the conclusions and recommendations from the study are presented.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

There is a low level of knowledge of ADR identification and reporting amongst most community pharmacists in Zimbabwe. Even though community pharmacists are able to relate some ADRs to the medicines causing them, such as thalidomide, astemizole, tetrazepam and rofecoxib, there is a critical lack of the ability to relate a particular ADR to its causative drug. This lack of knowledge is a cause of concern as community pharmacists represent a first line for the identification of ADRs owing to their daily interface with patients.

In addition, the present study has highlighted some of the barriers faced by community pharmacists that may contribute to under-reporting of ADRs. Community pharmacists in Zimbabwe seem to have a poor attitude to the issue of PCV, and they rarely report ADRs if they are encountered. Most Zimbabwean community pharmacists do not report the ADRs as they do not know the procedures or processes of reporting, and are afraid of legal liabilities and the risk of practice license revocation which they fear may occur as a result of the process. To some extent, some of the community pharmacists do not report ADRs because of limited resources and time.

The community pharmacists who responded to the present study acknowledged that all ADRs should be reported, but were uncertain as to which ADRs warranted reporting. As such, Zimbabwean community pharmacists appear to be inclined to report what they perceive as serious ADRs, which is what they feel the authorities require, as reporting minor ADRs is of no added value. The inability to relate an ADR to its causative agent, coupled with low levels of knowledge of ADR identification, means there is definitely under-reporting, even of serious ADRs. Zimbabwean community pharmacists possess the pharmacological knowledge to correctly diagnose ADRs, but they lack confidence in their clinical judgments. It is therefore imperative for community pharmacists to be empowered through proper training and guidance to enable them to take the lead role in PCV activities. Interventions are required to overcome these barriers and the solutions require a multiple stakeholder approach.

Very few Zimbabwean community pharmacists appreciate the importance of reporting ADRs caused by newly marketed medicines. There are very few pharmaceutical manufacturers in Zimbabwe that are still fully functional and as a result, most medicines are imported from abroad. As a result, those pharmaceutical companies responsible for importation are now more focused on marketing of these medicines, with less emphasis on their safety. It is imperative for pharmaceutical companies in Zimbabwe to take a more proactive and aggressive stance in ensuring the safety of the medicines they distribute, especially against the background that clinical trials would have been carried out on individuals with different genetics and physiological characteristics from those in the countries where the medicine are marketed. It is therefore prudent for the MCAZ to mandate pharmaceutical companies to take up a more responsible role in the interests of public safety.

Possession of a post-graduate qualification did not affect community pharmacists' knowledge of ADR reporting; neither did their duration of practice. Partly, this could be due to the type of post-graduate qualifications obtained, as some of the degrees being offered at the universities either lack professional application or are by design not fashioned to cater for pharmacists' specific requirements. Another reason could be that some pharmacists are pursuing degrees which are not directly related to their profession, such as the case of a pharmacist undertaking a Masters in Business Administration (MBA). As such, it is imperative to ensure a sound comprehension of pharmacovigilance at undergraduate level, so as to equip pharmacists with the necessary knowledge to report ADRs.

The major means through which Zimbabwean community pharmacists expressed a preference to report ADR cases were through the use of the Internet, particularly through the use of emails and websites. As such, these means must be taken full advantage of by both the pharmacy managers as well as the national medicines regulatory authority (MCAZ). Channels such as seminars and conferences should also be considered in order to provide information on ADR reporting to community pharmacists, and also to provide feedback. It is particularly recommended that the MCAZ puts in place monthly mailing lists to update pharmacists on any changes to PCV issues and also establishes a web-based form or application which makes it easy for pharmacists to upload ADR reports and other related data.

6.2 Recommendations

Based on the findings of the study the following specific and detailed recommendations are proposed:

- The PCZ and MCAZ should emphasize pharmacovigilance in undergraduate programmes for pharmacists, in order to better equip them to make operational and clinical judgments once in practice.
- The MCAZ, as the national medicines regulatory authority, should further investigate the barriers that prevent pharmacists from reporting and work on finding solutions to these. One such way would be to incentivize reporting of ADRs in the form of CPD points for those who would have reported. In addition, introduction of a Black Triangle system, which is currently in use in the United Kingdom to indicate new medicines or new use of a medicine which require increased surveillance, could enhance reporting for novel medicines.
- The MCAZ should establish monthly mailing lists to provide feedback and update pharmacists on any changes to PCV issues and also establish a web-based form or application which makes it easy for pharmacists to upload ADR reports and other related data.
- The MCAZ should mandate pharmaceutical companies to be proactive and more responsible in terms of patient safety. The obligations imposed in South Africa can form a model for such reporting.
- The MCAZ can develop and introduce a mobile phone application, like the Yellow Card app in United Kingdom, which would allow healthcare providers to report ADRs and receive ADR information.
- The PSZ should ensure that continuous professional development activities which focus on PCV are provided, to keep the practising pharmacists informed of their role in the healthcare system, the importance of keeping abreast with literature and the importance of PCV.

- To ensure that such knowledge is enhanced, it is imperative for pharmacy managers to put in place training workshops that equip pharmacists with the necessary knowledge regarding the identification and reporting of ADRs. Such training workshops should involve the national medicines regulatory authority, so that the pharmacists understand the legal requirements and implications of reporting ADRs in the country.
- Pharmacy managers should re-engineer pharmacy workflows to reduce workload and ultimately allow the pharmacist to comprehensively counsel patients to improve ADR detection.

As this study focused primarily on the knowledge, attitudes and practices of pharmacists who practice in the community setting in Harare, a follow-up study should be done to include hospital, research and industrial pharmacists to get a clearer and more accurate picture of the entire profession, and also to explore possible urban-rural differences within community pharmacy practice.

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ANNEXURES

ANNEX 1: WHO- UMC PROBABILITY SCALE

- WHO-UMC

Table 2. WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

ANNEX 2: NARANJO'S ADR SCALE (ALGORITHMIC)

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

ANNEX 3: CRITERIA FOR DETERMINING PREDICTABILITY OF AN ADR (SCHUMOCK AND THORNTON)

Definitely Preventable
1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5. Was there a known treatment for the Adverse Drug Reaction?

Probably Preventable
6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventative measures not prescribed or administered to the patient?

Not preventable
If all above criteria not fulfilled

ANNEX 4: ADR SEVERITY ASSESSMENT SCALE (HARTWIG AND SIEGEL)

Level 1 An ADR occurred but required no change in treatment with the suspected drug.

Level 2 The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)

Level 3 The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR
An Antidote or other treatment was required. No increase in length of stay (LOS)

Level 4 Any level 3 ADR which increases length of stay by at least 1 day OR The ADR was the reason for the admission

Level 5 Any level 4 ADR which requires intensive medical care

Level 6 The adverse reaction caused permanent harm to the patient

Level 7 The adverse reaction either directly or indirectly led to the death of the patient

ANNEX 5: INFORMED CONSENT FORM

Dear Pharmacist

My name is Tafadzwa Christine Mafundikwa. I am studying towards a Masters in Pharmacy Degree (Pharmacy Practice) with the University of KwaZulu-Natal in South Africa. My email address for correspondence is tcmafundikwa@yahoo.co.uk. You are being invited to consider participating in a study that involves research to establish the Knowledge, Attitudes and Practices (KAP) of pharmacists in Harare regarding the reporting of adverse drug reactions (ADRs). The aim and purpose of this research is to contribute to the safe use of medicines by strengthening reporting of adverse drug reactions by pharmacists in Harare, by identifying knowledge, attitudes and practices that hinder their involvement at present. The study is expected to use the census approach and will be conducted in Harare. It will involve use of a self administered questionnaire sent out via electronic mail. The duration of your participation if you choose to enroll and remain in the study is expected to be less than 30 minutes.

The study is not expected to be of any risk or to cause any discomfort. Based on the findings, the study will inform the pharmacy profession where it stands regards issues of pharmacovigilance (PCV) and what needs to be done to improve the current situation.

This study has been ethically reviewed and approved by the UKZN Humanities and Social Sciences Research Ethics Committee (approval number HSS/1325/015M).

In the event of any problems or concerns/questions you may contact the researcher on tcmafundikwa@yahoo.co.uk or +263 772 421 320 or the UKZN Humanities & Social Sciences Research Ethics Committee, contact details as follows:

HUMANITIES & SOCIAL SCIENCES RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604557- Fax: 27 31 2604609
Email: HSSREC@ukzn.ac.za

Your participation in this study is entirely voluntary and you can withdraw participation at any point. No penalties will be incurred as a result of withdrawing participation. In addition, no costs will be incurred by the participants as a result of participation in the study and also no incentives or reimbursements for participation will be given. No personal identifiers should be included on this questionnaire.

.....

CONSENT FORM

I……have been informed about the study entitled “Knowledge, attitudes and practices of pharmacists in Harare regarding the reporting of adverse drug reactions” by Tafadzwa C. Mafundikwa.

I understand the purpose and procedures of the study

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any of the benefits that I usually am entitled to.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at tcmafundikwa@yahoo.co.uk or +263 772 421 320.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

HUMANITIES & SOCIAL SCIENCES RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604557 - Fax: 27 31 2604609
Email: HSSREC@ukzn.ac.za

_____ _____

Signature of Participant **Date**

ANNEX 6: QUESTIONNAIRE

QUESTIONNAIRE

Please tick the appropriate responses

SECTION A: SOCIO-DEMOGRAPHIC DETAILS

1. Age: ----------
2. Gender: Male☐ Female☐

   Years of practising in pharmaceutical retail (community) sector----------

3. Any formal post-graduate training (e.g. post-graduate diploma, Masters or doctoral qualification)?

   Yes☐ No☐

I If yes, please specify qualification----------

SECTION B: KNOWLEDGE ON ADR REPORTING

4. On average, how many ADRs per week do you encounter?

   0-5☐ 6-10☐ more than 10☐

5. List 3 common ADRs that you encounter, along with the medicines that cause them

	Medicine	ADR
i.	----------	----------
ii.	----------	----------
iii.	----------	----------

6. Are you aware of any drug that has been banned due to ADR

   YES ☐ NO ☐

   If yes, name the drug and the ADR it caused

   _____

7. How important do you think it is to report ADRs?

   Very Important☐ Important☐ Not very important☐

8. Below is a list of reasons why people think it is important to report ADRs. On a scale of 1-4, with 1 being least important and 4 being very important, please indicate their order of importance to you

_____To identify and detect new ADRs

____To share information about ADRs with colleagues

_____To improve safety of patients

_____To measure the incidence of ADRs

SECTION C: ATTITUDES AND PRACTICES

9. Have you ever reported an ADR?

Yes ☐ No ☐

If yes, how many have you reported to date?----------

And where did you report?

MCAZ☐ The concerned pharmaceutical company☐

Other (please specify).....

10. In your opinion, what factors do you think are important while deciding to report an ADR? (You may tick many)

☐Seriousness of the ADR

☐Unusualness of the ADR

☐Involvement of a new drug

☐Confidence in your diagnosis of an ADR

11. What factors discourage you from reporting ADRS (You may tick many)

☐Did not know how to report

☐Did not know where to report

☐Did not think it was important

☐Lack of access to ADR Reporting forms

☐Legal liability issues

☐Concerns about professional liability

Others (please specify) ----------

12. In your view, which ADRs should be reported by pharmacists? (Tick 1 only)

☐None

☐ADRs to new drugs

☐Unknown ADRs to old drugs

☐ADRs to herbal drugs

☐ADRs to vaccines

☐ All ADRs

☐Others (please specify)----------

13. Are you aware of any centre or reporting system in Zimbabwe where you can report ADRs?

Yes ☐ No ☐

If yes, please specify----------

14. From which sources do you gather information about ADRs to new drugs? (You may tick many)

□Text books

□Journals

□Package inserts

□Medical representatives

□Seminars/Conferences

□Internet

15. Do you have free access to ADR reporting forms?

Yes ☐ No☐

16. Which method would you prefer to send ADR information? (tick 1)

☐Direct contact

☐Telephone

☐Post

☐Email/ on website

☐Other (please specify).....

Thank you for your time

ANNEX 7: ETHICS CLEARANCE CERTIFICATE UNIVERSITY OF KWAZULU NATAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

18 December 2015

Ms TC Mafundikwa 214525485
School of Health Sciences
Howard College Campus

Dear Ms Mafundikwa

Protocol reference number: HSS/1325/015M
Project title: Knowledge, attitudes and practices of Pharmacists in Harare regarding the reporting of Adverse Drug Reactions

Full Approval – Expedited Application

In response to your application received 18 September 2015, the Humanities & Social Sciences Research Ethics Committee has considered the abovementioned application and the protocol has been granted **FULL APPROVAL.**

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the amendment /modification prior to its implementation. In case you have further queries, please quote the above reference number.

PLEASE NOTE: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for a period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

.....
Dr Shenuka Singh (Chair)
Humanitities & Social Scinces Research Ethics Committee

/pm

Cc Supervisor: Mr AL Gray
Cc Academic Leader Research: Prof M Pillay
Cc School Administrator: Ms P Nene

Humanities & Social Sciences Research Ethics Committee
Dr Shenuka Singh (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 3587/8350/4557 **Facsimile:** +27 (0) 31 260 4609 **Email:** ximbap@ukzn.ac.za / snymanm@ukzn.ac.za / mohunp@ukzn.ac.za
Website: www.ukzn.ac.za

ANNEX 8: ETHICS CLEARANCE LETTER PHARMACISTS COUNCIL OF ZIMBABWE

Pharmacists Council of Zimbabwe
No. 2 Cork Road, Belgravia, Harare, P.O. Box CY 2138, Causeway, Harare, Zimbabwe
Tel: 04-740074, 741302, 740157
0772 137 039/ 0772 137 047/ 0712 833 817
Email: admin@pcz.co.zw
Website: www.pharmcouncil.co.zw

All correspondence to be addressed to the Registrar

TO WHOM IT MAY CONCERN

RE - PERMISSION TO COLLECT DATA FOR ACADEMIC PURPOSES FOR TAFADZWA C MAFUNDIKWA (214525485), PHARMACIST- A MASTERS STUDENT AT THE UNIVERSITY OF KWAZULU NATAL (UKN).

The Pharmacists Council of Zimbabwe has no objection for Ms Tafadzwa Mafundikwa, a pharmacist (Masters student at the University of Kwazulu Natal 214525485) to carry out an evaluation in retail pharmacies in Harare on **"Knowledge, attitudes and practices of pharmacists in Harare regarding the reporting of adverse drug reactions"**.

Kindly allow her to collect the relevant data for her research project only (academic purposes only).

A KARONGA (Mr)
REGISTRAR

PHARMACISTS COUNCIL OF ZIMBABWE
2 Cork Road, Belgravia, Harare
10 JUL 2017
P.O. BOX CY 2138, CAUSEWAY
TEL: 740074, 741302 FAX: 74...

ANNEX 9: MCAZ ADR REPORTING FORM

MCAZ Medicines Control Authority of Zimbabwe

PVF 01

Spontaneous Adverse Drug Reaction (ADR) Report Form						
Identities of Reporter, Patient and Institute will remain confidential						
MCAZ Reference Number (MCAZ use only)						
Patient Details (to allow linkage with other reports)						
Clinic/hospital Name:				**Clinic/Hospital Number**		
Patient Initials:				**VCT/OI/TB Number**		
Date of Birth:				Weight (Kg)	Sex:	
Age:				Height (meters)		
Adverse Reaction						
Date of Onset:						
Duration:	Less than one hour	Hours	Days	Weeks	Months	
Description of ADR						
Serious: Yes ☐ No ☐	Reason for Seriousness	☐ Death		☐ Life-threatening		
		☐ Hospitalization/prolonged		☐ Disabling		
		☐ Congenital-anomaly		☐ Other medically important condition		
Relevant Medical History						
Relevant Past Drug Therapy						
Outcome of ADR	Recovered	Not yet recovered	Fatal	Unknown		
Current Medication						
Generic Name	Brand Name	Batch Number	Dose	Indication	Date Started	Date Stopped
Concomitant (Other) drugs taken, including herbal medicines & Dates/period taken:	Name of drug:				Date started	Date stopped
Suspected drug(s), if known:						
Laboratory tests results:						
Reported by						
Forename(s) & Surname:						
Designation:						
Address:						
Signature:			Date:			
Send to: The Director-General, Medicines Control Authority of Zimbabwe, 106 Baines Avenue, P O Box 10559, Harare **Tel**: +263-4-708255 or 792165, **E-mail**: mcaz@mcaz.co.zw, **website**: www. mcaz.co.zw						

NB. This form may be completed for any ADR related to medicines or medical devices
***Please attach any other additional information, including an anonymized picture of the ADR (with patient's consent)**

Rev 6_November 2016 Page 1 of 1