OPTIMISING ADVERSE DRUG REACTIONS REPORTING AND STRENGTHENING OF PHARMACOVIGILANCE SYSTEMS IN NAMIBIA

A RESEARCH DISSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY IN PHARMACY PRACTICE

OF

THE UNIVERSITY OF NAMIBIA

BY

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APRIL 2021

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ABSTRACT

Spontaneous adverse drug reaction (ADR) reporting is a vital part of pharmacovigilance activities within a health system. Under-reporting of adverse drug reactions is a widespread phenomenon among healthcare workers. Little is known about the culture of reporting among healthcare workers in public healthcare settings in Namibia, in particular, in relation to adverse drug reactions. This required the determination of the basal effectiveness of pharmacovigilance systems and the capacity of the healthcare workers within the health system to carry out pharmacovigilance activities and the development of ways of mitigating whatever gaps exist within the system. This research depicted the current state of pharmacovigilance within the health system, healthcare workers' reporting abilities and capabilities, patient-level dynamics and possible pharmacovigilance system optimisation.

Chapter 1, the general introduction, provided a background to the need for and the state of pharmacovigilance in Namibia and other low- and middle-income countries. It highlighted the challenges faced by healthcare workers in reporting ADRs and the possible ways of mitigating the challenges.

Chapter 2, the literature review, discussed different aspects of therapeutics, links between therapy and development of adverse events, culture of pharmacovigilance in different regions of the world and identified ways of mitigation under-reporting among different cadres of healthcare workers.

Chapter 3 sought to know the treatment outcomes of patients after the introduction of atazanavir boosted with ritonavir (ATV/r) as a preferred second-line protease inhibitor on the health of patients compared with lopinavir boosted with ritonavir

(LPV/r) based second-line regimens with respect to the reported ADRs. Most ADR cases received on these two regimens were linked to ATV/r; however, no conclusion can be made considering the possibility of under-reporting of possible and suspected cases.

Following the results obtained at patient-level, Chapter 4 evaluated and explored the reasons for the underreporting of ADRs by healthcare workers and the factors associated with such reasons in Namibia through a cross-sectional quantitative survey. Nursing cadre was the only predicting factor for under-reporting of ADRs among the healthcare workers, adjusted odds ratio (aOR) = 0.17(95% CI: 0.07, 0.401, p<0.01). Particular attention may be focussed on the nursing cadre because they are the first healthcare professionals seen by patients in the public healthcare sector.

In a bid to develop an optimisation plan for strengthening the pharmacovigilance and ADRs reporting, a contextual study of the knowledge of 8 key informants about the pharmacovigilance system in Namibia and proposed ways of optimising the existing system was carried out in Chapter 5.

Chapter 6 presents an electronic tool (Epicollect5® as a platform) that was developed in a bid to mitigate the under-reporting of ADRs. The tool was introduced and piloted during several training sessions among healthcare workers in Namibia, both in the public and private healthcare sectors.

Chapter 7 presented the recommendations and conclusions drawn from the different studies in this research.

In conclusion, in order to optimise the pharmacovigilance and ADR reporting system in Namibia, there is a need for political will on the part of decision-makers,

mandating healthcare workers to report any suspected ADR by using designated means such as paper-based or electronic reporting platforms (considering the challenges related to paper-based reporting systems). Provision of feedback in the form of ADR case report analysis by the Therapeutic Information and Pharmacovigilance Centre to the reporting healthcare worker or facility will facilitate good rapport between the two parties. Incorporating pharmacovigilance into the curriculum of medical, pharmacy and nursing students can bridge the gap between knowledge and practice. Conducting in-service and continuing professional training might assist in providing the necessary education for older healthcare workers. The need for advocacy for pharmacovigilance among healthcare workers and patients cannot be overstated; involving facility-level and regional-level Therapeutic Committees in pharmacovigilance through advocacy, promotion and analysis of reported cases will go a long way in stimulating ownership of the activity.

KEYWORDS: Namibia; healthcare workers; pharmacovigilance; adverse drug reactions (ADRs)

LIST OF PUBLICATION(S)/CONFERENCE(S) PROCEEDINGS

1. **Adenuga BA**, Kibuule, D. A case for strengthening pharmacovigilance systems in Namibia. *Glob. J. Med. PUBLIC Heal.*, 2018; Vol. 7, Issue 1. Refer to Appendix 7
2. **Adenuga BA**, Kibuule, D, Rennie, TW. Optimizing spontaneous adverse drug reactions reporting in public healthcare setting in Namibia. *Basic Clin. Pharmacol. Toxicol.*, 2019; Vol 126, Issue 3. doi:10.1111/bcpt.13325. Refer to Appendix 6
3. **Adenuga BA**, Rennie, TW. A Profile of Adverse Drug Reactions of Atazanavir- and Lopinavir-Based Antiretroviral Regimens in Namibia. *Drug Saf.*, 2019; 42, pages 915–917. doi:10.1007/s40264-019-00832-3. Refer to Appendix 5
4. **Adenuga BA**, Kibuule D, Bamitale KDS, Rennie TW. Effective integration of pharmacovigilance systems at public health facilities in resource-limited settings: a qualitative study. Research in Social and Administrative Pharmacy. 2019. https://doi.org/10.1016/j.sapharm.2019.11.010. Refer to Appendix 8

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LIST OF ABBREVIATIONS AND/OR ACRONYMS

ADRs	Adverse Drug Reactions
ART	Antiretroviral Therapy
ATV/r	Atazanavir/ritonavir
HCW	Healthcare worker
LMICs	Low and Middle Income Countries
LPV/r	Lopinavir/ritonavir
MAH	Marketing Authorisation Holder
MoHSS	Ministry of Health and Social Sciences
NMRA	National Medicines Regulatory Authority
NMRC	Namibia Medicines Regulatory Council
PIL	Patient Information Leaflet
PV	Pharmacovigilance
SSA	Sub-Saharan Africa
SOP	Standard Operating Procedures
TIPC	Therapeutic Information and Pharmacovigilance Centre

ACKNOWLEDGEMENTS

Various individuals and institutions have supported this research project. First, I acknowledge the Lord God Almighty, who calls the things that are not as though they were. In addition, this project would not be possible without the countless support of my beautiful wife, Oluwaseun Olayemi Olafusi, and my beautiful daughters, Anuoluwapo Adenike Precious, Adetayo Adebusola Peace and Adedayo Moyinoluwa Pretty. Secondly, I appreciate my research supervisors, Prof Timothy William Rennie and Dr. Kayode Dominion Samuel Bamitale from whom I have learnt, acquired and bettered my scientific approach to research and for the priceless critique at various stages of design, implementation and reporting. Thirdly, I extend my appreciation to the staff of the Ministry of Health and Social Services and other healthcare workers, for the data collection processes. Fourthly, I acknowledge the co-authors particularly my supervisors, Dan Kibuule (my mentor), Francis Kalemeera and Anastasia Aluvilu, among others for appraising the various manuscripts and contributing to the conduct of the research. I thank Adolph Kauhonina and Tafadzwa Tirivangani who assisted in reading through the dissertation. I acknowledge my data collectors Johnson Alao, Amon, Mrs. Adebayo, Kenny Adenuga, including my wife and for their tireless assistance in data collection. I acknowledge all research and ethical review boards and healthcare workers that agreed to be part of this study to make it possible. Lastly, I would like to thank my fellow PhD students, Dr. Dan Kibuule, Mr. Anthony Ishola and Mr. Francis Kalemeera for the encouragement and support they have extended to me throughout this project.

May the Lord bless you all!

DEDICATION

I would like to dedicate this dissertation to the people that motivated and inspired me to undertake a doctoral study at times when I felt it was not “necessary”. My inspirational elder brothers, Adebayo Adenuga and Babafemi Adenuga and my younger siblings – Aderonke, Adeola and Babatola, my parents, Mr. Bankole Adeoye Adenuga (late) and to my mother Mrs. Adeyemi Iyabosola Adenuga for their parental care and investment in my education.

My dear wife Oluwaseun Olayemi Olafusi and children Anuoluwapo Adenike Precious, Adetayo Adebusola Peace and Adedayo Moyinoluwa Pretty for the support you always provide for me.

Finally, to my former Pharmacy School friends, Yomi Olusanya and Ibrahim Amolegbe, who I told my desire was to become a professor of pharmacognosy on a bright sunny day back in 1995. This is the main reason I decided to pursue my passion and registered for studies in 2016 and will always remember that day. Also, to the School of Pharmacy, University of Namibia for giving me the opportunity to undergo this program.

Lastly, this dissertation is dedicated to all the healthcare workers in Namibia who are striving to improve the healthcare delivery system and contribute their quota to better patient care.

DECLARATIONS

I, Babafunso Aderemi Adenuga, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

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Name of Student	**Signature**	**Date**

CHAPTER 1: INTRODUCTION

1.1 Background

Pharmacovigilance has been defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (1). Pharmacovigilance is derived from two words, *Pharmakon* (Greek), meaning medicinal substance and *Vigilia* (Latin), meaning to keep watch (2). Pharmacovigilance, carried out as post-marketing surveillance studies, is a Phase IV clinical trial (when it is actively conducted by marketing authorisation holders or manufacturers of marketed drugs) involving the collection of drug safety reports related to a newly introduced and approved chemical agent or drug within the general population or drugs already on the market (3,4). It is evident that not every adverse reaction can be picked up during clinical trials prior to granting marketing authorisations for medicines, due to the number of individuals recruited, population type, the health status of individuals in the study (this depends on the therapeutic indications of the drug undergoing clinical trials), including factors such as the paediatrics, geriatrics and pregnant women which excludes potential patients from studies (5,6), thus, continuous collection of drug safety evidence is paramount.

1.1.1 Historical perspective of pharmacovigilance development

The history of pharmacovigilance started about 172 years ago in 1848 when a girl reacted and died after receiving chloroform as anaesthesia during an infected toenail removal procedure. Prior to the event, it was not known in clinical practice that chloroform administration in patients could lead to death (7). Though, the cause of death

was investigated; it was not possible to ascertain the cause. In 1937, sulfanilamide elixir containing diethyl glycol as the solvent was the cause of 107 deaths in the USA; the deaths were attributed to diethyl glycol (8). As a consequence of the event, the Federal Food, Drug and Cosmetic Act was enacted in 1938. It was confirmed in 1955 that acetylsalicylic acid (ASA) can cause gastrointestinal bleeding, thus, it was contraindicated in patients with gastric ulcers (9), however, Douthwaite alluded to the link between ASA and melena in 1938 (10). ADR attributable to thalidomide which resulted in congenital malformation of thousands of children whose mothers were administered thalidomide for the treatment of nausea and sedation in the 1960s necessitated the World Health Organization (WHO) to call for intensified monitoring of the safety of drugs after regulatory approval by national medicines regulatory authorities (NMRA) all over the world (11–16). However, new cases of birth defects due to thalidomide administration have been reported in South America (16–18). Dr. McBride, an Australian doctor (19) suggested a link between foetal malformations and the use of thalidomide by pregnant women in 1961. Correlation between foetal malformations and the use of thalidomide during pregnancy was shown in a study in 1973 (20).

Timeline of evolution of pharmacovigilance post-thalidomide tragedy:

1962 – USA approved the amendment requiring the submission of safety and efficacy data of drugs prior to marketing (8).

1964 – United Kingdom (UK) introduced the “Yellow Card” (YC) scheme (21).

1965 – Thalidomide disaster prompted pharmacovigilance activities in Europe, necessitating European legislation (22,23).

1966 – Boston Collaborative Drug Surveillance Program was started in USA (24).

1968 – WHO Programme for International Drug Monitoring was started.

1992 – European Society of Pharmacovigilance was founded, changed into the International Society of Pharmacovigilance (IsoP).

1995 – European Medicines Agency (EMA) was formed. It is the centralised medicine regulatory authority within the European Union (EU).

2001 – EudraVigilance was founded. It is the official body that manages and analyses information on suspected ADR within the EU.

2012 - Directive 2010/84/EU changed how pharmacovigilance is conducted within the EU (25).

1.2 Classification of adverse drug reactions

ADRs have been classified as Type A (augmented or dose-related) reactions and Type B reactions. Type A reactions are those ADRs with known pharmacology of the suspect drug; these are associated with high morbidity and low mortality. An example of this will be the sedative effect of some antihistamines. On the other hand, type B reactions (bizarre) are those ADRs with idiosyncratic onset, the reactions may not be predicted from drug pharmacology; they have low morbidity and high mortality (26). These are patient-related rather than the drug itself, they occur in a small portion of the population (27,28).

Types C, D, E and F were added to make up for the gaps in the classification of ADRs that did not fall within the definitions of Types A and B ADRs. Type C reactions are

chronic reactions while Type D reactions are delayed onset reactions. Withdrawal symptoms fall within Type E and unexpected therapy failure is categorized as Type F ADRs (27,29).

1.3 Burden of adverse drug reactions

The need for healthcare professionals and healthcare policymakers to know the implications and what impact ADRs can have on health systems has been underscored by many authors (1,4,30–32). Mortality and morbidity attributable to ADRs have major impacts on both the patients and health systems, these can be emotional, fatal, or economic (33,34). In a study carried out among patients on admission at hospitals in the United Kingdom, it was found that ADRs accounted for about 6.5% of all admissions (35). In a prospective study conducted in the Netherlands among patients on admission in hospitals, 1 in 7 patients admitted suffered an ADR while on admission; older patients with chronic medications were believed to be more prone to developing ADRs while on admission (36).

1.3.1 Pharmacovigilance and ADR reporting in Namibia

Namibia is a country in Southern Africa, with a population of about 2.5 million (37). The country is a full member of the WHO Programme for International Drug Monitoring, joining the programme in 2008 (38). It is resource-limited, both human and financial, and has a relatively high prevalence of communicable diseases such as HIV/AIDS, tuberculosis and malaria, and non-communicable diseases. The need for pharmacovigilance and accurate reporting of suspected cases of adverse events cannot be overemphasised. As part of the drug regulatory functions of the Namibia Medicines

Regulatory Council, it is necessary to ensure the safety of the medicines on the market, thus, the need for the introduction of a Therapeutic Information and Pharmacovigilance Centre (TIPC). The unit was established in 2007 with the assistance of donor funding organizations such as the United States of Agency for International Development (USAID) and supported in-country by Management Sciences for Health. It is a part of the Pharmaceutical Control and Inspectorate, sub-directorate within the Ministry of Health and Social Services. TIPC coordinates pharmacovigilance activities in the public and private healthcare settings in Namibia. Periodic Safety Update Report (PSUR) [a periodic report on adverse events experienced by patients, submitted by marketing authorisation holders (MAH)] and Individual Case Safety Reports (ICSR), which are spontaneous suspected ADRs picked up or diagnosed by healthcare workers, are sent to the centre. These are collated, aggregated, analysed and reported to the WHO Uppsala Monitoring Centre (WHO-UMC) through Vigibase. Paper-based reporting is the current mode of relaying suspected ADRs by healthcare professionals from the public healthcare facilities, these may be faxed, scanned and emailed or hand-delivered. The system is fraught with possible under-reporting of events that might not be picked up due to lack of competence, nonchalant attitude, non-availability of the reporting tool, or inability to convey reports in the absence of appropriate transmission mode (for example, fax machine or access to internet/email service). Reports may lose their value if they are not conveyed at the right time and patient care might be impacted by such systems.

The pharmacovigilance system in Namibia is not robust. Though, it serves both the public and private healthcare sectors, human and financial capacities limit the

effectiveness of the current system (39,40). This is similar to what is obtainable in other resource-limited settings (41).

Between January 2016 and September 2019, almost 700 ADR reports were received by the TIPC, giving an average of 20 reports per month. In a recent study using the ICSR submitted to TIPC focussed on atazanavir boosted with ritonavir, and lopinavir boosted with ritonavir, it was found that ADRs occurring among the specific patient population might be under-reported (42), in comparison to the frequency and time to onset of ADRs associated with these regimens as reported in other settings (43,44). Under-reporting of ADRs might be attributed to the knowledge, attitude and practices of the healthcare workers who are directly in contact with patients (45–49).

1.3.2 Challenges identified that can contribute to under-reporting of ADRs

Some of the factors that may contribute to under-reporting of ADRs, are lack of awareness of pharmacovigilance systems in the settings where healthcare workers are, deficiency in training to identify and report suspected ADRs, fear of being reprimanded or litigation due to possible negligence, and lack of risk perception of the consequences of ADRs (50,51). According to Khan et al. (2015) about half of the health workers interviewed do not know how to report ADRs and/or are not aware of the existence of a formal ADR reporting scheme (52). They classified the factors that may contribute to the under-reporting of ADRs into two categories, namely, provider-influenced and patient-influenced factors.

1.3.2.1 Provider-influenced ADR under-reporting

The insignificance of suspected ADRs identified by healthcare workers was too inconsequential or too well known to be reported (53). Jaundice and other ADRs associated which might be linked with atazanavir in atazanavir/ritonavir combination have been reported by word of mouth by some healthcare workers in Namibia; however, the majority of such ADRs have not been documented officially. The impact of some activity on the general overview of the PV system in the country may be undermined, and the expected outcomes or goals of the pharmacovigilance system might not be achieved.

Awareness or knowledge about how ADRs should be reported or what should be reported may be a deterrent to some healthcare workers to be able to identify and report suspected ADRs whenever they detect any (54).

ADR reporting forms may be too complex to complete for some healthcare workers, thus, causing neglect of the activity. Lack of an electronic reporting system was identified as a possible hindrance to ADR reporting in some settings, therefore, may be a cause of under-reporting of ADRs (54,55).

Accessible means to communicate compiled suspected ADR reports to a central point for collation may discourage healthcare workers from reporting and the possibility of overlooking the importance of the suspected ADR over time, considering the possible remission of the ADR. The motivation to report suspected ADRs might be linked to incentives. Incentives such as public acknowledgement has been identified as a tool to motivate health workers to report suspected ADRs (56,57).

Time spent in attending to patients and the perceived workload do not encourage healthcare workers to document suspected ADR (58,59).

1.3.2.2 Patient-influenced ADR under-reporting

Patient reporting of ADRs is not common in most LMICs; thus, patients may have minimal knowledge of ADRs and where to report suspected ADRs. They might not know the meaning, implications, and what to do whenever an ADR occurs; this may contribute to the under-reporting of ADRs within a health system (53,60).

1.4 Pharmacovigilance and the need for Adverse Drug Reaction Reporting

The need for and importance of pharmacovigilance in LMICs such as Namibia has grown over the years, especially with the high prevalence of HIV/AIDS and the attendant opportunistic infections such as communicable diseases like tuberculosis. Monitoring and reporting of ADRs have been suboptimal in most LMICs, owing partly to resource constraints, both human capacity and financial consequences of embarking on robust pharmacovigilance systems (61).

The need for identifying and reporting suspected ADRs cannot be over-emphasised as this contributes to the post-marketing surveillance data gathered while a drug has been introduced into the larger population after regulatory approval.

1.5 Aims and objectives of the research

The main aim of this research was to evaluate the current pharmacovigilance and ADR reporting system in Namibia based on existing data, for example, ADR reports submitted to TIPC, knowledge, attitude, awareness and practices (KAAP) of healthcare workers and to design and test an intervention to explore how the system can be optimised. The outcomes will be used to develop a conceptual model for policy

development to optimise ADR reporting and pharmacovigilance systems in Namibia. The research sought to address the following objectives:

(i) To explore the current state of ADR reporting and pharmacovigilance among the public healthcare workers in Namibia.

(ii) To understand what can be done to improve the state of pharmacovigilance among the healthcare workers and patients in Namibia.

(iii) To develop possible innovative tools that can be introduced to optimise the pharmacovigilance system in Namibia.

1.6 Research overview and scope

The scope of the research is to interrogate evidence to inform policy or guidelines to optimise the ADR reporting and pharmacovigilance systems in Namibia. This required the determination of the basal effectiveness and capacity of the healthcare workers within the health system and the development of ways of mitigating whatever gaps exist within the system. The dissertation is organised in seven chapters depicting health systems, healthcare workers, patient-level dynamics, system optimisation, and general introduction and discussion sections.

Chapter 1, the general introduction, provides a background to the need for and the state of pharmacovigilance in Namibia and other LMICs. The chapter also highlights the challenges faced by healthcare workers in reporting ADRs and the possible ways of mitigating the challenges.

Chapter 2 is a literature review of the current evidence on ADR reporting and pharmacovigilance in Africa and elsewhere in the world.

Chapter 3 presented a retrospective analysis of data reporting in Namibia using the impact of the introduction and adverse events attributable to ATV/r as a preferred second-line protease inhibitor on the health outcomes of patients compared to LPV/r based second-line regimens, a reflection of pharmacovigilance practice among public healthcare workers.

Chapter 4 was a cross-sectional survey of healthcare workers' (HCW) KAAP towards pharmacovigilance to identify the reasons for underreporting of ADRs, and the factors associated with such reasons and possible interventions to address ADR under-reporting in Namibia.

Chapter 5 was a qualitative study probing the background knowledge of key informants about the pharmacovigilance system in Namibia and proposed ways of optimising the existing system.

Chapter 6 was a feasibility study of an electronic mobile reporting tool that was introduced and piloted among healthcare workers in Namibia.

Chapter 7 provided the recommendations and conclusions based on the results obtained from the studies.

1.7 Research setting

The research setting was the Namibian public healthcare setting with an emphasis on the Ministry of Health and Social Services facilities (MoHSS), i.e. hospitals, health centres

and clinics. Namibia is a country that is located in the South-western part of Africa; the country gained independence in 1990. Most healthcare workers are employed by the MoHSS, in addition, TIPC is situated within the ministry thus, the need to capture the needs or challenges of those that attend to the majority of Namibian patients.

The Namibia Medicines Regulatory Council (NMRC), a statutory body set up by the Medicines and Related Substances Act 13 of 2003, is charged with regulating medicines and medical products within the country. It ensures safe, efficacious and quality medicines are registered and distributed at different levels of healthcare delivery systems. TIPC forms one of the units within the NMRC, having pharmacovigilance within the Namibian health system as one of its roles.

Ethical approvals were sought through formal research proposal submission and application, from the Ethics of the Ministry of Health and Social Services and University Research Ethics Committee of the University of Namibia. This was done after the PhD research proposal presentation at the School of Pharmacy, University of Namibia and approval by the Research Ethics Committee of the School of Pharmacy.

There are a total of 43 hospitals, 44 health centres and 267 clinics spread across the 14 regional health directorates and 35 health districts in Namibia.

1.8 Summary

This chapter outlined the need for pharmacovigilance, including the issues that limit healthcare workers from carrying out ADR reporting as part of their routine clinical work. The next chapter, which is the literature review, will seek to broadly look at what ADRs are, how ADR reporting is coordinated globally and locally. Also, the KAAP,

concerning pharmacovigilance, of different cadres of healthcare workers in various regions of the world will be reviewed.

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CHAPTER 2 – LITERATURE REVIEW

2.1 Introduction

A literature review of studies published up to September 2019, which assessed ADR reporting or pharmacovigilance systems strengthening or knowledge, attitude and practices of healthcare workers of pharmacovigilance. The search strategy applied search terms unique to each study, using the keywords Knowledge, Attitude, Awareness and Practices (KAAP), adverse drug reactions, adverse events, qualitative research, electronic reporting and pharmacovigilance. The search was conducted in Mendeley, PubMed, Google Scholar, ScienceDirect and the reference lists of retrieved articles to identify other studies in grey literature. Articles of relevance were selected to inform the literature review.

2.2 Medicines and Drug Development

Medicines or drugs have been used by humankind in treating different ailments from time immemorial. These are presented in various forms such as herbs, roots, human or animal dung, leaves, barks and whole plants, including marine sources (1–3). However, modern medicine has revolutionised medicine use and the presentation of different medicines as distinct dosage forms intended for applications in different conditions/disease states – tablets, injections, solutions, etc. these are formulated with or without excipients (4). The two terms i.e. medicine and drug are used interchangeably; however, drugs may have strong public connotation referring to substances like narcotics, for example, morphine, heroin and other opioid drugs or opiates.

Modern medicines have inherent toxicity due to their chemical, or synthetic or semi-synthetic nature, or if the drug is not used as prescribed or if it is exhibiting other activities that the user/patient did not anticipate.

2.2.1 *Drug development*

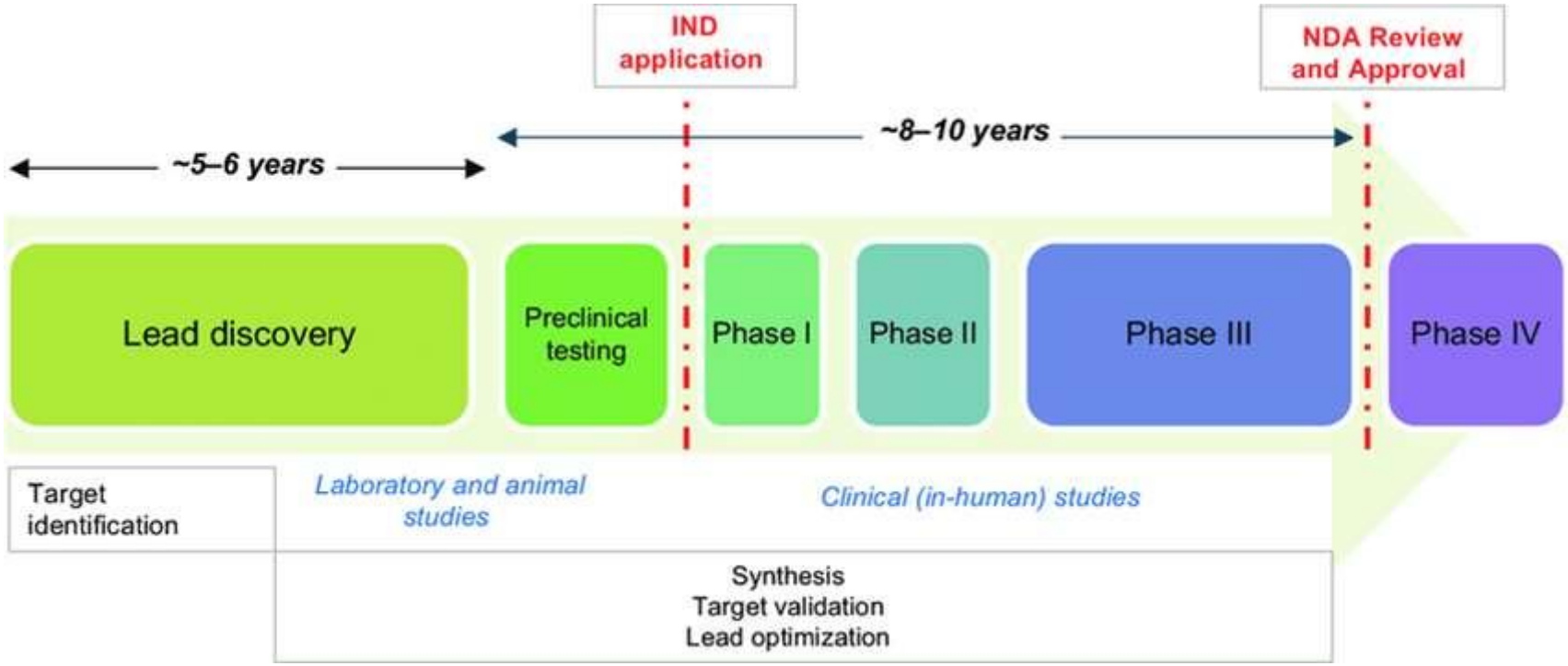
Drug development refers to "the process of developing a new drug that effectively targets a specific weakness in a cell. This process involves specific pre-clinical development and testing, followed by trials in humans to determine the efficacy of the drug." (5,6). Pharmaceutical manufacturers of either innovator or generic products are subject to the prevailing regulatory laws and guidelines applicable to the manufacture of finished pharmaceutical products, both locally such as Namibia Medicines Regulatory Council (NMRC) and internationally such as the World Health Organization (WHO), United States Food Drug and Administration (USFDA), European Medicines Agency (EMA) and such other regulatory bodies (6,7).

The introduction of new chemical entities (NCE) requires rigorous pharmaceutical development processes and clinical trials to ensure the optimal finished pharmaceutical product (FPP), with good release profile both *in vitro* and *in vivo* or after administration. Such drugs go through clinical trials to ensure their safety, efficacy and quality, before, during and after obtaining regulatory approval. At the lapse of the patency of an NCE, generic manufacturers are allowed to manufacture such medicines following strict regulatory rules. Generic product manufacturers do not need to carry out clinical trials as part of the regulatory approval process for their product.

2.2.2 *Phases of drug development*

There are various stages involved when a new drug is being developed. The primary goal of the drug development process is to produce a drug that is safe, efficacious and of good quality when used at intended doses by humans or desired organisms. The stages are depicted in Figure 1.

Figure 1 New Drug Development pathway



Coloma, Preciosa. Phase 0 clinical trials: Theoretical and practical implications in oncologic drug development. Open Access Journal of Clinical Trials. 5. 119-126. 10.2147/OAJCT.S32978.

2.3 Clinical trials

After drug discovery and drug formulation, a new drug molecule/new chemical entity (NCE) will be subjected to clinical trials. Prior to the marketing of a new drug, researchers need to ensure the efficacy and safety of the NCE. Clinical trials are performed in four phases; the initial three phases of the trials are carried out before a drug developed by the Research & Development of a pharmaceutical manufacturing company can be marketed and allowed to be used in humans (8–10). The last phase (Phase IV), which is the post-marketing period, ensures the continuous monitoring of the safety of an approved NCE. A critical phase in clinical trials is the non-clinical stage, where the drug is tested in animal models for toxicity. The dose of the drug used in animals is either reduced or increased when introducing to humans, depending on the apparent therapeutic index (ratio of effective dose (ED_{50}) to lethal dose (LD_{50}) of the drug) (11,12).

2.3.1 Phases of clinical trials

Phase I – Initial safety and dose determination trials are carried out in either ill patients or healthy volunteers, depending on the indications that will be proposed for the new molecule. The acceptable dose range for the drug is determined at this stage. Instances, where ill patients are included in Phase I clinical trial, will be among cancer patients or epileptics (13).

Phase IIa – Efficacy and safety of the drug are tested in selected patients with the disease to be treated, diagnosed, or prevented. This is conducted on a pilot-scale; thus, the number of participants may not be more than 300.

Phase IIb – Efficacy and safety of the drug are also tested at this stage in patients with the disease; however, this is more rigorous compared to Phase IIa. The efficacy of the drug is confirmed at this stage.

Phase IIIa – These are trials conducted in a large population of patients with the disease of concern. It confirms the efficacy and safety of the new chemical entity. The trials are carried out before the submission of dossiers for regulatory approvals. Data needed for package insert such as pharmacokinetics, pharmacology, contraindications, interactions, etc. are generated at this stage.

Phase IIIb – This is a trial conducted prior to a product's regulatory approval. This may complement earlier submissions.

Phase IV – This is also called post-marketing surveillance. Pharmacovigilance falls within Phase IV trials. This is when other safety issues are picked in real life, rather than in a trial setting. Adverse events that were not seen or picked up during the initial phases of clinical trials will be reported by clinicians and patients at this stage, having in mind that the Phases I – III clinical trials were conducted in controlled settings within which the number of participants, their characteristics such as demographics like the age group, gender and race would not cover all the population that the new drug/medicine is intended to be administered to.

Such ADRs are reported to pharmacovigilance centres by the manufacturers, practitioners, or patients. The pharmacovigilance centres collate, aggregate and transmit the ADRs or adverse events to the World Health Organization-Uppsala Monitoring Centre (WHO-UMC).

2.4 World Health Organization (WHO) and Pharmacovigilance

Pharmacovigilance is a well-established medical discipline in developed countries while low- and middle-income countries (LMICs) are lagging (14). The thalidomide tragedy which occurred in the early 1960s necessitated the need for a coordinated effort in ensuring the safety of patients through the provision of safe, efficacious and quality assured products (15). To this end, the WHO, through its policy-making body, World Health Assembly (WHA), encouraged every country to institute a pharmacovigilance monitoring body (16).

WHO-UMC started in 1978, with the mandate to coordinate pharmacovigilance activities among member states. Minimum standards necessary to achieve the goals of pharmacovigilance and enhance patient safety were provided by the WHO (17). In order to achieve success in pharmacovigilance within the context of a country, health authorities have to realise the need for a national pharmacovigilance centre, provision of a spontaneous reporting system by healthcare workers and patients (this is achieved by the use of individual case safety report (ICSR) forms called Yellow form), develop a national database for collation and management of reports submitted by healthcare workers and patients to the national pharmacovigilance centre and workable communication link between reporters and national pharmacovigilance centre. It is vital to ensure safe and efficacious medicines are administered to patients.

2.5 Adverse Drug Reactions

Adverse Drug Reactions (ADR) has been defined by the WHO as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of

physiological function" (18) or "a harmful effect suspected to be caused by a drug" (19). Side effects are commonly used in place of adverse events, though they are not the same. A side effect "is an unintended outcome that seems to be associated with treatment, including negative or positive effects" (19). Thus, sedation associated with sedating antihistamines (20,21) such as chlorpheniramine may be a positive side effect if it alleviates the symptoms felt by a patient, whereas a negative side effect that worsens the symptoms felt by a patient needing relief from a particular ailment may not encourage the use of such treatment at a later time (22).

2.5.1 Causes of adverse drug reactions

ADRs are preventable; however, awareness and knowledge of healthcare workers concerning ADR development might hinder the notification of suspected ADRs. ADRs or adverse drug events have been attributed to young age (23), advanced age (24,25), polypharmacy (26–28) and genetic factors (29). The occurrence of adverse drug reactions increases with age, with more geriatrics being hospitalised due to adverse events (24,30–34). Polypharmacy is common among this age group due to ageing and morbidities associated with ageing such as hypertension, diabetes mellitus etc. (35); with these come the possibility of occurrence of adverse drug reactions (26,36–38).

2.5.2 Mitigating ADR development

Rational use of drugs has been suggested as one of the ways to minimise occurrence of ADR, especially among ambulatory patients (39–41). The goal of rational drug use is to encourage quality pharmaceutical care, control costs due to drug procurement either by patients or government, and invariably reduce possible drug-drug interactions or adverse events; all these will help in promoting positive health

outcomes in patients (42). It is important for patients to be prescribed drugs that are appropriate for their ailment. Minimizing the number of medicines prescribed to a patient, and prescribing the right medicines to treat particular ailments or diseases, might reduce the incidence of adverse drug reactions in the most affected populations (43).

Knowing that ADRs are undesirable or unpremeditated harmful effects experienced by patients after the administration of drugs in their regular doses, these can be isolated or linked to the drug or individual patient (i.e. idiosyncratic), depending on the disease that the drug is used to treat; such incidences might assist healthcare workers realise the importance of such reactions and the impact they may have on treatment outcomes (44). ADRs are a cause for significant morbidity and mortality in populations (45–48). Dealing with ADRs requires a multi-professional approach by the healthcare workers engaged in both public and private healthcare settings; thus, the medical practitioners, pharmacists, nurses and all other allied health professions have a role to play in safeguarding public health (49,50). It has been reported that the side effects of some drugs might have strong socioeconomic and psychological implications among patients and this may affect their intention to seek particular treatment options (51).

Most patients in Namibia visit public facilities such as the hospital, clinics and health centres for their healthcare needs (52). It is necessary for the healthcare professionals working at these facilities to know and understand the importance of detecting, reporting and management of ADRs whenever they occur. ADRs have debilitating effects on patients and may be fatal in some cases, thus, ensuring that healthcare workers are knowledgeable about detection, mitigation and the need to report suspected ADRs becomes crucial (47,53).

2.6 Pharmacovigilance in Low- and Middle-Income Countries (LMICs)

Developed countries have more robust pharmacovigilance systems to monitor and mitigate ADRs or AE that are suspected and reported by healthcare workers and patients; however, this is not the case in most Sub-Saharan African (SSA) countries such as Namibia (54–56). The WHO came up with a guide for low resource countries geared towards the detection, reporting and management of ADRs that are suspected in routine healthcare delivery (49). Pharmacovigilance activities are carried out as part of the regulatory functions of NMRAs, as is the case in Namibia (Namibia Medicines Regulatory Council (NMRC)) (57,58).

2.7 Therapeutics, ADRs and Causality determination

Spontaneous reporting of ADRs by healthcare workers affords the health system the capability to monitor and document the incidence and frequency of adverse events that are attributable to or suspected to be caused by drugs or medicines used within the system. Harvard Medical Practice study carried out in 1984 among patients in acute hospitals, revealed that the drug classes frequently linked to adverse events among in-patients were antibiotics, analgesics, sedatives, cytotoxics, cardiovascular drugs, anticoagulants, antipsychotics, anti-diabetics and electrolytes (59). It should be noted that the adverse events reported in the study included medication errors and drug overdose; however, in a study carried out by the Boston Collaborative Drug Surveillance over seven years, associations between drug exposures and acute ADRs were established (60).

2.7.1 Causality determination

Determining the causal relationship between a drug and a suspected ADR in practice can be daunting. Pharmacovigilance centres are charged with the responsibility of

confirming if there is a relationship between an observed or suspected ADR and any drug a patient might be taking at the time an adverse event occurs (61). Naranjo algorithm (62) and WHO-UMC criteria (63,64) for case causality assessment are the major tools used for causality determination of ADRs. The two systems rely on spontaneous ADR reporting by healthcare workers using the standardised ICSR form.

2.8 Knowledge, attitude, perception and practices of healthcare workers to ADR reporting and pharmacovigilance

The level of knowledge of healthcare professionals will determine the quality of service that will be provided to the population within which they practice. It is necessary to understand the gap in knowledge of healthcare professionals concerning different practice areas; this will assist in developing customized health systems improvement efforts. A number of studies have been conducted to assess the level of knowledge, attitude, awareness, practices and perception of healthcare workers and students in different settings concerning pharmacovigilance and adverse drug reactions reporting with varying results.

In a cross-sectional survey conducted in Nigeria, assessing the knowledge and perception of pharmacy students in various universities on pharmacovigilance activities; most of the students had a good perception of pharmacovigilance activities; however, it was realized that their knowledge of pharmacovigilance activities was poor. This was adduced to the non-incorporation of pharmacovigilance training as part of the pharmacy curriculum (65). This observation is vital in ensuring the exposure of healthcare students and continued practice of pharmacovigilance after graduation and eventual pharmacy practice. In another

cross-sectional study carried out among 372 healthcare workers in Nigeria, the factors associated with under-reporting of ADRs among healthcare workers included non-availability of electronic reporting platform, paper-based reporting forms and ignorance of ADR reporting. Training of healthcare workers on issues related to ADR reporting was identified as a way of mitigating the under-reporting of ADRs in the setting (66). A similar study was carried out in West Ethiopia among the healthcare professionals in the region; the study showed a low level of knowledge, poor attitude towards and practices of ADR reporting among the healthcare workers (67). It was noted that knowledge of pharmacovigilance and ADRs might be a determining factor that can impact inculcation of the right attitude and correct practice of pharmacovigilance and ADR reporting among healthcare workers. Such knowledge can be gained during pre-service training, as highlighted in the study conducted among pharmacy students in Nigeria. In a study carried out to explore the knowledge, attitudes and practices of pharmacists and nurses in six private hospitals and clinics in Johannesburg, South Africa, it was reported that the majority of the respondents (76.2%) believed ADR reporting is important; however, more than half (54.5%) did not know how to report suspected ADRs while less than a quarter (23.8%) had received pharmacovigilance training before (68). Awareness of the ADR reporting system and the availability of reporting forms were some of the reasons contributing to the under-reporting of ADRs in the setting.

In a descriptive cross-sectional study carried out among healthcare workers at King Fahd Hospital of the University of Saudi Arabia, 37.5% were aware of the term pharmacovigilance while more than 60% of the participants who were pharmacists had a better awareness of pharmacovigilance systems compared to other healthcare cadres in the study. A low level of knowledge and awareness of pharmacovigilance

systems and adverse drug reaction reporting were reported in the study (69). In another study carried out among pharmacists working in primary and tertiary healthcare institutions in Kuwait, it was realized that most of the participants were knowledgeable about pharmacovigilance systems and had a positive attitude towards ADR reporting; however, less than 30% of the participants have reported an ADR before. Hindrance to reporting ADRs included lack of time to report suspected ADR (70). In another study involving pharmacists, it was found that the level of pharmacovigilance knowledge and ADR reporting of the participants was abysmal, they have shallow awareness of the systems in place, thus, the observed under-reporting of ADRs. Contributing factors to under-reporting included the unavailability of ADR forms and non-realisation of the need to report ADRs (71). Cascading down of awareness about the need for pharmacovigilance among policymakers, through ministries of health and other decision-makers, can be a catalyst for health service improvement in settings where healthcare workers have a poor attitude and low level of knowledge of pharmacovigilance and ADR reporting. This can be achieved by initiating policies that will promote good reporting culture and practice among the healthcare workers within the system. A cross-sectional study on the perception and knowledge of healthcare workers regarding pharmacovigilance in a tertiary care teaching hospital in Aden, Yemen revealed good knowledge of pharmacovigilance among the medical doctors and nurses included in the survey. However, the nurses showed a more positive attitude to pharmacovigilance compared to medical doctors (72). The results obtained in this study are in contrast to what was obtained in Namibia, where a cross-sectional study carried out among healthcare workers revealed less positive attitude towards ADR

reporting and pharmacovigilance among the nursing cadre compared to the medical doctors (73).

Cross-sectional research carried out in a tertiary care teaching hospital in South India to assess the knowledge, attitude and practices of medical and nurses on spontaneous ADR reporting revealed a better practice of pharmacovigilance among the medical doctors compared to the nurses; however, there was no significant difference in knowledge of the nurses and medical doctors. Access to reporting forms and introduction of an electronic reporting system were recommended as possible means of improving ADR reporting among the group (74). In another study assessing the knowledge, attitude and practices of pharmacovigilance among undergraduate medical students in a teaching hospital in North India; the researchers observed differences in the mean score for knowledge and attitude of the three groups of students in the study (2^{nd}, penultimate and final year students); nevertheless, no differences were observed in their practice of pharmacovigilance. Incorporation of pharmacovigilance activities into the undergraduate curriculum was suggested as a means of mitigating the inadequacy in knowledge thus, improving the practice of pharmacovigilance (75). In a study conducted among postgraduate medical, pharmacy and nursing students in the clinical department of a tertiary care hospital, Gujarat, India, it was found out that the attitude of the students towards pharmacovigilance was good, on the other hand, they are deficient in their knowledge and practices of pharmacovigilance (76). In another study assessing the awareness of healthcare workers about pharmacovigilance in a teaching hospital in Northern India, the researchers found out that the majority of the respondents (77%) know the meaning of the term “pharmacovigilance”, less than a quarter volunteered to report ADRs. Reasons for not reporting ADRs included lack of time, knowledge

of the reporting scheme and inadequate expertise to report ADRs. The study participants proposed training as a way to improve pharmacovigilance in the setting (77). In a systematic review of the studies published with a focus on the KAP of pharmacovigilance and ADR reporting of Indian healthcare workers between January 2011 and July 2015, it was suggested that there should be a procedural assessment of the KAP of healthcare workers (78).

In a recent study carried out in Turkey among medical doctors and nurses in a university hospital, more than 65% of the respondents were aware of the term "pharmacovigilance"; nurses have better-claimed reporting of ADRs compared to medical doctors. The study suggested the support of focal points of pharmacovigilance at health facilities to be supported by the Ministry of Health as a way to improve pharmacovigilance and reduce under-reporting of ADRs at the facility level (79).

Limited information is available concerning the knowledge, attitude, awareness, practices and perception of healthcare workers to ADRs, ADR reporting and pharmacovigilance in Namibia; thus, it is necessary to have baseline data concerning these and also, help in strengthening the pharmacovigilance systems in the country. A recent pivotal cross-sectional study carried out in Namibia to assess the knowledge, attitude and practices of pharmacovigilance and ADR reporting revealed nurses are less likely to report ADRs compared to medical doctors and pharmacists. Introduction of pharmacovigilance into the curriculum of healthcare students and in-service training for healthcare workers are some of the ways the participants in the Namibian study suggested can improve ADR reporting in the public healthcare setting of Namibia, including the introduction of an electronic platform for reporting (80).

2.9 Approaches to augmenting ADR reporting by healthcare workers

Electronic data collection platforms have been said to be the future of health data collection, collation and transmission, this includes ADR reporting and pharmacovigilance in general (81). Electronic health records have become commonplace in the healthcare delivery systems of developed countries, affording the system the opportunity of better monitoring of the health-related data and being able to proffer interventions when they are needed (82–85). The same technology has been adopted by different authorities to improve their pharmacovigilance systems (86) and also, advocating for the integration of e-pharmacovigilance reporting into routine clinical care (87,88). Mobile applications such as the Innovative Medicines Initiative WEB-Recognising Adverse Drug Reactions (IMI WEB-RADR) in the European Union captures ADR information through social media (89,90). Electronic pharmacovigilance and ADR reporting platforms using desktop internet access were introduced in Kenya around 2014 to improve reporting; though it has its advantages, some barriers that may limit reporting were identified such as the unavailable, unreliable or expensive internet access (91).

2.10 Gaps in the current literature

Though some studies have been carried in SSA among healthcare workers to evaluate their KAAP with respect to ADR and a limited number seeking to proffer ways of strengthening pharmacovigilance systems, there has been no study carried out in Namibia.

2.11 Summary

This chapter looked at literature that are pertinent to pharmacovigilance and ADR reporting. The next chapter is both a provider-level and patient-level study. It showed

the number of ADR reports submitted to TIPC over a period of 12 months. Under-reporting of ADR was highlighted by the number of reports submitted by healthcare workers during the period under study, including the types and severity of ADRs experienced by patients on ATV/r and LPV/r based regimens. Reporting culture of the Namibian public healthcare workers, under-reporting in particular, was highlighted by the number of ADR reports submitted to TIPC during the period under study.

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Chapter 3 A PROFILE OF ADVERSE DRUG REACTIONS OF ATAZANAVIR AND LOPINAVIR BASED SECOND-LINE ANTIRETROVIRAL REGIMENS IN NAMIBIA

Published: as a Data Letter in *Drug Safety*, 2019

ABSTRACT

Background: ATV/r is the mainstay of treatment for second-line or modified first-line ARV regimens according to Namibian guidelines.

Aim: To describe the type of adverse drug reactions (ADRs) of ATV/r and LPV/r based regimens presenting in the Namibian population.

Methods: A retrospective case series analysis of ADR reports notified to the national pharmacovigilance centre in Namibia between August 2017 and August 2018. The main outcomes were the prevalence and types of ADRs associated with ATV/r and (LPV/r). Data were analysed descriptively.

Results: Of the 17 ADR reports reviewed, the mean age and weight of the patients were 42.1 years and 67.3kg, respectively. Most ADRs reported were detected in patients prescribed ATV/r (88.2%, n=15/17) compared to LPV/r (11.8%, n=2/17) based regimens. Over 60% of the ADRs occurred among cases on ATV/r based regimens developed clinical hepatitis, gastrointestinal and renal failure.

Conclusion: Patients on ATV/r may be at increased risk of serious hepatic and renal adverse events, however, due to the number of cases analysed, the findings cannot be generalised. There is a need for active surveillance to identify risk factors and grades of ATV/r related ADRs in the Namibian population.

Keywords: Adverse drug reactions, protease inhibitors, antiretroviral, Namibia, LMICs

3.1 INTRODUCTION

HIV/AIDS is a significant public health challenge, globally. Over 80% of the new infections and deaths associated with HIV occurred among sub-Saharan Africans (WHO, 2018a). In 2017, the estimated prevalence of HIV/AIDS in Namibia was 12.6% (MoHSS, 2017). However, global scale-up of universal access to free antiretroviral therapy (ART) in most sub-Saharan countries, including Namibia, has substantially reduced HIV related morbidity and mortality (WHO, 2008). In 2015, the World Health Organization (WHO) implemented the 90:90:90 strategy that aims, for example, to have over 90% HIV/AIDS patients initiated on ART. This has increased the number of HIV patients receiving treatment and therefore, exposure of patients to first-line regimens as well as modified first line and second-line ART regimens. The modified first-line and second-line antiretroviral regimens recommended in Namibia (MoHSS, 2016) were based on protease inhibitors (for example, ritonavir-boosted atazanavir, ATV/r and lopinavir, LPV/r) as fixed-dose antiretroviral combinations (Atazanavir, 2018). In 2014, the Ministry of Health and Social Services of Namibia (MoHSS) updated its HIV treatment guidelines from LPV/r to ATV/r as the preferred modified first-line and second-line ART regimen (MoHSS, 2014). Despite the change in guidelines, a significant number of HIV patients continue to be prescribed LPV/r (Adenuga, Kibuule, Bamitale, 2018).

Nonetheless, few studies in sub-Saharan Africa have profiled the safety of ATV/r based regimens despite the widespread use (Chowta *et al.*, 2018; Mukherjee *et al.*, 2017). Protease inhibitors (PI) are associated with debilitating adverse drug reactions (ADRs) such as hepatitis, lipoatrophy and diarrhoea that compromise adherence to antiretroviral therapy (Sevilla-Sanchez *et al*, 2017; TFDA, 2012). In particular, patients naive to PI-based antiretroviral therapy are at risk of early gastrointestinal

related ADRs especially diarrhoea (Wegzyn *et al*, 2012, Bonjoch *et al*, 2010). Similarly, three previous revisions of the first-line and second-line Namibian ART regimens guidelines were based on the increased burden of ADRs linked with different antiretroviral medicines, such as anaemia associated with zidovudine, peripheral neuropathy associated with stavudine and cutaneous reactions associated with efavirenz and nevirapine.

3.2 AIM OF THE STUDY

Consequently, the current study aims to describe the burden of ADRs associated with ATV/r and LPV/r based modified first-line and second-line ART regimens in Namibia.

3.3 METHODS

3.3.1 Design and population

A descriptive case series analysis of reports on ADRs at Namibia's Therapeutics Information and Pharmacovigilance Center (TIPC) in Windhoek, Namibia (**Table 1**). TIPC aggregates ADR reporting forms from all public and private health facilities in 14 regions of Namibia. The reports originate from the public healthcare facilities including hospitals, health centers and clinics. The ADR reports are faxed (i.e. for facilities outside the capital city, Windhoek) or collected by TIPC staff during monthly support visits to the facilities. The target population was the ADRs reports associated with patients initiated on modified first line- and second-line ATV/r or LPV/r based ART regimens. About 5% of all the patients on antiretroviral therapies are on PI-based regimens in Namibia. The accessible population was only ADR reports notified to the TIPC at the time of the study. A case of ADR in this study refers to any untoward, unexpected, or noxious response or reaction that can be

attributed to the regimen on which the patient is on, experienced by the patient while on the same regimen; in this case, ATV/r and LPV/r based regimens.

The study included ADR reports of cases that were 16 years old or more and initiated receiving either ATV/r or LPV/r based regimens at the time study. We excluded all ADR reports for first-line regimens, incomplete or missing data on ADR or drug regimens or cases with less than 3 ARVs for the modified first-line and less than 4 ARVs for second-line regimens.

Table 1 Individual Case Series Reports of ADRs experienced by patients on ATV/r and LPV/r based regimens submitted to TIPC between August 2017 and August 2018

Case No.	Reports
S1	A female, on ABC/3TC/AZT/ATV/r combination, aged 23 weighing 53 kg at the time of visit to the facility. Presented with yellow eyes (jaundice) after initiation of ATV/r on 05/04/2017. ATV/r was started on 22/03/2017. The regimen was stopped after the diagnosis of jaundice was made. No laboratory test was conducted. The event was deemed non-serious and the patient was recovering after the stopping the offending medicine.
S2	A female, on TDF/3TC/AZT/ATV/r combination, aged 51 weighing 80kg at the time of visit to the facility. Presented with yellow eye sclera after switching from LPV/r based second-line regimen on 06/12/2016. ATV/r was started on 06/12/2016. The regimen was stopped on 03/07/2017 after a diagnosis of jaundice was made; however, the first discovery of the event was in April 2017. Liver function tests were done to confirm the diagnosis. The event was judged to be non-serious.
S3	A male, on TDF/3TC/AZT/ATV/r combination, aged 42 at the time of visit to the facility. Diagnosed with jaundice after initiation of ATV/r on 30/05/2018. ATV/r was started on 20/03/2018. The regimen was stopped on 30/05/2018. The event was judged to be non-serious. The patient was recovering after stoppage of the offending medicine.
S4	A male, on TDF/FTC/AZT/ATV/r combination, aged 46 weighing 65kg at the time of visit to the facility. Diagnosed with jaundice, history of previous regimen was not given. The regimen was initiated on 15/11/2016 and stopped on 23/03/2018. Liver function tests were carried out to confirm the diagnosis; it revealed increased bilirubin and liver enzymes. The event was judged to be non-serious and the patient recovered.
S5	A male, on TDF/FTC/AZT/ATV/r combination, aged 51 weighing 62.7 kg at the time of visit to the facility. Diagnosed with indirect hyperbilirubinaemia secondary to ATV/r. ATV/r was initiated on 25/04/2017 and event diagnosed on 02/05/2017. The regimen was not discontinued. Liver function tests were carried out; it revealed elevated liver enzymes and increased bilirubin level. Event was judged to be other serious medical event and the patient did not recover while on the offending regimen.
S6	A female, on TDF/FTC/AZT/ATV/r combination, aged 35 weighing 59.2 kg at the time of visit to the facility. Diagnosed with jaundice after ATV/r was stopped and restarted on 12/08/2016. Liver function tests were carried out to confirm the diagnosis. The regimen was stopped on 02/09/2017 after the event. The event was judged to be non-serious and the patient was recovering.
S7	A female, on TDF/FTC/AZT/ATV/r combination, aged 29 weighing 71 kg at the time of visit to the facility. Diagnosed with jaundice after initiation of ATV/r in August 2017. ATV/r was started on 22/05/2016 and discontinued on 14/04/2018. No test was carried out.
S8	A female, on TDF/FTC/AZT/ATV/r combination, aged 38 at the time of visit to the facility. Diagnosed with jaundice after initiation of ATV/r in August 2016. The regimen was stopped on 16/04/2018. No test was carried out. The event was judged to be non-serious and the patient did not recover from the event.
S9	A male, on TDF/FTC/ATV/r combination, aged 52 weighing 58 kg at the time of visit to the facility. Diagnosed with ATV/r indirect hyperbilirubinaemia on 20/03/2018. ATV/r was discontinued. Total bilirubin, indirect bilirubin and direct bilirubin tests were conducted, revealing elevated bilirubin. The event was judged to be non-serious and the patient did not recover.
S10	A male, on TDF/FTCATV/r combination, aged 29 weighing 85 kg at the time of visit to the facility. Diagnosed with yellow eye sclera on 28/08/2017. ATV/r was discontinued. FBC, LFT and creatinine clearance tests were conducted. Event was judged to be non-serious.
S11	A female, on TDF/FTC/AZT/ATV/r combination, aged 45 at the time of visit to the facility. Patient complained of nausea and joint pains on 03/05/2018; patient was initiated on ATV/r on the same day and the event stopped on 01/06/2018. ATV/r was not discontinued. The event was judged to be non-serious and the patient was recovering.

Case No.	Reports
S12	A male, on TDF/FTC/AZT/ATV/r combination, aged 36 at the time of visit to the facility. Diagnosed with renal failure on 20/07/2018. ATV/r was initiated on 30/04/2018. Creatinine level was 135g/dl. Event was judged to be life-threatening and the patient was recovering. The regimen was substituted.
S13	A female, on TDF/3TC/ATV/r combination, aged 42 at the time of visit to the facility. Complained of severe headache, back pain and generalized body weakness. Also, had red spot on the left eye (hyphema). Patient was initiated on ATV/r on 02/12/2017. No test was carried out. The regimen was not discontinued.
S14	A female, on TDF/FTC/ATV/r combination, aged 49 at the time of visit to the facility. Also, on CTX prophylaxis. Diagnosed with hepatitis in August 2017. The regimen was changed on 17/10/2017. Liver function tests revealed elevated liver enzymes. The patient was recovering.
S15	A female, on TDF/FTC/AZT/LPV/r combination, aged 53 at the time of visit to the facility. Diagnosed with LPV/r induced GIT side effects on 16/02/2016. LPV/r was switched to ATV/r after the event. No test was carried out. Event was judged to be other non-serious and the patient recovered.
S16	A female, on TDF/FTC/LPV/r combination, aged 29 at the time of visit to the facility. Complained of diarrhoea which started in February 2018 and stopped in April 2018. LPV/r was substituted after the event on 17/04/2018. No test was carried out. Event was judged to be non-serious and the patient was recovering.
S17	A male, on TDF/FTC/AZT/LPV/r combination, aged 39 at the time of visit to the facility. Complained of severe itchy throat, cough and diarrhoea, which started on 13/07/2017 and stopped on 27/07/2017. The regimen was discontinued. No test was carried out. The event was judged to be non-serious.

3.3.2 Procedure

The individual case safety reports (ICSR i.e. Yellow form) are the National tool used to collect ADR information at the facility level in Namibia (**See Appendix 1**). The ICSR contains the socio-demographic details of the patients, a description of adverse events, relevant medical history, information on medicines and the reporter information.

The ADR reports of the cases were obtained from TIPC were collected and data abstracted into Microsoft Excel®. Data on antiretroviral regimen and co-medication, socio-demographic characteristics such as gender and type of adverse drug reactions were abstracted from the ICSR. The reports were collected over a period of 12 months, between August 2017 and August 2018, to investigate the burden of ADR among the patients on ATV/r and LPV/r based regimens in Namibia. The category of adverse drug reaction was determined based on the Summary of Product

Characteristics (SmPC) of the product and against the WHO-UMC event classification system. In this study, yellow eye sclera and hyperbilirubinaemia were included in the jaundice cases, and cough and itchy eyes were grouped as allergies. The ADRs were categorized by organ-system that affected by the reported event (Table 2). Some patients had more than one ADR, thus the number of ADRs analyzed was more than the case reports of patients analysed.

3.3.3 Data analysis

Variables such as the age at the time of the report, the weight of patent, current regimen, patient outcomes etc., were entered as such from the ADR forms submitted to the TIPC. Adverse drug reactions following initiation or after switching PI therapy were the main outcome measures in this study. Simple count was used in determining the number of ADRs observed in the patients while they were on the offending regimen. Data were entered into a spreadsheet (Microsoft Excel™). The data were later exported into SPSS version 22 for analysis. Frequencies such as percentages and nominal variables such as gender and age in years were used in describing the population. Descriptive statistics such as mean and range were also determined for age and weight. Causality (the probability of the event occurring in the presence of the medicine used) was determined based on the SmPC for both LPV/r and ATV/r as exemplified by the innovator SmPC (Agbabiaka *et al*, 2008; Arimone *et al*, 2010; Laine *et al*, 2009; Lemer *et al*, 2009; Martys, 1979; Turner, 1984). The diagnosis of the causality by the reporting healthcare worker was used to establish the association between the regimen and the ADR observed. Naranjo ADR Probability scale was used to ascertain the possible link between the regimen and the event that was reported.

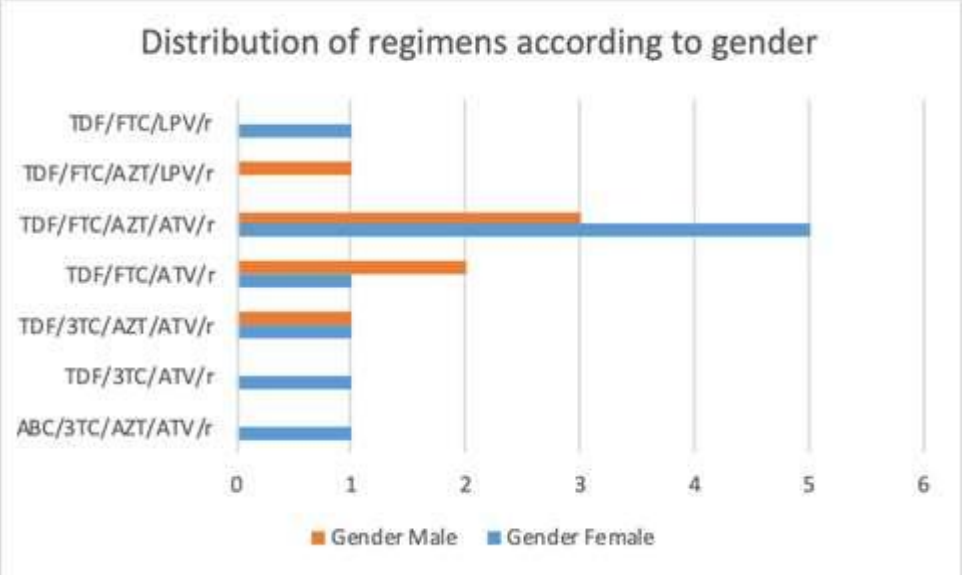
3.4 Ethical clearance

The research ethics boards of the MoHSS (Reference No. 17/3/3) and Ethics Committee of the University of Namibia (Reference No. SOPHA/209/2017) approved the study. Secondary data was used in this study and the need for written informed consent was waived by the REC.

3.5 RESULTS

Of the 17 case reports reviewed, 58.8 % (n=10) were for females, the mean age was 42.1±9.3 years (range: 23–53) and body weight of 67±7.1kg (range: 53-85). Most patients were on ATV/r based regimens 82.3% (n=14) compared to LPV/r 17.7% (n=3) at the time of ADR occurrence. Figure 1 shows the distribution of regimens by gender.

Figure 1 Distribution of cases by PI regimens and gender (n=17)



Of the 8 different types of ADRs notified, the majority were hepatic (i.e. jaundice and hepatitis), these accounted for more than 50% of all ADRs. Majority of the cases were among patients on ATV/r (82.4%) compared to LPV/r based regimen (17.6%). Out of the 14 cases on ATV/r based regimens, majority developed jaundice 71.4% (n=10) (Table 2).

Table 2 Occurrence of PI associated ADR by organ-system (n=20)

Adverse Event	Organ -system	Adverse events (%)
Hepatitis	Liver	1(5)
Jaundice	Liver	10(50)
Hyphema	Eye**	1(5)
Diarrhoea	GIT*	3(15)
General malaise	Others	2(10)
Severe itchy throat	GIT*	1(5)
Cough	Lungs	1(5)
Renal failure	Kidney	1(5)
All ADE		20(100)

*GIT = Gastrointestinal, **Hyphema = Red eyes

A total of 20 events were reported, average ADR per patient was 1.2.

3.5.1 Outcomes of ATV/r and LPV/r adverse drug reactions

Of the 17 cases of ADRs, 23.5% (n=4/17) did not show causality, according to the healthcare worker reporting the case, due to the regimen that the patient was on (Table 3). Out of the reported cases, 35.3% (6) were recovering from the ADR, 41.2% (7) had no indication of the patient outcome; 17.7% (3) of the reported cases recovered from the ADR, while 5.9% (1) did not recover from the ADR suffered. Of the 17 reports reviewed, 5.9% (1) was hospitalized; 64.7% (11) had non-serious adverse events. Life-threatening adverse drug reaction was reported in 5.9% (1) of

the cases. Out of the cases, 17.7% (3) were reported as having other serious medical events; 5.9% (1) of the cases did not indicate the seriousness of the observed ADR.

3.5.2 Causality of the ADRs

Table 3 depicts the causality evaluation using Naranjo's ADR Probability Scale. Out of the 17 reported cases, only two were probable while the rest were possible ADRs according to Naranjo's algorithm (Naranjo et al, 1981).

Table 3 ADRs causality determination using Naranjo's ADR Probability Scale

ADR	Regimen	Naranjo's score	ADR Probability
Hepatitis	TDF/FTC/ATV/r	4	Possible
Jaundice	ABC/3TC/AZT/ATV/r	6	Probable
	TDF/FTC/ATV/r	5	Probable
	TDF/FTC/ATV/r (1)	3	Possible
	TDF/3TC/AZT/ATV/r	4	Possible
	TDF/3TC/AZT/ATV/r (1)	4	Possible
	TDF/FTC/AZT/ATV/r	4	Possible
	TDF/FTC/AZT/ATV/r (1)	4	Possible
	TDF/FTC/AZT/ATV/r (2)	4	Possible
	TDF/FTC/AZT/ATV/r (3)	3	Possible
	TDF/FTC/AZT/ATV/r (4)	3	Possible
Hyphema	TDF/3TC/ATV/r	3	Possible
Diarrhoea	TDF/FTC/AZT/LPV/r	4	Possible
	TDF/FTC/AZT/LPV/r (1)	4	Possible
	TDF/FTC/LPV/r	4	Possible
Nausea and joint pains	TDF/FTC/AZT/ATV/r	2	Possible
	TDF/FTC/ATV/r	2	Possible
Allergy	TDF/FTC/AZT/ATV/r	3	Possible
	TDF/FTC/AZT/LPV/r	4	Possible
Renal failure	TDF/FTC/AZT/ATV/r	4	Possible

3.6 DISCUSSIONS

The study aimed to determine the burden of ADRs among patients initiated on ATV/r and LPV/r based modified first-line and second-line ARV regimens. We found that the prevalence of ADRs among patients on ATV/r based regimens was

higher compared to those on LPV/r regimens; diarrhoea was the only ADR reported in relation to LPV/r based regimens.

In the CASTLE Study carried out by Molina et al (2010) among PI naïve patients, it was found out that ATV/r based regimens had lesser gastrointestinal ADRs, this is not the case in the present study, in which gastrointestinal ADRs were the major events reported.

A study reported ADRs of the innovator product for atazanavir, Reyataz®, included uncommon ADRs such as hypersensitivity, chronic kidney disease, weight gain, hepatitis, anorexia, depression, anxiety and insomnia; common ADRs included headache, ocular icterus, jaundice, diarrhea, abdominal pain, rash, arthralgia, myalgia while rare ADRs included erythema multiforme, kidney pain, eczema and myopathy (Reyataz®, 2018). In this study, jaundice had the highest number of reports; this is consistent with the expected ADRs of atazanavir. Hepatitis was reported in a patient co-administered with co-trimozaxole, though, the report indicated no inferred causality between atazanavir and hepatitis; however, atazanavir can be a possible cause of hepatitis.

Anzavir R®, a fixed-dose combination of atazanavir and ritonavir has possible adverse events such as nephrolithiasis, haematuria, proteinuria and pollakiuria, all are uncommon events. Other possible events include jaundice, a common event and hepatitis (uncommon event) (Mylan Laboratories Limited, 2014). The reported jaundice and hepatitis are consistent with the adverse events stated in the SmPC of ATV/r combination.

Renal failure was reported in one of the patients, this is an uncommon event with respect to the SmPC of atazanavir. There was no indication of the severity of the

renal function of the patient. Aetiology of the disease can be pursued by the pharmacovigilance centre.

Hyperbilirubinaemia was reported in two individuals, the symptoms were mild and the patients recovered. This is an unreported ADR that may be due to atazanavir. Hyperbilirubinaemia may be a cause for jaundice. Tests carried on the patients' blood revealed elevated bilirubin. In a study carried out by Rodriguez-Novoa et al (2007), hyperbilirubinaemia was reported in 88% of the 118 patients that were followed up; the subjects were on ATV/r based antiretroviral regimens for 12 weeks. The two patients reported in this study had developed hyperbilirubinaemia within 12 weeks of initiation of the therapy; this is similar to results obtained by Rodrigues-Novoa et al.

There was no relationship between the age or weight of the cases reviewed and the time to development of the adverse event.

3.7 Limitations

The number of reports used in the study may not reveal all the possible or observed ADRs in the population studied. Under-reporting of ADRs is a well-documented phenomenon in pharmacovigilance. Spontaneous ADR reporting compared to active ADR surveillance limits the number of cases that are picked up during practice and subsequently reported to the National Pharmacovigilance Centre, however, it remains the mainstay for ADR reporting by healthcare workers.

3.8 Conclusions

Despite the better safety profile of atazanavir, most of the reported adverse drug reactions/events were due to the regimens containing the protease inhibitor, only one

case was reported for lopinavir containing regimens during the period under review. This can be due to under-reporting of cases or some cases may not be identified due to the level of expertise of personnel involved.

3.9 Summary

This chapter looked at the extent of under-reporting of ADRs among healthcare workers in the Namibian public healthcare setting. The number of reports received by TIPC between August 2017 and August 2018 on ATV/r and LPV/r based regimens was followed up and reviewed.

The next chapter sought to know the level of knowledge, attitude and practices of pharmacovigilance and ADR reporting among healthcare workers in the public setting, with a goal to identify the gaps limiting the healthcare workers from reporting.

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Chapter 4 OPTIMIZING SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN PUBLIC HEALTHCARE SETTING IN NAMIBIA

Published: *Basic and Clinical Pharmacology and Toxicology*, September 2019

ABSTRACT

Despite the universal scale-up of pharmacovigilance systems globally, adverse drug reaction (ADR) reporting remains sub-optimal among resource-limited countries. Few studies in sub-Saharan Africa evaluate the effectiveness of adverse drug reactions (ADR) reporting programmes.

A cross-sectional survey using a self-administered questionnaire to assess ADR reporting knowledge, attitude and practices among healthcare workers in Namibia's public sector was conducted between September and December 2018. The primary outcomes were practices, knowledge and attitude of the respondents towards ADR reporting. Quantitative and qualitative data were analysed using descriptive statistics and thematic analysis respectively.

Of the 197 healthcare workers surveyed, 43.1% were nurses, 63.4% of the respondents know about the ADR reporting system in Namibia, 76.7% knew the pharmacovigilance/ADR reporting centre in Namibia while 37.3% had reported an ADR before. Nurses were less likely to be knowledgeable and report ADRs. The independent predictor of ADR reporting was the nursing cadre, adjusted odds ratio (aOR) = 0.17(95% CI: 0.07, 0.401, p<0.01). Pre- and in-service training including the introduction of electronic reporting platforms were some of the identified ways of optimising the pharmacovigilance and ADR reporting systems by the respondents.

As pharmacovigilance in Namibia relies on spontaneous reporting of ADRs, there is a need for advocacy and workforce strengthening for ADR reporting in the public health sector.

KEYWORDS: Adverse drugs reactions, Reporting, Namibia, Public Health Care

4.1 INTRODUCTION

The HIV/AIDS epidemic amongst other communicable and non-communicable diseases have devastated public health in sub-Saharan Africa (SSA), necessitating the scale-up of pharmacovigilance systems for surveillance of the safety of standard treatment, which change frequently [1]. For instance, the retrospective study among patients on second-line antiretroviral therapy in South Africa underscored the importance of optimal pharmacovigilance systems [2].

Moreover, adverse drug reactions (ADRs) remain a major cause of morbidity and mortality particularly in limited-resource settings such as SSA [3]. In the United Kingdom, ADRs are estimated to contribute to 6.5% of hospital admissions [4]. This is a public health concern as most ADRs are preventable. Unfortunately, most countries in SSA worst hit by communicable and non-communicable diseases have limited capacity for pharmacovigilance of essential medicines such as antiretroviral therapies (ART) [5]. As newer medicines are increasingly integrated into standard treatment guidelines for public health care in SSA, the strengthening of adverse drug reaction reporting becomes critical to improve the quality of care [6 -7].

In addition, this integration of new essential medicines into standard treatment guidelines not only demands improved pharmacovigilance but also raises the need for training and awareness of healthcare workers concerning ADRs and ADR reporting. Dealing with ADRs requires a multi-professional approach by healthcare

workers – including medical practitioners, pharmacists, and nurses – both in public and private healthcare settings to safeguard population health [8].

Namibia, a country in Southern Africa with a population of about 2.5 million people, has a high burden of infectious diseases such as HIV, tuberculosis and malaria as well as a growing burden of non-communicable diseases. The HIV prevalence in Namibia was estimated at 12.6% in 2017 among adults aged 15–64 [9]; the burden of the disease has reduced dramatically in the last two decades largely as a result of the effective roll-out of efficacious ARVs and other essential medicines. Nevertheless, the establishment of the Therapeutics Information and Pharmacovigilance Centre (TIPC) in 2007, in the Ministry of Health and Social Services (MoHSS) has improved the access to pharmacovigilance services in public healthcare in Namibia. [10]. Most healthcare workers at public health facilities mainly report ADRs by use of a paper-based spontaneous reporting system (i.e. voluntary adverse drug reaction reporting by healthcare workers or patients on suspected improper effects of a medicine). The reports can be faxed, scanned and emailed or hand-delivered to the TIPC office, depending on the proximity of the facility and resources available at the reporting facility.

The current study aimed to better understand the reasons for under-reporting of ADRs in the Namibian public healthcare setting context and from the perspective of the healthcare workers empowered to report through the existing pharmacovigilance system.

4.2 METHODS

4.2.1 Design and setting

Between September and December 2018, a cross-sectional survey was carried out among healthcare workers working in the public healthcare facilities in Namibia. A self-administered questionnaire was adapted from previous studies that assessed the knowledge, attitude and practices of healthcare workers in Nigeria [11-12]. There are 14 geographical regions in Namibia. The study respondents were stratified by 7 regions; the 7 regions were purposively selected with varying settings and populations, i.e. 2 coastal towns (ǁKaras and Erongo regions), 2 border towns (Caprivi and Omaheke regions), 1 centrally located town (Otjozonjdupa region) and 2 central business districts (Khomas and Oshana regions). Healthcare workers at the respective state/regional referral hospital were included in the study.

4.2.2 Population

Public healthcare workers from different cadres (medical doctors, nurses, midwives, pharmacists, dentists, radiographers etc.) participated in the study. They were invited by the researcher to voluntarily complete anonymous questionnaire (online or paper-based). Target number of respondents was estimated at 200 respondents using the Kish Leslie method for a one-sample cross-sectional study with the power set at 80% and level of significance at 0.05; 197 respondents participated in the study, thus, the response rate was 98.5%.

4.2.3 Pharmacovigilance program in Namibia

TIPC coordinates pharmacovigilance activities in Namibia. Namibia is a full member of the World Health Organization Programme for International Drug Monitoring. ICSR from healthcare facilities submitted to the TIPC is collated, aggregated and sent to the WHO-UMC through Vigibase, a database for reporting ADRs.

4.2.4 Procedure

Data on awareness, knowledge and practice of ADR reporting were collected using a standardized self-administered questionnaire. The research instrument comprised of 5 sections; demographics of the health worker, knowledge on ADRs reporting, attitude towards ADRs reporting, and ADRs reporting practices. Four items were used to assess knowledge (score=4). A Likert scale rating system was used to measure the negative and positive attitudinal item responses (strongly agree = 5, agree = 4, neutral = 3, disagree = 2, strongly disagree = 1); negatively worded items were reverse coded so that higher scores represented more negative attitudes. Respondents were asked to report on their actual pharmacovigilance practice in response to two questions relating to whether they had reported ADRs to the centralised pharmacovigilance reporting system or within their practice setting. Finally, participants were asked an open-ended question about possible ways of improving the current pharmacovigilance systems in Namibia.

The questionnaire was disseminated using an online platform (i.e. Google Forms®) as well as paper format. A network sampling method was used in the online questionnaire administration. Index healthcare professionals were identified and asked to request their fellow professionals to complete the questionnaire. A purposive sampling method was used in the paper questionnaire administration whereby a focal person was identified for seven different health facilities around the country with a high patient turnover. The focal person was sent questionnaires to distribute locally and collect responses to be couriered or hand-delivered back to the main investigator.

For responses to the attitudinal scales in the questionnaire, reliability analysis was determined using Cronbach's alpha. Cronbach alpha for positive and negative

intentions were 0.839 and 0.811 respectively, showing acceptable reliability for both scales (Supplemental Table 1).

The questionnaire was validated through face validity and pilot study. Face validity was carried out by one of the faculty members at the School of Pharmacy, University of Namibia prior to pilot phase. Five (5) respondents working with the MoHSS were selected; these completed the paper-based questionnaire in July 2018 and also three (3) staff among academic faculty of the Faculty of Health Sciences, University of Namibia completed the online format in August 2018. Feedback was received and incorporated to improve the questionnaire tool.

4.3 Data analysis

SPSS (ver. 25) software was used for data analyses; electronic survey response data were imported and paper-based questionnaire data were entered manually. Descriptive analyses were performed on responses to the questionnaire including sample characteristics and questionnaire items. Bivariate analysis was conducted to examine the relationships between ADR reporting, and willingness or ability to report suspected ADRs and other variables. A multivariate logistic regression model was constructed to explore the independent associations with the under-reporting of ADRs. The following variables were entered for regression analysis: professional group, negative intention to report, knowledge of pharmacovigilance and number of years of experience. Also, responses to the open-ended question were thematically analysed.

4.3.1 Factor analysis

Factor analysis was conducted to determine the construct validity of the questionnaire items for the three domains, knowledge, attitude and practice of ADR

reporting. Most questionnaire items loaded onto the common scales that were included in the questionnaire tool (Supplementary Table 2). The question loading were between 0.42 and 0.89. Three items did not load onto pre-existing scale but did not appear to show any rational commonality. From this analysis we were reasonably satisfied that the survey tool - including those scales within - was valid for the measurement of perceptions towards pharmacovigilance in Namibia. However, further work can explore why the three items did not load as anticipated including whether this was related to insufficient sample size or whether they were measuring a distinct theme not captured adequately by the questionnaire. A qualitative approach may help in this.

4.4 ETHICS

Research ethics approvals were obtained from the Research and Ethics Division of the MoHSS (Reference No. 17/3/3) and Ethics Committee of the University of Namibia (Reference No. SOPHA/209/2017).

4.5 RESULTS

4.5.1 Population characteristics

A total of 197 health workers completed the survey. Of the 145 questionnaires distributed physically, 88.3% (n=128) were completed. Of the 70 questionnaires completed online, one was a duplicate response which was excluded from the analysis. The majority of the respondents were nursing (43.2%) or pharmaceutical personnel (31.5%). The mean age and years of experience of the respondents were 35.4 (SD 9.1) years and 10.1 (SD 8.3) years respectively. The majority of the respondents were female (60.9%; Table 2) and worked at either at a district hospital (31.5%) or clinic (27.4%) setting.

Table 1 Demographics of respondents

Demographic variables	Categories	N = 197 (%)
Age, years (median, range)		(33, 44)
Age, years categorised (n. %)	20 - 29	60 (30.5)
	30 - 39	82 (41.5)
	40 - 49	34 (17.3)
	50 - 69	21 (10.6)
Years of experience (median, range)		(8.0, 38)
Years of experience categorised (n, %)	0 - 9	111 (56.3)
	10 - 19	55 (27.9)
	20 - 39	31 (15.8)
Gender (n, %)	Female	120 (60.9)
	Male	77 (39.1)
Type of facility (n, %)	District Hospital	62 (31.5)
	Clinic	54 (27.4)
	Intermediate Hospital	32 (16.2)
	Health centre	19 (9.7)
	NMRC	10 (5.1)
	National Referral Hospital	8 (4.1)
	Others	12 (6.0)
Professional group (n, %)	Nursing	85 (43.1)
	Medical	31 (15.7)
	Pharmacy	62 (31.5)
	Dental	5 (2.5)
	Allied	5 (2.5)

	Others	9 (4.6)

Key
NMRC – Namibia Medicines Regulatory Council
Allied – Radiographer

4.5.2 Knowledge, attitude and practice of adverse drug reactions reporting

Of the 197 respondents, 63.4% were aware of the ADR reporting and monitoring system in Namibia; 76.7% were able to locate the centre responsible for pharmacovigilance activities. Although most respondents (75.1%) acknowledged that every healthcare worker is responsible for ADR reporting, only 64.4% disclosed knowing how to report ADRs. Of the respondents, only 16.5% had attended a pharmacovigilance training while just over one-third (37.3%) had reported an ADR before.

The level of knowledge on ADR reporting was significantly different among nurses, pharmaceutical professionals and medical doctors (Kruskal-Wallis test: chi-square χ^2 = 11.087, p = 0.004). Inaccurate responses to knowledge question items were more prevalent among nurses (mean rank, 71.77), compared to medical professionals (mean rank, 92.02) and pharmacists (mean rank, 97.12). Pharmaceutical cadres (62.9%) reported ADR most frequently compared to medical personnel (51.6%) and nursing personnel (33.3%) (Kruskal-Wallis test: chi-square χ^2 = 19.494, $p < 0.001$).

There was a significant correlation between prior pharmacovigilance training and increased ADR reporting (r=0.178, p=0.013), as well as a poor attitude (i.e. non-intention to report) with decreased ADR reporting (r= - 0.202, p=0.003) (Table 2).

In logistic regression analysis, only the nursing profession emerged as a potential predictor of ADR reporting such that respondents from the nursing profession were about eight times less likely to report ADRs compared with the reference group, pharmacy profession respondents (Table 3: CI 0.070-0.401, $p<0.001$).

Table 2 Correlations for training and willingness/ability to report ADRs

Variables (N=197)	**ADRs reported ever**		**ADRs reports in respondent's setting**	
	r	*p*	*r*	*p*
Negative intention to report (n=184)	-0.115	0.060	-0.202	0.003
Positive intention to report (n=187)	-0.028	0.703	0.086	0.245
Age of respondents (n=197)	0.118	0.099	0.084	0.244
Number of years of experience (n=184)	0.168	0.011	0.135	0.034
Ever attended PV training (n=194)	0.178*	0.013	0.274**	0.000
Knowledge of pharmacovigilance (n=185)	0.229	0.001	0.189	0.005
Professional group (n=197)	-0.065	0.365	0.023	0.752
ADRs reported ever	--	--	0.401**	0.000

* Number of respondents varies as per the answered paper questionnaire items; ADR = Adverse Drug Reaction; r = Pearson coefficient; $p<0.05$ level was set to infer statistical significance.

Note. **Correlation is significant at the 0.05 level (2-tailed) **Correlation is significant at the 0.01 level (2-tailed)*

Table 3 Predictors of adverse drugs reactions reporting based on the multivariate logistic regression model

			95% C.I. for aOR	
Variables	***p***	**aOR**	Lower	Upper
Profession				
Medical	0.288	0.60	0.229	1.549
Nursing	0.000	0.17	0.070	0.401
Pharmacist		1		
Number of years of experience	0.248	1.03	0.981	1.078
Ever attended PV training				
Yes	0.997	0.998	0.379	2.629
No		1		
Negative intention to report				
No	0.092	0.66	0.406	1.071
Yes		1		
Knowledge of pharmacovigilance				
Not knowledgeable	0.451	1.80	0.389	8.369
Knowledgeable		1		

p<0.05 level was set to infer statistical significance. Odds ratio (OR) and 95% confidence interval (CI) were calculated using multivariate logistic regression and all variables were entered by forward stepwise method. Wald test statistic shows the variables that contribute to the logistic regression model (Wald test statistic was 5.361, *p* = 0.021), Nagelkerke R square for the model was 0.251

4.5.3 Responses to open-ended question

Out of 197 respondents who participated in the survey, 168 (85.3%) respondents answered the open-ended question "*What other ways would you propose/suggest to improve adverse drug reactions reporting and pharmacovigilance system in Namibia*". Five (5) themes were identified such as training gaps, electronic reporting, feedback from TIPC and community engagement; subthemes identified included training on pharmacovigilance, awareness creation in the community and digital/electronic reporting (**Table 4**).

Table 4 Thematic summary of responses for improvement of Pharmacovigilance and ADR reporting system in Namibia

Theme	Sub-theme	Quotes from respondents
Training gaps	- Training on pharmacovigilance - Training on how to complete ADR report forms - Training on how to detect ADRs in practice	*"Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivate all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects (it is a responsibility for Pharmacists to educate or motivate other health care providers)"* *"Create awareness about pharmacovigilance and provide relevant information in regards to the centers where adverse reactions can be reported to and the necessary steps that one will need to follow to report adverse drug reactions."* *"Educate all pharmacists and other healthcare workers on the importance of drug safety and post-marketing surveillance"* *"Health workers and health care providers should be regularly trained and appraised on the importance of Adverse Drug Reactions reporting"* *"Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivate all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivate all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects."* *"Training of all healthcare workers, especially nurse, on ADR reporting and pharmacovigilance because they are the first to be seen by the patients. In-service training on what should be reported."*
Electronic ADR reporting system	- Use of a mobile or cell phone	*"Electronic/online options e.g. TIPC mobile application"*

Theme	Sub-theme	Quotes from respondents
	application - Digital reporting system	*"electronically reporting, like database"* *"Digitalization of the ADR reporting and pharmacy vigilance system"*
Decentralization of pharmacovigilance/ADR reporting system	- Creation of reporting hubs at district/facility level	*"Each hospital must have a specific staff responsible for giving awareness assessing, detecting and receiving and reporting to TIPC."* *"Get a focal person to deal with ADR reporting"*
Community engagement	- Awareness creation in the community	*"Encourage patient/user of medicine to report directly all the adverse reactions in writing to the pharmacy/clinic near him/her"*
Feedback	- Communication between TIPC and ADR reporters	*"Feedbacks and should come back to the person or the organization who report the ADR report"* *"Provision of feedback on reports and regular feedback to stakeholders on the TIPCs ADR related activities and country status. Pre and post-training field visits to health facilities to maximize impacts of training and to motivate reporting by professionals - raising public/patients awareness on ADR identification and reporting using various platforms including TV, MOHSS website, social media platforms, etc. (I wonder if there exist any report from patients so far)."*

4.6 DISCUSSION

This is the first study in Namibia to explore the knowledge, attitudes and practices of healthcare workers concerning ADR reporting. Findings suggest that pharmacovigilance practice among healthcare workers in Namibia could be substantially improved, given that a minority has undergone pharmacovigilance training before. Training also appeared to be an important factor that may be related to ADR-reporting practices [13]. In a recent audit carried out between August 2017 and August 2018, using the Individual Case Safety Report (ICSR) submitted by healthcare workers to TIPC, it was found that, although patients may be experiencing ADRs due to atazanavir and lopinavir containing regimens, cases were under-reported [14], though; the under-reporting may not be limited to these regimens.

Respondents themselves suggested that training and education around pharmacovigilance could empower current systems of reporting. Strengthening the communication channel between TIPC and healthcare workers through Therapeutics

Committees at the facility level as well as the provision of analytical feedback on TIPC reports could serve as an incentive for the reporters.

Studies have elsewhere been carried out to assess the knowledge, attitudes, awareness, practices and perceptions of healthcare workers in different settings in Africa. In Nigeria, for example, the knowledge and perception of pharmacy students of pharmacovigilance activities in three Nigerian universities were assessed [15]. It was found that the knowledge of pharmacovigilance activities was low among the students. In another study in Nigeria among healthcare workers factors associated with under-reporting of ADRs included the lack of availability of reporting forms and lack of awareness of how to report ADRs [16]. Other studies have reported that not knowing how to report can be a barrier to ADR report among clinicians [17, 18]. The introduction of an electronic reporting platform was suggested by the respondents as a way to improve and encourage ADR reporting in Namibia. Furthermore, in western Ethiopia, a lack of awareness and knowledge of pharmacovigilance and pharmacovigilance systems were reported to contribute to the under-reporting of ADRs among healthcare professionals [16].

The level of awareness of ADR reporting among the respondents was found to be 37.1%. The result is similar to other studies conducted in Nigeria and India which estimated the awareness of the Yellow Card ADR reporting scheme and/or had reported an ADR at 32% and 37% respectively [19-20].

More reports were received from the nursing cadre, these are more in number within the health system and the pharmacy cadre which is more involved with pharmacovigilance activities, and this raises questions relating to the representation of the sample. However, in general, the survey was inclusive and able to distinguish

subtle differences between the professional groups, for example, knowledge levels. Indeed, the only emerging variable that may serve to predict ADR reporting through regression analysis was found to be respondents belonging to the nursing profession. Further research in this area needs to focus on how to strengthen the pharmacovigilance systems through engagement with stakeholders and the development of innovative ways of reporting ADRs in Namibia. Specifically, a better focus on the nursing profession – who are often at the frontline of patient care where they will be administering medicines and observing the effects – in terms of improving competence in recognising and reporting ADRs may be necessary. As the largest health profession worldwide and in Namibia, this also stands to have significant public health impact especially following any introduction of new standard treatment guidelines incorporating new treatment regimens such as the antimalarials, antituberculosis drugs or antiretroviral medicines or other drug classes [9].

This study relied on voluntary participation and purposive sampling of healthcare workers. This type of study has the potential for selection bias and limited generalisability. However, the survey of healthcare workers in Namibia was regionally stratified focussing on locations with a high number of healthcare workers or locus of activity. The current study did not focus on independent patient-reported ADRs which remains a limitation of the study but can be further investigated through future research.

Depending on the setting, centralised, national reporting systems may not always be the solution to pharmacovigilance but if they are adopted – as is the case in Namibia – there is a need to continually support their function and improvement. This may include ongoing training and education at pre-service and in-service levels, the

involvement of Therapeutic Committees at the facility and regional levels and introduction, for example, of innovative electronic reporting to improve efficiency and boost the response rate amongst healthcare workers [20-23].

In conclusion, the study revealed a high level of knowledge of pharmacovigilance and ADR reporting system among the healthcare workers, though, this has informed neither their attitude nor their practice of ADR reporting as seen in their reported attitude and practice. In other to optimise the current system, there is a need for effective communications between TIPC and the healthcare workers; this may be in the form of feedbacks, Continuing Professional Development lectures, advocacy within the health sector and community engagement.

4.7 Summary

This chapter explored the knowledge, attitude and practices of healthcare workers in the public healthcare setting of Namibia concerning pharmacovigilance and ADR reporting. It seemed the healthcare workers had a high level of knowledge, however, their attitude or culture was bad; the attitude has a direct relationship to their practice of pharmacovigilance and ADR reporting.

The next chapter sought to know the possible challenges faced by healthcare workers to practice pharmacovigilance and report suspected ADRs, using a key informant approach. Ways of mitigating under-reporting of ADR in the health system were proffered by the key informants.

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CHAPTER 5 EFFECTIVE INTEGRATION OF PHARMACOVIGILANCE SYSTEMS AT PUBLIC HEALTH FACILITIES IN RESOURCE LIMITED SETTINGS: A QUALITATIVE STUDY

Published: *Research in Social and Administrative Pharmacy*, November 2019

ABSTRACT

Background: Pharmacovigilance systems increase access to safe medicines and healthcare, but their integration in public healthcare remains a challenge in most African countries. The main barriers to pharmacovigilance integration are attributed to high patient load and limited capacities.

Objective: To explore the challenges associated with the effective integration of pharmacovigilance systems in public healthcare in Namibia.

Methods: A nationwide qualitative assessment of the integration of pharmacovigilance systems particularly spontaneous adverse drug reaction (ADR) reporting at public health facility level was carried out. Key informant interviews were conducted among pivotal healthcare professionals involved in pharmacovigilance. The main outcomes were themes on challenges and strategies for the effective integration of PV services at facility level. Qualitative data were collected over a month (i.e. March 2019), and thematically analysed.

Results: Eight (8) key informants were recruited; the majority were pharmacists (n=7) or male (n=5). The main challenges affecting the effective integration of pharmacovigilance systems reporting at public health facilities were *"weak pharmacovigilance policies and structures", "negative attitude of healthcare workers towards pharmacovigilance"*, and *"limited capacity and support for implementation of pharmacovigilance activities"*. The main strategies for effective integration of PV systems at facilities included local capacity building through continuing professional education and support, advocacy, stakeholder engagement and facility/region based pharmacovigilance champions, facility-based policies for a

universal and inclusive reporting (i.e. patients and health workers at all levels) as well as the development of workable standard operational procedures.

Conclusion: The pharmacovigilance system at healthcare facilities in Namibia was observed to have sub-optimal policies, structures and support systems, and lack of healthcare worker buy-in. There is a need for a policy framework to ensure effective and sustainable integration of pharmacovigilance activities at public healthcare facilities.

KEYWORDS: Qualitative, Namibia, pharmacovigilance, public healthcare

5.1 Background

The need for monitoring the safety of medicines became apparent after the use of thalidomide in the early 1960s led to more than 10,000 children developing phocomelia, a birth defect affecting the limbs of new-borns; thalidomide had been used as a sedative and treatment of nausea in pregnant women [1]. This prompted rigorous toxicity testing of new drug candidates by manufacturers and improved post-marketing surveillance monitoring of newly approved drugs. Since then, the World Health Organisation (WHO) mandated national governments to incorporate medicine safety programs into their public healthcare; this led to the scale-up of pharmacovigilance activities globally [2].

Pharmacovigilance activities are commonly carried out by National Medicines Regulatory Authorities (NMRA) housed within the Ministries of Health in most sub-Saharan African (SSA) countries; and has become the norm in an era of donor-funded public health programmes such as for antiretroviral therapy (ART), Tuberculosis and malaria programmes [3–5]. Subsequently, most NMRAs in SSA, including Namibia, have incorporated pharmacovigilance activities in public healthcare to support and promote the safe use of medicines.

Moreover, in the recent decade, SSA has seen an unprecedented surge in the number of manufacturers and marketers involved in medicines distribution within the sub-continent [6]. SSA, being the global region hardest hit by the HIV pandemic, has a prevalence of HIV infection in some of the countries such as Namibia above 10% as of 2017 [7]. This has required the integration of novel regimens in public healthcare with the parallel implementation of pharmacovigilance programs.

Some of the challenges facing the integration of a comprehensive and effective pharmacovigilance system in SSA include over-reliance on donor funding to execute critical public health programs, low human capacity and expertise required to implement programs, and the lack of integration of such programs into the existing public health strategies in place [8].

In Namibia, the Therapeutics Information and Pharmacovigilance Centre (TIPC), this was implemented through the assistance of donor funder, within the Ministry of Health and Social Services (MoHSS) as the largest publicly-funded provider of healthcare. Paper-based spontaneous adverse drug reaction (ADR) reporting system has been in use in Namibia since the inception of TIPC, however, there are challenges associated with such a reporting modality; the need for printed material (paper), storage of returned reports, relaying or faxing the report to the central coordinating unit, and eventual collation of and action on the reports. The time between identifying a suspected ADR and possible action to be taken by the coordinating centre may limit the usefulness of some of the reports, rendering pharmacovigilance activities unreliable and risking patient care by not being responsive to hazards that may arise. Identified areas of need in the Namibian healthcare setting that are necessary to close the human and financial capacity gaps created by the donor funders' exit include in-country training of healthcare workers (HCW) and health scientists which might be achieved by the commencement of the School of Pharmacy, Faculty of Health Sciences, which provides a local needs-based curriculum [9–11].

Evidence suggests [12] that ADRs developed or experienced by patients may be under-reported; this has a direct link to the pharmacovigilance systems in place, both at the central coordinating unit and facility level. However, under-reporting of ADRs is a

common phenomenon among low and middle-income countries (LMICs) [13,14]. With the continued digitalisation of healthcare services and programmes, it has necessitated the development of solutions to bridge the gap between effective reporting and available tools to achieve the goal of improved patient safety. Notable intervention using the digital platform in Namibia included the introduction of a pharmacist's intervention tool through the use of smartphones [11]. It is important to conceptualise the prevailing circumstances within the healthcare system, optimise and develop locally appropriate ways in which the challenges identified within the pharmacovigilance system can be mitigated.

This study aimed to better understand the problems within the Namibian healthcare sector with regard to integrating pharmacovigilance activities and routine clinical practice as perceived by key informants in various settings/sectors, to strengthen and optimise the pharmacovigilance systems, thus, improving ADR reporting amongst the healthcare workers.

5.2 METHODS

5.2.1 Design and setting

A descriptive qualitative study was conducted through key informant interviews using an investigator-administered, semi-structured interview schedule involving strategic healthcare professionals from different sectors in Namibia. Only personnel conversant with the pharmacovigilance system in Namibia and beyond were targeted for the study.

5.2.2 Population

Eight (8) key informants were purposely selected taking into consideration their understanding of pharmacovigilance and the systems to support pharmacovigilance in Namibia, and previous positions within the healthcare sector. These included healthcare professionals – seven pharmacists and one medical doctor – working in the medicines regulatory authority, public sector hospitals, non-governmental organisations (NGO), or academia. The interviews were conducted sequentially until saturation of themes was attained.

5.2.3 Procedure

Key informant interviews were conducted over one month, March 2019. The framing question for the interview was:

'*In your view, what are the ways or how can the pharmacovigilance and adverse drugs reactions reporting system be improved in Namibia?'*

Subsequently, participants were presented pertinent areas for discussion including subjects around current practices of pharmacovigilance in Namibia, barriers to reporting ADRs from the healthcare workers' perspectives, and possible ways of strengthening the existing pharmacovigilance and ADR reporting systems. Further, participant responses were probed for clarification or to provide more depth. The responses were audio-recorded on an electronic device and later transcribed. The principal researcher (BAA) moderated all the interviews which were conducted in English Language. Permission to conduct the study was obtained from the ethics committees of the Ministry of Health and Social Services (MoHSS) and the University of Namibia.

5.3 Data analysis

Audio-recorded responses were transcribed verbatim and double-coded by two researchers (BAA and DK) in the research team using thematic content analysis; a third researcher (TWR) reviewed the coding to identify inconsistencies that were clarified between the three researchers. Confidentiality of the participants was ensured.

5.4 Results

5.4.1 Participant characteristics

Eight eligible participants were recruited and all of them agreed to be part of the key informant interviews. Breakdown of respondents included chief pharmacists (2), medical doctor (1), TIPC pharmacist (1), academic pharmacists (3) and a pharmacist working in an NGO (1). Of the 8 participants, there were 5 males and 3 females, all of whom were resident in the capital city except one regular visiting academic.

5.4.2 Thematic analyses

Through analyses, a total of 3 themes related to challenges faced by healthcare workers (Table 1) and 7 themes related to ways of improving the pharmacovigilance and ADR reporting systems were derived (Table 2). There were a total of 43 identified challenges and 80 identified improvements were derived. A number of challenges limiting the healthcare workers to report ADRs were similar in both public and private healthcare settings.

5.4.2.1 Challenges faced by healthcare workers to report ADRs in Namibia

In relation to challenges faced by healthcare workers in reporting ADRs, three emergent themes were identified: (1) Weak pharmacovigilance policies and structures, (2) Limited capacity and support for the implementation of

pharmacovigilance activities, and (3) Negative attitude of healthcare workers towards pharmacovigilance.

Of the 8 key informants, the challenges on reporting ADRs among the healthcare workers were related to systems issues with subthemes such as outdated reporting modalities, reporting by patients and feedbacks from TIPC. Limited capacity of both the healthcare workers and TIPC staff and competency of health workers to identify, record and report suspected ADRs was the second identified theme. Attitude of healthcare workers to report identified ADR was the third identified theme with subthemes such as resistance to change, willingness to report and sense of responsibility. (**Table 1**)

Table 1 Themes and subthemes identified from participants' responses on challenges faced by healthcare workers to report ADRs

Themes	Sub-themes	Quotes
Systems-related challenges limiting ADR reporting	Outdated mode of reporting	*"But not only the private sector, there are those health workers who still prefer electronic reporting system it might be much more convenient, so sort of like eliminate the logistics of completing the form, fax it, or scan it and email it"* *"And erh, like the details one can get back to the person making the report but that initial report, can we make it a bit simple and user friendly?"*
	Reporting by patients	*"Maybe, ok, maybe we encourage the patients to report ADR but he will not know. He goes to the doctor, patient who got the medication, then, he got ADR, right. And then, he will go to the doctor, he will report it"*
	Trained staff attrition	*"Like in our setting here, we've trained two of our staff members have been trained and I think a doctor too was trained but that doctor is no longer in the system. And those are the issues, you know you train people after training them either they resign or they are no longer in the system"*
	Centralised pharmacovigilance centre	*"Of course, em Namibia being a vast country, em having one central point for coordinating all the pharmacovigilance activities which include ADR reporting, product quality, you know, reporting, also giving medicine information may be a very demanding task"*
	Feedback (TIPC)	*"And that should, that should be well structured, you know and standard, right across the country, because people, they say we report [laughter] but we rarely get, we rarely get feedback and that's a fact;"* *"I think it comes back to feedback still, uhm, intensified central level feedback, you know, to the facilities when they report, you know, we have the bulletin like what we used to have but the bulletin content should contain more of the scientific analysis, you know ahm, ahm, than the descriptive, you know ehm ehm feedback that is normally given"*
Limited Capacity	Capability at TIPC	*"Okay so what this means is that at the moment ahnn, TIPC is operating, it is in charge of pharmacovigilance, and it struggles to promote it"*
	Competence (Healthcare workers)	*"You know when people, you know you want a pharmacist assistant to report, what you expect from that report, is it too detailed? You may want to look into that. You know making the form a bit er er, making the form, simplifying aspects in the form that makes it user friendly, let me put it that way"* *"Patient is telling the pharmacist that I, I, the doctor changed my medicine and the pharmacist is asking oh, why? Because I*

Themes	Sub-themes	Quotes
		was coughing too much, now on this new medication. Pharmacist just go ahead, it doesn't trigger anything in that pharmacist that no, this needs to be reported because there are a lot of patients, filling that form will take time. He doesn't want to waste time, he wants to finish the patients"
	Workload	*"It shouldn't be looked at as one of those ectopic activities which if apart from says they are very busy they won't be able to report"* *"Like in our setting, really doctors are busy with their clinical work and they've not seen adverse medicine reaction reporting as part of their clinical work."*
Healthcare worker attitude	Resistance to change	*"Change, you know, there is resistant to change. There is one, to, to change your behaviour, first you have to have the knowledge and good attitude towards ……. Change doesn't come because we say, please act like this or behave like this. So we need to be consistent, and other thing, other thing is that pharmacovigilance"*
	Willingness to report	*"Those are the things that affect adverse medicines reporting, people feel ok, it might affect their performance rating, yea"*
	Sense of responsibility	*"Perhaps people we nominate to go for those training are not eh, passionate about er ADR reporting. Like in our setting here, we've trained two of our staff members have been trained and I think a doctor too was trained but that doctor is no longer in the system"*

5.4.2.1.1 Theme 1: Weak pharmacovigilance policies and structures

The respondents described the challenges that government institutions such as the MoHSS and the TIPC have to address in order to strengthen the pharmacovigilance systems and improve ADR reporting by healthcare workers. Respondents commented on the unsuitability of the paper-based reporting system, which they suggested was outdated and there was a need to come up with more versatile and responsive systems to ensure prompt transmission of reports from the healthcare worker to TIPC. The need to decentralise the coordination centre by involving the Therapeutic Committees at the facility/regional level was highlighted by one of the participants.

5.4.2.1.2 Theme 2: Limited capacity and support for the implementation of pharmacovigilance activities

It was suggested by one of the participants that limited capacities, including human and financial resources, at the TIPC did not allow for proper follow-up and coordination of pharmacovigilance activities within the country. This reportedly has an impact on the promotion of pharmacovigilance among healthcare workers as highlighted by the participants concerning the competence, willingness to report, and workload of medical doctors. It was further suggested that healthcare workers cannot appropriately identify ADRs or differentiate side-effects from ADRs, which undermines accurate reporting.

5.4.2.1.3 Theme 3: Negative attitude of healthcare workers towards pharmacovigilance

Participants suggested resistance to change as a barrier to reporting. It was emphasised that after training there can be an increase in ADR reports, however, over time the number of reports decline which, according to participants, may be due to the way pharmacovigilance activities are being promoted currently.

1

5.4.2.2 Improving the pharmacovigilance and ADR-reporting systems dynamics

In relation to improving pharmacovigilance reporting, seven emergent themes were identified: (1) Systems-related ways of improving pharmacovigilance and ADR-reporting, (2) policy, (3) advocacy, (4) training, (5) incentives, (6) inclusive reporting, and (7) stakeholder engagement. (**Table 2**)

Table 2 Themes and subthemes identified from participants' responses on improving the pharmacovigilance and ADR reporting systems dynamics in Namibia

Themes	Sub-themes	Quotes
Policy	Integrating PV activities into routine clinical work	*".So I think that's another area we need to find a way to integrate adverse medicine reactions reporting as part of a clinical work of the clinician"* *"You see, you already collection information to manage a patient, not to report, you collect the information to manage a patient, but it will prompt you to say, ok, when you make a provisional diagnosis of adverse drug reaction, then it will populate and will say 'do you like to submit this report'? A click, then it will, it will submit. If you miss very important information to do the causality assessment, it will ask you, 'please, this is a mandatory field', you'll complete that one and then send it. You have a report. So, it is possible. But erh, how far we are, I am not sure. Yea, and any reporting system, should also be compatible with Vigiflow, with the Vigibase"*
	Facility level involvement	*"The other thing, erh, drug and therapeutic committees, they should also be involved, in creating awareness, in analysing data, looking into event and trying to make, to come up with some kind of intervention and so on. So the therapeutic committee, should be involved."*
Advocacy	Insurance providers/Private practice involvement	*"the private sector also needs to take part in this and that could work through insurance provider"*
	Patient reporting	*"Another area that we really need to do a lot of exploration is ahm, patient reporting. We currently don't have ahm, patient reporting system in Namibia"*
	Awareness	*"So my point here is to, in general, to create awareness for the doctors, nurses, pharmacists about the ADR, right, and about the importance of reporting"*
	Manufacturers/Marketing Authorisation Holder	*"Erh, like I said, making sure that their product is safe, is the responsibility of the producer, the pharmaceutical company. So there is a need for them to do big chunk of the work, but there is a need for regulation as well because you can downplay some of the events, if they are not regulated"*
Systems-related	Performance appraisal	*"For example, everyone being employed in*

Themes	Sub-themes	Quotes
ways of improving pharmacovigilance and ADR-reporting systems		*government they need to be required to report adverse drug reactions, it needs to be part of the appraisal () of the healthcare worker"*
	Competence	*"They should have the forms, they should have basic ideas on how, you know, maybe to do a mini analysis of what is happening before sending the report to TIPC, so that people, even in the facilities first hand, ahm, ahm, feedback from their coordinators of what collected from their facilities, so I will say it's not only you know, the relay of the reports to the central centre for it to be put in a database, is analysed from there"* *"The facility, the team in facility, they should be able to make use of that data, the report"*
	Insurance providers	*"Insurance providers needs to make it a requirement, for the healthcare worker to detect and report these adverse drug reactions and then through insurance service mechanisms they can see how ahh remittances to this kind of activities how it's made."*
	Electronic reporting	*"The future is going electronic, you know, there is no other alternative. So, erh, there is a need for us to prepare for electronic reporting system"*
	HCW assurance of absolution from reprimand	*"I think it will be…also, I think as part of the enlightenment let people know that it's not going to affect their work, especially, when you shouldn't have given a particular medicine and you gave that medicine and there's an adverse medicine reaction, then the person is, ok I might be sanctioned, could it be anonymous?"* *"I don't know how to put it now, department we are not sanctioning you because the patient reacted ok. Or now the HOD got to know then there is a, you know."*
Training	Pre-registration curricula/ Incorporating PV training into pre-service health professionals' curriculum	*"There is a very good reason why we need to monitor the safety of the product. So this should be incorporated into the graduate program in the pharmacology and the therapeutic, er, er, what do you call it, in the pharmacology curriculum [cleared his throat]. And when they come out, they should know that there is a need for reporting and there is a system for reporting. That is one."*

Themes	Sub-themes	Quotes
	In-service professional/personal development	*"it goes beyond just having leaflets and banners, you know, we have to have probably, a midday event as well, where we talk about pharmacovigilance should be a theme for pharmacy week, times where we advocate for pharmacists to, as champions of pharmacovigilance, to encourage each other, healthcare workers to report."*
	Data analysis at facility	*"they should have basic ideas on how, you know, maybe to do a mini analysis of what is happening before sending the report to TIPC, so that people, even in the facilities first hand, ahm, ahm, feedback from their coordinators of what collected from their facilities, so I will say it's not only you know, the relay of the reports to the central centre for it to be put in a database, is analysed from there"*
Incentivisation	Feedback from TIPC	*"When somebody begins to see the impact of his work, then he's encouraged to do more. You know, either you get feedback, timely feedback to say ok based on the reports you made, these are the outcomes. That also is important. You get timely feedback to those that made those reports. It's also important"* *"I think it comes back to feedback still, uhm, intensified central level feedback, you know, to the facilities when they report, you know, we have the bulletin like what we used to have but the bulletin content should contain more of the scientific analysis, you know ahm, ahm, than the descriptive, you know ehm ehm feedback that is normally given."* *"For me, it's improving the awareness about ADR and the reporting system and give feedback, what happened after you have reported on these ADR for the doctors and for the nurses."*
	CPD points	*"Sure the CPD points can attract some of the doctors, nurses……..also giving the feedback as I am saying, is considered to be a reward."*
	Recognition at professional meetings	*"When the doctor will hear their name, that we got this from dr. who who at central hospital, or the next time, they know that it's valuable towards, when I sent it somebody looked at it and document it and send it on the next meeting. You know like, we all like to hear our names in the meetings. [Laughter]."*

Themes	Sub-themes	Quotes
Inclusive reporting	Integrated electronic reporting/ Introducing electronic data capturing system/Integrating	*"They don't think that it is their day to day activities. So that it the main, main challenge. So it needs to be integrated into the day to day activities, into the clinical practice, nothing else, patient care. If they see it as something else, it's totally wrong"*
Stakeholder engagement	Private sector/MAH engagement	*"you know because of erh, business, business principles, they may not be, or I can say, they can downplay the adverse events for the mere reason that they want to lose. It has to be regulated. But at the same time, they have to contribute a lot to the safety of their pharmaceutical product"*
	Community enlightenment/engagement	*"You know, devote like in a year, like twice in a year or so, you devote erh, you devote you say a week, adverse medicines reactions week. Just to create awareness, not only in the hospital even in the community. Let patients know, they have a right, not a right, a responsibility, you know to report. That even if the doctor is not reporting it, they too they will say I want to report what happened to me."* *"But increasingly we can go into the media, TV, radio. We have people talk about the subject, why is it important, why we should we document and send the reports."*

5.4.2.2.1 Theme 1: Systems-related ways of improving pharmacovigilance and ADR-reporting systems

Participants identified making pharmacovigilance a national activity as part of the daily routine medical personnel attending to patients and linked to the performance appraisal of healthcare workers. Other reported ways of improving the system included the implementation of an electronic reporting system, constant feedback from TIPC, and integration of ADR reporting into the clinical work of healthcare workers.

5.4.2.2.2 Theme 2: Policy

Establishment of policies addressing pharmacovigilance activities was suggested as a measure that can help in integrating the pharmacovigilance systems and, invariably, ADR reporting within the healthcare system.

5.4.2.2.3 Theme 3: Advocacy

Participants reported that creating awareness of pharmacovigilance activities among healthcare workers and the community at large was a possible way to improve ADR reporting. Also, the involvement of marketing authorisation holders (MAH) or holder of a certificate of registration (HCR) of registered pharmaceutical products, medical aid insurance firms, initiating pharmacovigilance week, or incorporating such into pharmacy week could be mechanisms to promote pharmacovigilance. Political will on the part of policymakers in embracing pharmacovigilance activities was seen as a means to encourage healthcare workers.

5.4.2.2.4 Theme 4: Training

Inclusion of pharmacovigilance into undergraduate healthcare trainees' curricula such as medicine, nursing, and pharmacy was identified as a way of optimising the system. Continuing Profession Development (CPD) or in-service training/lectures was suggested as another training avenue for healthcare workers.

5.4.2.2.5 Theme 5: Incentivisation

Provision of feedback to healthcare workers individually and in a group setting such as pharmacy week was identified as a reporting incentive. Recognition of best performers in specific settings was deemed to be an incentive for healthcare workers to report identified ADRs. Another incentive identified by the participants was the provision of CPD credit as CPD is a requirement for practicing medical doctors, pharmacists and dentists, for example.

5.4.2.2.6 Theme 6: Inclusive reporting

As there is no platform for patients to report ADRs in Namibia, provision of user-friendly ways such as the use of mobile phones and other digital platforms may be warranted.

5.4.2.2.7 Theme 7: Stakeholder engagement

Involving the community through the provision of information on mass media such as national radio and television or newspapers, and other avenues were mentioned as a way to create awareness and improve patient reporting. Marketing authorisation holders were believed to be vital in extending the frontiers of pharmacovigilance within the country, engaging such pharmaceutical companies and mandating them to

liaise with the private practitioners/entities they serve was suggested as a way of improving the pharmacovigilance within the private healthcare sector in Namibia.

5.5 Discussion

Key informant study was carried out among healthcare workers from different sectors within the Namibian public healthcare setting to explore the ways that challenges faced by healthcare workers with respect to the integration of ADR reporting and pharmacovigilance with routine clinical practice can be mitigated with the focus of integrating pharmacovigilance activities into routine clinical practice. Challenges related to the pharmacovigilance centre included awareness of the system in place, feedback from the centre to healthcare workers and training of healthcare workers. Provision of incentives, prompt and appropriate feedback from TIPC, pre-service training of healthcare workers on pharmacovigilance and CPD training have been identified as ways of bridging the gap of under-reporting of ADRs in our study [14,15]

Knowledge, diagnosis and reporting of suspected ADR by healthcare workers are some of the challenges contributing to the under-reporting of ADRs within the healthcare delivery system [16]. Workload or the time to identify and report an ADR was suggested reasons for under-reporting since healthcare workers want to 'move the queue'. Similar findings have been reported by some studies [17,18]. Lack of feedback contributes to under-reporting as reported in our study and this is similar to other studies carried out elsewhere [19,20].

It is necessary for the Namibian government to take responsibility for the pharmacovigilance activities, thus, providing the necessary political will that will drive the pharmacovigilance system itself. An electronic or digital reporting system incorporated into an Electronic Patient Monitoring System (EPMS) has been

suggested as a way forward, though, not doing away with the paper-based ADR reporting system currently in place [20]. This will enhance the submission of reports of suspected ADRs and it will reduce the duplication of medical records as it is today. Encouraging the Therapeutic Committees at different levels of the healthcare system, to take over pharmacovigilance activities within their setting will give more credence to the importance of ADR and ADR reporting in the country.

Though patient reporting seems a bit far-fetched in the Namibian context, educating the population about basic pharmacovigilance and the necessity for reporting whatever reaction occurred after the administration of a medicine will assist in strengthening the system and creating a knowledgeable population [13,21]. Also, an enabling environment is needed to achieve a workable patient-reporting system; this may be achieved through the introduction of a mobile telephonic system which may be at no cost to the reporter and feeds directly into the TIPC database.

The regulatory authority in conjunction with the MoHSS, has to make concerted effort in carrying the healthcare workers along with the pharmacovigilance issues, creating awareness and advocating for incorporating pharmacovigilance training into the pre-service curricula of healthcare professionals-in-training [7].

5.6 Conclusions

In conclusion, our key informants have identified challenges facing the pharmacovigilance system in Namibia and suggested ways to mitigate the challenges so as to improve the system. The suggestions might be useful for the regulatory authority in order to enhance spontaneous ADR reporting and promote the culture of pharmacovigilance in the country. Also, integrating pharmacovigilance activities into the existing electronic patient monitoring and reporting system and routine clinical

work of healthcare workers will minimise the loss of information, thus, improving the reporting of adverse events in general.

5.7 Acknowledgement

I wish to thank all the participants who took part in this study for their invaluable time and contributions.

5.8 Ethical Approval and Consent to participate

Research ethics approvals were obtained from the Research and Ethics Division of the MoHSS (Reference No. 17/3/3) and Ethics Committee of the University of Namibia (Reference No. SOPHA/209/2017).

5.9 Summary

The chapter presented the views of key informants on the perceived and experienced challenges of healthcare workers in performing pharmacovigilance activities and reporting ADRs. It also, presented suggested ways of optimising the current system, thus, mitigating whatever challenge is faced by the healthcare workers. Stakeholder engagement and introductions of an integrated electronic platform were part of the identified ways of strengthening the system.

The next chapter presents an electronic mobile platform which is one of the suggested ways of optimising the pharmacovigilance system in Namibia, as seen in the preceding chapters.

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CHAPTER 6: INTRODUCING AN ELECTRONIC MOBILE REPORTING MODALITY FOR PHARMACOVIGILANCE IN NAMIBIA

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Abstract

Objective: To develop an electronic mobile reporting platform for pharmacovigilance and adverse drug reactions reporting in Namibia with the aim of improved monitoring of the reporting system used for pharmacovigilance by healthcare workers in Namibia.

Methods and Materials: An existing mobile data-gathering platform was populated with the information on the Individual Case Safety Report form used by the healthcare workers in Namibia to report suspected adverse drug reactions (ADRs) to the Therapeutics Information and Pharmacovigilance Centre. Face validity was carried out among prospective users of the electronic mobile reporting tool, to ensure accuracy of content, format and information flow. The tool was piloted among attendees of continuing education training on pharmacovigilance who were given access to the reporting tool.

Results: Eighty-eight healthcare workers were engaged in three continuing education events between June and October 2019. The electronic mobile ADR reporting tool was introduced to healthcare during these training sessions. At the time of compiling this initial report, none of the healthcare workers had submitted a report using the mobile application.

Discussion

We developed an electronic mobile reporting system for pharmacovigilance in Namibia based on an existing data gathering platform with a computer application that can be installed on mobile devices, and used in practice without the need for immediate or

continuous access to the internet. The uptake of this tool is likely to rely on a systematic roll-out by the national medicines regulator that is underpinned by training.

Conclusion

An online mobile platform for the collection of health data may improve the reporting habits of healthcare workers when they encounter ADRs in practice although this remains to be seen in Namibia. Policymakers, healthcare workers and social engagement with the community are vital to the success of an electronic intervention for pharmacovigilance in Namibia.

Keywords: pharmacovigilance, adverse drug reactions, electronic mobile application, reporting systems, healthcare workers

6.1 Background and Significance

A number of studies have explored different ways of optimising pharmacovigilance systems and mitigating under-reporting of suspected adverse drug reactions (ADRs); approaches include incorporation of electronic reporting modalities through internet-based desktop reporting systems [1,2], mining ADR information from social media platforms [3], and the use of mobile phone applications interfaced with pharmacovigilance centre reporting platforms [4,5]. Developing innovative ways of capturing data from patient clinical records - or at the point of consultation with patients - using information and technology platforms such as electronic health records, make data collection, reporting and clinical research, of better quality, augment data management and promote the improvement of patient safety and quality of care[6–8]. New reporting modalities have to be locally appropriate and also recognize the need for buy-in of both health policymakers and healthcare workers.

Pharmacovigilance in Namibia mainly relies on spontaneous ADR-reporting or events reported by healthcare workers using a paper-based reporting modality that has limitations [9], with the likelihood of under-reporting of adverse events experienced by patients[10]. Similar paper-based spontaneous ADR-reporting systems are critiqued in many settings with barriers identified by healthcare workers as possible reasons for under-reporting including workload, unavailability of the reporting tool, the need for suitable record-keeping, availability of ways to communicate collected reports to the

pharmacovigilance centre through fax or scanning and emailing of reports, or need for hand delivery in the absence of other means of conveying reports to the pharmacovigilance centre [11–16].

In Namibia, between January 2009 and September 2019, about 650 Individual Case Safety Reports (ICSR) were submitted to the Therapeutics Information and Pharmacovigilance Centre (TIPC), an average of 221 reports per month [unpublished data] (Figure 1); though there were yearly fluctuations in the number of reports. According to the World Health Organisation (WHO), each national pharmacovigilance centre should receive at least 200 ADR reports per 1,000000 inhabitants per year suggesting, in Namibia, TIPC should receive at least 400 ADR reports annually.

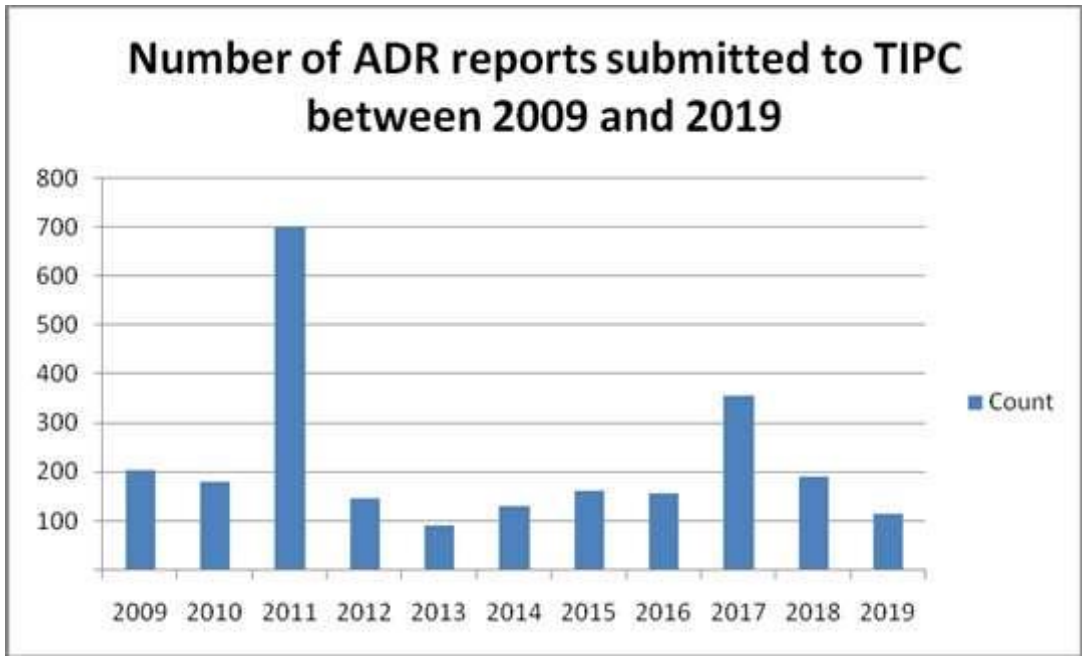

Figure 1: Number of reports submitted to TIPC per year, between 2009 and 2019

Peaks in 2011 and 2017 have been attributed to the impact of pharmacovigilance training and awareness creation [17]. It is therefore likely that ADRs are underreported especially considering the introduction of new antiretroviral (ARV) regimens in the country over the last few decades [18–20]; we also recently reported data from Namibia that suggested underreporting of ARV regimens compared with neighboring South Africa [10]. Furthermore, studies have shown a skewed reporting pattern between developed and developing countries - ICSRs submitted to WHO Uppsala Monitoring Centre accounted for less than 1% of all reports on the global database compared to the developing countries contributing more than 80% [21]; the example in Namibia is not an exception [22,23]. In order to ensure patients' safety, pharmacovigilance systems and reporting tools used to collect pharmacovigilance data have to be user-friendly and accessible to healthcare workers and patients. In a recent study carried out among healthcare workers in the public healthcare setting in Namibia, electronic reporting was identified as a potential approach to optimise pharmacovigilance [9].

As part of health systems improvement initiatives an electronic mobile application for ADR-reporting aimed at improving the quality, rate of reporting and number of reports submitted to TIPC, was developed and piloted.

6.2 METHOD AND MATERIALS

6.2.1 Procedure

Three continuing education (CE) events on pharmacovigilance were conducted in three different settings in the Namibian capital city, Windhoek, between June and October 2019. During the events, an electronic mobile application for ADR reporting was

introduced to participants. The CE events deliberately targeted different practice groups including: (1) open event to encourage participation from the private sector; (2) public sector training session with medical interns and medical staff; (3) public sector training with pharmacist interns and pharmacy staff.

An open-access mobile data-gathering platform (Epicollect5®) was populated with the information contained in the ICSR form used by healthcare workers to collect and report ADRs to TIPC in Namibia. The data-frame was developed by researchers at the School of Pharmacy, Faculty of Health Sciences at the University of Namibia in February 2019 and tested by the researchers prior to face validity, to check for any inconsistency and improve the flow of information. The reporting tool can be installed on mobile devices of healthcare workers.

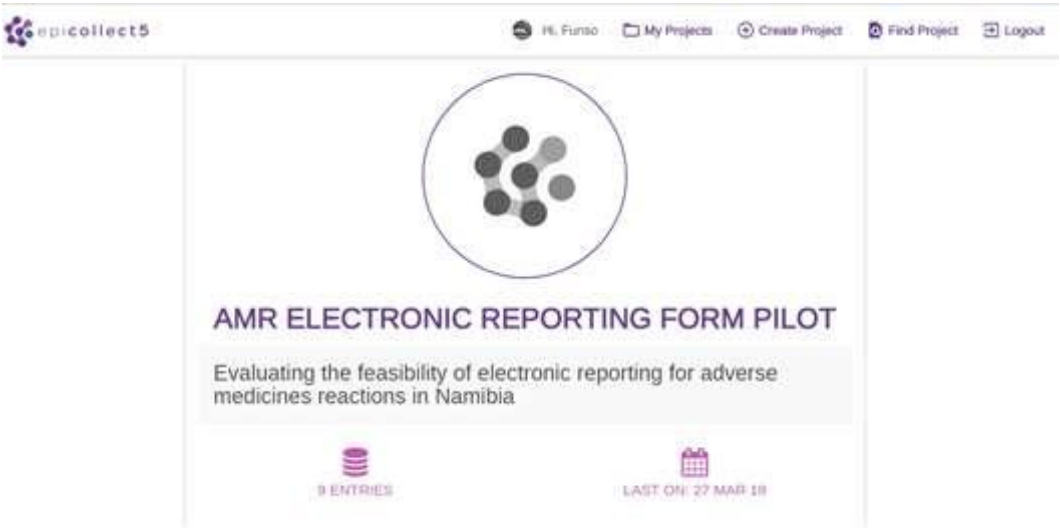

Figure 2: Screenshot of the project home page

6.3 Results

6.3.1 Face validity

Briefly, this was carried out among eight participants from varying backgrounds within the health sector, to ensure the tool contained and conveyed the right information required by healthcare workers to make and submit correct ADR reports, in addition to ensuring that the reporting platform was able to capture data critical for TIPC reporting. The electronic reporting tool, at the time of conducting this study, was only compatible with mobile devices with Android or IOS operating systems. Healthcare workers were required to install the application on their mobile phones/devices and use it as an on-the-go reporting modality.

6.3.2 Pilot phase

We engaged 88 healthcare workers from different settings in the Namibian healthcare sector, belonging to different professional groups in this research (**Table 1**). The healthcare workers were followed up after one month to remind them about the application and the need for the healthcare workers to report suspected ADR using the application. As at the time of compiling this report, none of the healthcare workers involved in the training had used the application to report.

Table 1: Demographics of attendees

Demographic variables	Categories	N = 88 (%)
Age, years (mean, S. D.)		32.51 (11.3)
Age, years categorised (n. %)*	18 - 29	44 (50.0)
	30 - 39	18 (20.5)
	40 - 49	7 (8.0)
	50 - 69	12 (13.6)
Years of experience (mean, S. D.)		6.1 (9.1)
Gender (n, %)	Female	56 (63.6)
	Male	32 (36.4)
Type of facility (n, %)		
	Intermediate Hospital	47 (53.3)
	**Others	15 (17.1)
	National Referral Hospital	12 (13.6)
	Clinic	8 (9.1)
	Central Medical Stores	3 (3.4)
	NMRC	2 (2.3)
	Health centre	1 (1.1)
Professional status (n, %)		
	Medical student	18 (20.5)
	Pharmacist	17 (19.3)
	Medical intern	13 (14.6)
	Medical doctor	12 (13.6)
	Intern Pharmacist	10 (11.4)
	Registered Nurse	6 (6.8)
	Alternate Medical	1 (1.1)

Practitioner

Key
*Missing data
NMRC – Namibia Medicines Regulatory Council
**Others – Community Pharmacy, Wholesaler, National Health Training Centre, Private Hospital/Practice

6.4 Discussion

The current project proposes an electronic mobile reporting system for pharmacovigilance, through a link between the pharmacovigilance centre and mobile telecommunication companies, which might support pharmacovigilance activities as a social responsibility service. Community engagement using enlightenment and advocacy programs on varying media platforms such as social media and conventional media platforms like television and radio might be helpful in encouraging patient reporting through this mobile electronic reporting modality.

Considering the need for government buy-in, advocacy and stakeholder engagement with the MoHSS being the primary stakeholder will be implemented on a stepwise basis. This will involve the identified community entities with vested interest in patient safety. In order to ensure the success of a new reporting modality, government policies that legitimise such platform and enforce its use are necessary.

Healthcare workers need to be aware of possible ADRs while administering medicines or attending to patients and be able to detect such events whenever they occur. Development and use of electronic mobile platforms in reporting ADRs may improve reporting systems, awareness and interventions[24]. Such a reporting system could be a

part of a broader national e-health programme incorporating broader aspects of clinical care[25].

Access to the internet was part of the barriers identified that may limit the use of such electronic platforms within a health system[26], especially in areas with limited or no internet connectivity. Considering the cost that might accrue to sending messages via the internet or mobile network by healthcare workers, liaising with local stakeholders such as mobile telecommunication companies may assist in encouraging healthcare workers and patients to report suspected adverse drug reactions[27].

Some of the limitations of this study were the method used to introduce the proposed electronic mobile application to healthcare workers, including the coverage of the training which were carried out only in Windhoek, the capital city. Regional training on pharmacovigilance, including the need for ADR reporting and introduction of the proposed electronic mobile reporting modality, will be conducted in the next phase of the study to inform healthcare workers on the developments anticipated for pharmacovigilance.

6.5 Conclusion

In order to ensure the uptake of the online mobile electronic pharmacovigilance intervention, advocacy with the policymakers and ongoing training of the healthcare workers is necessary. Implementation of the online mobile platform will require multi-sector contributions, thus the need for social engagement, to show the need for pharmacovigilance and the impact that an on-the-go mobile platform will have on public health and the safety of the population in general.

6.6 Acknowledgements

I would like to thank the healthcare workers in Windhoek, Namibia who were part of the continuing professional development lectures during which the platform was introduced.

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Chapter 7 DISCUSSIONS, CONCLUSIONS AND RECOMMENDATIONS

7.1 General discussion

7.1.1 Overview of optimisation of adverse drug reactions reporting and pharmacovigilance systems in Namibia

Pharmacovigilance is an essential feature of a healthcare delivery system because it ensures that the safety of patients seeking and accessing healthcare are taken care of. This can be achieved through the use of safe, efficacious and quality medicines, including adequate documentation of critical events occurring in a patient after administration of therapies, that are not limited to medicines such as radiological interventions, by healthcare professionals who deal directly with patients, for example, medical doctors and nurses or indirectly such as laboratory technicians. It is necessary for policymakers, healthcare workers and other stakeholders such as patients to realise the need for effective pharmacovigilance and reporting of suspected or identified adverse events.

This research explored different aspects of pharmacovigilance activities as envisaged within Namibian public healthcare sector, with the focal point being to come up with

workable solutions to address the culture of reporting, especially in relation to ADRs. Chapter 3 assessed the reporting culture of the healthcare workers with emphasis on ATV/r (newly introduced PI for modified first-line and second-line ARV regimens according to National ART guideline of 2014 and updated in 2016) and LPV/r based regimens; also, the types and severity of ADRs experienced by patients on these regimens were documented. This study revealed a low number of reports submitted to TIPC by healthcare workers during the period of data collection, though, jaundice is one of the early signs of adverse reaction due to ATV/r and this was reported by word of mouth rather than documented and reported when such reactions were identified. Due to the low number of reports used in the study, incidence or prevalence data cannot be generated for the ADRs seen within the population included in the study.

Chapters 4 and 5 dealt with the KAP of healthcare workers and ways of optimising the current pharmacovigilance systems, respectively. Continuing education and creation of awareness among stakeholders were highlighted in both studies as ways of optimising the pharmacovigilance systems in Namibia. The sample size used in the KAP study might not be representative of the healthcare workers in Namibia; however, the results obtained depicted the state of pharmacovigilance within the public healthcare sector.

Chapter 6 put forward a proposed mobile electronic reporting platform as envisaged by healthcare workers involved in the studies carried out in Chapters 4 and 5. The average number of ADR report submitted to TIPC per year indicated a probable level of under-reporting among the public healthcare workers.

7.1.2 Optimising adverse drug reactions reporting

The impact of adverse events such as ADRs, medication errors, etc. on the individual patient and the health system as a whole, can be enormous, thus the need to develop policies, guidelines and advocacy programs geared towards better patient management, which might include proper record keeping at every level of the healthcare delivery system. Public and private healthcare workers have to know and realise the necessity of reporting suspected adverse events, regardless of how insignificant such an event can be. With pharmacovigilance being a collaborative activity, it is required that every stakeholder should be involved, the need to engage every stakeholder including patients cannot be over-emphasised.

Continuous education of the healthcare workers and the public at large can contribute to improved reporting and enhance pharmacovigilance in Namibia, thus, mitigating the impact of ADR on patients and the health system in general.

7.1.3 General limitations

The author accepts that the research studies in this dissertation might have some limitations. For example, long term implications of switching patients on LPV/r to ATV/r based regimens were not assessed. This was a result of most healthcare workers who are directly involved with patients, such as medical doctors, nurses and pharmacists, who do not report suspected ADRs or might not see a reason for reporting any event experienced by their patients.

Due to the unavailability of funding, the researcher was not able to sample more healthcare workers in all the regions of Namibia as part of the cross-sectional study on KAP of pharmacovigilance and ADR reporting. Nonetheless, the study identified an

educational gap in particular, in relation to nursing cadre, which has a direct relationship with the knowledge and practices of pharmacovigilance among healthcare workers.

7.2 Recommendations

It is apparent from the research that pharmacovigilance activities and their uptake are sub-optimal and this necessitates the strengthening of the existing system. The following recommendations should be implemented by the MoHSS in conjunction with other stakeholders in both private and public settings to achieve the goal of improved health status for every Namibian.

7.2.1 Programmatic interventions

This research recommends the continued creation of awareness among patients/general population (primary stakeholder), healthcare workers at different levels of the health system (students and workers), policymakers (government, non-governmental organisations (NGOs), community-based organisations (CBOs) and private sector (health- and non-health related)). Such awareness programmes have to be suited to the group in question, so as to be able to produce the desired results.

In addition to awareness creation, advocacy for pharmacovigilance will be a necessity to ensure buy-in from different stakeholders, having the safety of patients at the centre of such activities.

7.2.2 Policy implications

Results of the research will inform the development of policies and guidelines by the health policymakers at different levels of the healthcare delivery system, in conjunction

with other stakeholders, that will put into effect the reporting of suspected ADRs while assuring healthcare workers there will be no litigation or reprimand for reporting whatever event they picked up or encounter in the course of managing their patients.

7.2.3 Inclusive pharmacovigilance systems

The involvement of Therapeutic Committees at the facility and regional levels in pharmacovigilance activities will enhance the cause of better patient management and contribute to a reduction in the costs due to ADR. Therapeutic Committees can be the focal point for pharmacovigilance activities within a region; the focal person for PV activities can be appointed within the Therapeutic Committee, thus, putting the responsibility of pharmacovigilance on the Committee rather than an individual who may be absent or not be able to carry out the needed activities due to various reasons as highlighted in Chapter 5.

Patient reporting platforms, either in an electronic format or paper-based systems, will assist in getting firsthand reports, thus, boosting the number of ADR reports received by TIPC.

7.2.4 Integration of clinical reporting platforms

There is a need to integrate all clinical reporting platforms to reduce duplication of efforts and workload. This can be in the form of e-health program, custom-made for Namibia. Also, it can be linked to the patient's identification (ID) number; this has been achieved in other healthcare settings. Such a system will flag whatever field has not been completed by a healthcare worker during a patient's hospital visit, including current reactions experienced by patients that might be unrelated to their present therapy. The

modalities for the e-health program can be described during advocacy sessions with different stakeholders.

7.2.5 Escalating the reach of TIPC through stakeholder engagement

Greater involvement of MAH in patient management with regard to pharmacovigilance, especially, with respect to applicants registering generic products might assist in better pharmacovigilance of such medicines or products. Also, NMRC might enforce the use of brand names or identifiers by every prescriber linked to the manufacturer and specific product to help out in traceability during a suspected adverse event occurrence.

7.2.6 Platform for ADR reporting by healthcare workers and patients

The introduction of a mobile electronic platform for reporting ADRs in conjunction with mobile telephone networks at no cost to reporters might assist in boosting the number of reports received or submitted to TIPC. This will be done in conjunction with the paper-based reporting modality in place, taking into consideration those areas within the country or individuals with no internet access. Patient reporting has been identified as one of the avenues that might contribute to more ADR pool within a country in some settings. In this vein, allowing the general population to provide the regulatory authority with reports will be seen as improved awareness and such an initiative will in the long run reduce ADR burden thus affording the State better patient management.

7.2.7 Mandatory inclusion of local Pharmacovigilance Contact Person details in Patient Information Leaflets (PIL)

MAH should be mandated to include the details of their pharmacovigilance person within their organisation in the PIL accompanying medicines dispensed to patients to promote ease of reporting by the public. In other for this initiative to be effective, NMRC along with the policymakers at the MoHSS will have to develop regulations that will strengthen this position. In view of this, the Medicines and Related Substances Act 13 of 2003 and its Regulations has to be reviewed.

7.2.8 Mandatory inclusion of PIL in every product

Inclusion of PIL in medicines packs that patients self-administer will help patients attain knowledge of the medicines they are taking and what ADRs to expect. Hence, patients will have the ability to report any such ADRs to TIPC.

7.2.9 Adoption of Standard Operating Procedures (SOP) in private practice settings

TIPC in conjunction with private healthcare practitioners should develop SOPs that will be kept at facilities. Such SOP will assist healthcare workers in ADR management and reporting, and all employees within the practice should be trained on such. The private practice envisaged should include suppliers of pharmaceuticals and manufacturers.

7.2.10 Public awareness campaign

NMRC can carry out public awareness campaigns for example road-shows or through dedicated activities during cultural events, to highlight the need for pharmacovigilance.

Such an initiative will help improve public awareness regarding pharmacovigilance, ADRs and their reporting.

7.3 Conclusions

This research has explored the basal reasons for the under-reporting of ADRs and possible ways of improving pharmacovigilance among healthcare workers within the public healthcare setting in Namibia. It is pivotal in understanding the current state of pharmacovigilance in the country; other initiatives or studies can build on the findings of the studies included in the research. A reporting tool was developed seeking to improve the reporting pattern and quality of reports submitted to TIPC.

7.3.1 Follow-on studies

The Therapeutic Information and Pharmacovigilance Centre should look at strategic research areas focussing on the feasibility of patient reporting, and the impact of advocacy on pharmacovigilance after engagement with different stakeholders over time. Also, a prospective study on the impact of awareness creation among different groups of healthcare students at various institutions of learning and, including different cadres of healthcare workers working in different settings such as old age home, rural clinics and private settings.

Costs due to ADRs in both out-patients and in-patients settings are other areas of possible research. This can be pivotal in creating awareness and informing the government on the financial losses incurred through improper management of ADR and patients at large.

Comparative studies of different drug interventions can be carried out to optimise the use of each regimen, such as the introduction of new ARV regimens.

7.3.2 Educational interventions

Pharmacovigilance has an impact on the overall health of a population and the cost of healthcare services. In particular, strengthening the health system through incorporation of pharmacovigilance into the curricula of different healthcare cadres training schedules will add value to the academic learning and invariably assist in reducing the cost that might have been incurred due to ADRs. Thus, emphasis should be placed on inculcating good reporting culture by the students, not neglecting continued professional training of healthcare workers within the public and private healthcare settings.

7.3.3 Advocacy

Different stakeholders that contribute or are involved in healthcare provision and consumption (patients) need to be reached and made aware of the place of pharmacovigilance and the need for ADR reporting in patient management. Enlightening healthcare workers, policymakers and patients is an essential aspect of the promotion of pharmacovigilance; they need to be acquainted with ways of identifying whatever reaction occurs after the use of any clinical intervention such as medicines or unusual laboratory results and realise that such event requires reporting to the TIPC or any reporting centre within their region, will be paramount to optimising the pharmacovigilance system.

7.4 Contributions

This study has made significant contributions to the body of knowledge and research on pharmacovigilance and especially, ADR reporting among healthcare workers.

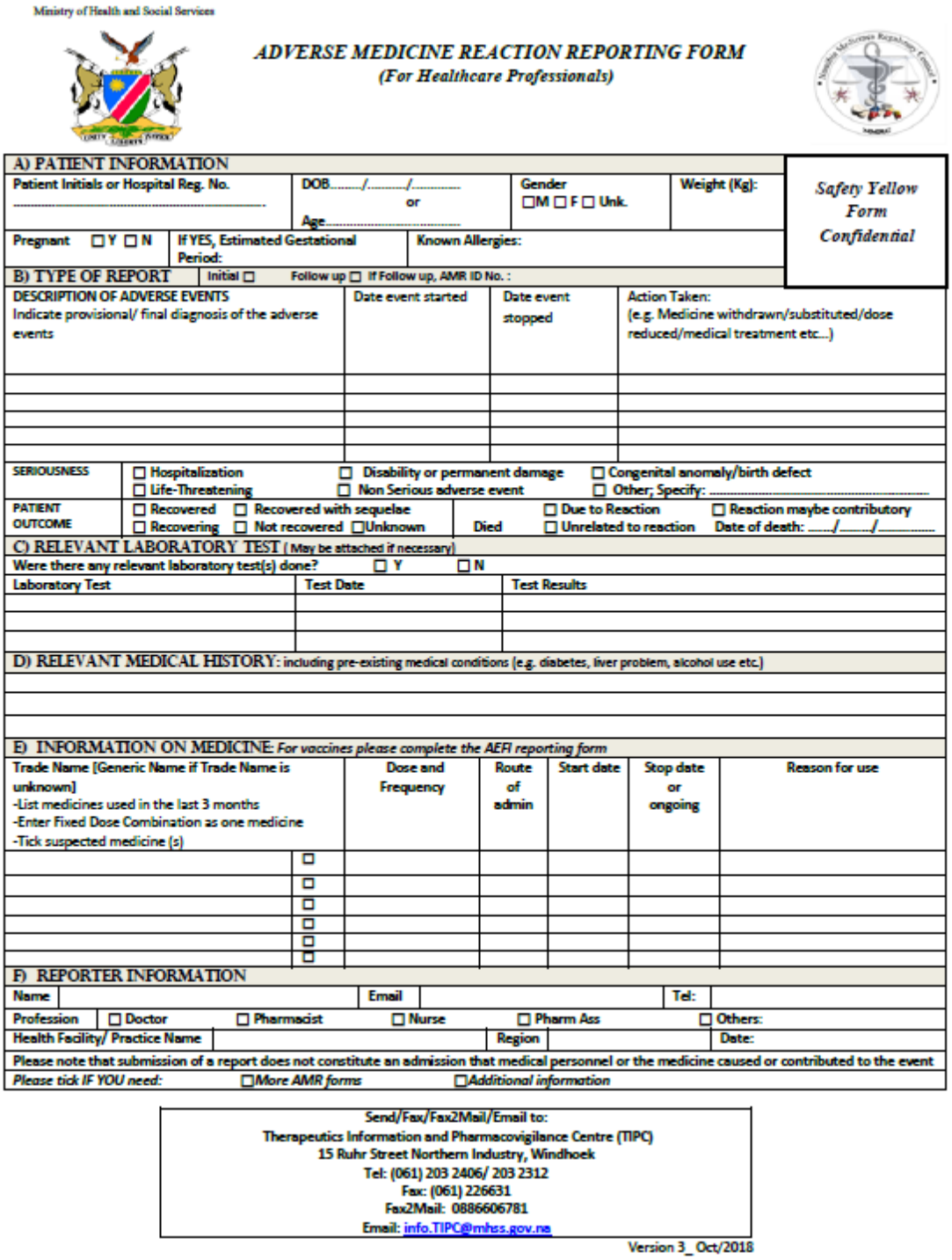
- **Determination basal Knowledge, Attitude and Practices (KAP)** of healthcare workers in Namibia concerning pharmacovigilance and ADR reporting.

- **Knowledge and research direction**, this study has described the current pharmacovigilance system and possible ways of optimising pharmacovigilance and ADR reporting systems.

- **Policy direction,** the need for the government and related policymakers to develop policies that will enforce pharmacovigilance and ADR reporting as one of the primary clinical responsibilities of healthcare workers. Also, incorporating patient ADR reporting and platforms for such reporting to be achieved.

APPENDICES

Appendix 1 – Individual Case Safety Report Form (ICSR)



Ministry of Health and Social Services

ADVERSE MEDICINE REACTION REPORTING FORM
(For Healthcare Professionals)

A) PATIENT INFORMATION

Patient Initials or Hospital Reg. No.	DOB...../...../..... or Age.....	Gender ☐M ☐F ☐Unk.	Weight (Kg):
Pregnant ☐Y ☐N	If YES, Estimated Gestational Period:	Known Allergies:	

Safety Yellow Form Confidential

B) TYPE OF REPORT Initial ☐ Follow up ☐ If Follow up, AMR ID No. :

DESCRIPTION OF ADVERSE EVENTS Indicate provisional/ final diagnosis of the adverse events	Date event started	Date event stopped	Action Taken: (e.g. Medicine withdrawn/substituted/dose reduced/medical treatment etc...)

SERIOUSNESS	☐ Hospitalization	☐ Disability or permanent damage	☐ Congenital anomaly/birth defect
	☐ Life-Threatening	☐ Non Serious adverse event	☐ Other; Specify: .....
PATIENT OUTCOME	☐ Recovered ☐ Recovered with sequelae	Died	☐ Due to Reaction ☐ Reaction maybe contributory
	☐ Recovering ☐ Not recovered ☐ Unknown		☐ Unrelated to reaction Date of death: ...../...../.....

C) RELEVANT LABORATORY TEST (May be attached if necessary)

Were there any relevant laboratory test(s) done? ☐Y ☐N

Laboratory Test	Test Date	Test Results

D) RELEVANT MEDICAL HISTORY: including pre-existing medical conditions (e.g. diabetes, liver problem, alcohol use etc.)

E) INFORMATION ON MEDICINE: *For vaccines please complete the AEFI reporting form*

Trade Name [Generic Name if Trade Name is unknown] -List medicines used in the last 3 months -Enter Fixed Dose Combination as one medicine -Tick suspected medicine (s)		Dose and Frequency	Route of admin	Start date	Stop date or ongoing	Reason for use
	☐					
	☐					
	☐					
	☐					
	☐					
	☐					

F) REPORTER INFORMATION

Name		Email		Tel:	
Profession	☐ Doctor ☐ Pharmacist ☐ Nurse ☐ Pharm Ass ☐ Others:				
Health Facility/ Practice Name		Region		Date:	

Please note that submission of a report does not constitute an admission that medical personnel or the medicine caused or contributed to the event

Please tick IF YOU need: ☐*More AMR forms* ☐*Additional information*

Send/Fax/Fax2Mail/Email to:
Therapeutics Information and Pharmacovigilance Centre (TIPC)
15 Ruhr Street Northern Industry, Windhoek
Tel: (061) 203 2406/ 203 2312
Fax: (061) 226631
Fax2Mail: 0886606781
Email: info.TIPC@mhss.gov.na

Version 3_ Oct/2018

Appendix 2: Face validity testing for Adverse Medicines Reactions eReporting Pilot – Issues identified by participants

Participant	Comments	General/specific issue	Action taken
1	Need to add DOB and age? Seems duplicative	Specific	None – retain TIPC form content

Participant	Comments	General/specific issue	Action taken
	Many of the fields are mandatory – what if you don't have all the information. Spelling will matter in some sections when you're downloading the results (i.e. medication name, laboratory results) Is there a process to help fix any problems? Maybe drop down boxes. Patient outcome – should only be able to choose 1? Died – should there be a N/A option? Profession, Region – dropdown box Date of report – is there a reason this wouldn't be the date that it was submitted? You don't need to ask it.	General General Specific Specific Specific Specific	None It will be looked into Dropbox Dropbox None None – retain TIPC form content
2	Age of pt: ?? months/weeks/years Weight: state "unknown" Type of report: Follow up#? Description of event • Under date stopped: if not stopped (event ongoing) Medication • If ongoing (leave blank) Medicine – if more than 6?? Profession: consider indicating professions Exclude field with"no answer given" in the summary Saving name – anonymity should be considered in the name of the report	Specific Specific Specific Specific Specific Specific Specific Specific Specific	None – retain TIPC form content None – retain TIPC form content Format changed. Follow up# line added. Event ongoing line added None None – retain TIPC form content Will be looked into Will be looked into
3	Weight – does not accept "unknown" Date event stopped? – what if not ended Labs reports – you can enter test date + result without entering test name What is sequel? Asked about death even tho' not said patient died Make phone number compulsory NB - "**Sequela**: A pathological condition resulting from a prior disease, injury, or attack. As for example, a **sequela** of polio. Verbatim from the Latin "**sequela**" (**meaning**sequel). Plural: **sequelae"**. https://www.medicinenet.com/script/main/art.asp?articlekey=23895	Specific Specific Specific General Specific Specific	Dropdown Ongoing added None Defined Dropdown and made not compulsory Made compulsory
4	Consider populating with the list of medicines (NEMLIST),	Specific	Will be looked into

Participant	Comments	General/specific issue	Action taken
	• To minimise errors by reporters Ongoing event should be incorporated	Specific	 Addressed
5	No comment		
6	No comments		
7	Age in patient – Make numeric Weight in kg – Make numeric Are there any more laboratory tests to report? – Ask first? Died (if patient died, what was the cause?) – Drop down	Specific Specific Specific Specific	Addressed Addressed Will be looked into Addressed

Appendix 3: Proposed/suggested ways by respondents to improve Adverse Drug Reactions reporting and Pharmacovigilance system in Namibia

Comments/Proposals	Frequency
2. Active participation in drug reaction surveillance	1
3. Adverse drug awareness or reporting should be discussed on a daily basis. People should be reminded at morning meetings to look out for adverse drug reactions as they go about their daily jobs. The adverse drug reporting form should remain in the yellow colour format and be printed in enough quantities like the NIP form and placed where it is readily visible for use.	1
4. Adverse Drug Reactions reporting should be remunerated or offered incentives.	1
5. Always reporting	1
6. An online system that is made available to health professionals would make it easier to report incidents	1
7. Appoint focal persons at each facility.	1
8. Awareness	1
9. Awareness sessions in health facilities	1
10. Awareness campaign through training on a large scale.	1
11. Awareness campaigns	1
12. Awareness or seminar concerning these	1
13. Awareness through CME meetings and government enactment as requirement for all hospitals and clinics including private, to have a pharmacovigilance policy and follow it.	1
14. Better advertise the system to medical doctors	1
15. Break down this system of supervisor or medical officer to be the one responsible for reporting. Otherwise, no one will want to report on their behalf on their absence.	1
16. By periodic surveys	1
17. by providing feedback to the reporting facilities or regions to ascertain that something is being done with the submitted reports	1
18. Cellphone hotline/SMS for ADR cases	1
19. Communities should be educated on adverse drug reactions and pharmacovigilance systems and feel free to report such incidence	1
20. Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivate all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects (it is a responsibility for Pharmacists to educate or motivate other health care providers)	1
21. Create awareness about pharmacovigilance and provide relevant information in regards to the centers where adverse reactions can be reported to and the necessary steps that one will need to follow to report adverse drug reactions.	1
22. Creating more awareness amongst junior health professionals of the importance of reporting, where and how to report.	1

Comments/Proposals	Frequency
23. Develop a model to report ADR and place these models in all medical consultations	1
24. Digitalization of the ADR reporting and pharmacy vigilance system	1
25. District-level pharmacovigilance training	1
26. Each hospital must have a specific staff responsible for giving awareness assessing,detecting and receiving and reporting to TIPC.	1
27. Educate all pharmacists and other healthcare workers on the importance of drug safety and post-marketing surveillance	1
28. Electronic/online options e.g. TIPC mobile application	1
29. Electronically reporting, like database	1
30. Encourage patient/user of medicine to report directly all the adverse reactions in writing to the pharmacy/clinic near him/her	1
31. Facilitated/ active reporting	1
32. Feedbacks and should come back to the person or the organisation who report the ADR report	1
33. For health care workers to go for training	1
34. Form should be available in the different departments in the hospital in order to record immediately	1
35. Frequent workshops on ADR at hospital and health facility levels.	1
36. Functional	1
37. Get a focal person to deal with ADR reporting	1
38. Give detailed training on pharmacovigilance to all staff members	1
39. Give feedback to members	1
40. Give in-services training about ADR to health workers e.g. to nurses	1
41. Have focal people at each health centre/hospital	1
42. Health care providers should be encouraged and enlighten to report adverse drug reactions	1
43. Health practitioners should undergo proper training on drug reaction reporting	1
44. Health workers and health care providers should be regularly trained and appraised on the importance of Adverse Drug Reactions reporting	1
45. Health workers need to be trained on how to act on ADRs	1
46. Hospital Therapeutic Committees need to be functional and need strengthening	1
47. I have no idea of this subject, although, I have a small understanding about some of the questions.	1
48. I need training for the objectives of this centre and better management of reports and reporting systems	1
49. I wish most medicines that are distributed within the health system go through the medicine check system and are all licensed.	1
50. In-service training on what exactly should be reported	1
51. Increase awareness on ADR reporting and training for health care workers on ADR reporting	1
52. increase supply of ADRS forms at each facility and maybe let's have an electronic version of it.	1
53. Increased sensitization of the private sector and reporting by health professionals other than doctors and pharmacists	1

Comments/Proposals	Frequency
54. Integrate the module in the current dispensing tool on the patient profile	1
55. introduce a pharmacist or health worker in each every clinic who will be responsible for reporting the reactions	1
56. Let the new staff members in hospitals and clinics to be train or in-training soo that they understand when to report and to understand the positive outcome on reporting.	1
57. MORE EDUCATION OF HEALTH WORKERS	1
58. More interactions with healthcare workers, TIPC staff be part of hospital and ward to visits to familiarize first hand with adv. Events and encourage healthcare to report	1
59. More training on pharmacovigilance at the hospitals regularly	1
60. no comment	1
61. None	2
62. None. Just to strengthen the one we have on the ground	1
63. Not aware of the correct procedures of reporting forms. Provide training to dentists.	1
64. Observation card system to help remind people	1
65. pharmacovigilance training is needed.	1
66. Phone call	1
67. Promote studies related to pharmacovigilance to hospitalised patients.	1
68. Provide incentives as well as convert the reporting process into an electronic online reporting system so the data can be utilized more efficiently.	1
69. Provide training on pharmacovigilance	1
70. Provide training organised for all staff members	1
71. Providing incentives and more training will help to improve reporting of adverse drug reaction	1
72. Public must be informed of ADR reporting	1
73. Raising awareness	1
74. Recognizing and Incentifying reporters - Provision of feedback on reports and regular feedback to stakeholders on the TIPCs ADR related activities and country status - provision of trainings on regular basis - pre and post-training field visits to health facilities to maximize impacts of training and to motivate reporting by professionals - raising public/patients awareness on ADR identification and reporting using various platforms including TV, MOHSS website, social media platforms, etc. (I wonder if there exist any report from patients so far).	1
75. Regular feedback and awarding the most reporting facilities to motivate health workers.	1
76. Reporting adverse events should be part of routine work. ADR forms should be part of each client record to remind HCWs of any case if one might occur	1
77. Reporting center should be in all the hospital	1
78. Reporting via social media or SMS	1
79. Reviewing the reporting form to make it more straight forward and easy	1
80. Scheduled and frequent feedback by TIPC to health care workers/facilities	1
81. sensitization to the communities	1
82. simpler/straight forward reporting form	1

Comments/Proposals	Frequency
83. Sms line to report to.	1
84. Stop the drug consult your doctor for a replacement.	1
85. The ADR form should be simplified, available in all clinics, training of ADR to health care providers on how to fill it and report, there should be overall feedback from the TIPC, either monthly report or quarterly, this should be shared back to prescribers, Moreover, The report can be in the electronic form or an APP which will be available in the phones or gadgets	1
86. The HCWs should be trained on it & how to properly fill in the forms	1
87. The level of awareness of ADRs is pretty low. HCW needs to be trained and reminded of the negative effect of not reporting. Sensitisation is key to the improvement of ADR reporting.	1
88. The must inform health worker of the existence	1
89. There must be a channeled communication between patient, the healthcare provider and the pharmaceutical. To ensure that all the adverse reactions are detected and reported in a timely manner.	1
90. TIPC should need to be established at regional level (or hospital level). Training concerning ADR needs to be emphasised.	1
91. To provide more emergency kits in each dispensing room, so that if a person reacts you don't have to run to emergency room.	1
92. To train all health professionals, patients and caretakers on how to report and the benefits of it.	1
93. Train all health workers to know the side effects of drugs	1
94. Train HCWs on reporting system and importance of reporting	1
95. Training	3
96. Training for staff	1
97. Training health personnel	1
98. Training needed on how to identify and report	1
99. Training of all health workers on this matter.	1
100. Training of health care workers, teaching them about the name list too	1
101. Training of health workers	1
102. Training of staff needed. Channel of communication after completing the ADR form, that is, where to hand in the form	1
103. Training on all prescribers regarding ADR and reporting and completion of forms. Feedback from TIPC would also be beneficial toward all HCW involved in certain cases of ADR.	1
104. Training on and reporting to all health care workers especially nurses because they are the first people patients reports to. Provision of all necessary forms for reporting drug adverse reactions.	1
105. Training should be provided for nurses. We are not sure who needs to fill the form	1
106. Training for all healthcare providers. Offer prizes to those who report more Adverse Drug	1
107. Use of online on website for ease of reporting	1
108. We need training on ADR reporting since most of the time the health workers are not reporting due to time management and lack of knowledge.	1
109. Weekly therapeutic committee meeting and feedback	1

Appendix 4: Transcript of key informant interviews

EFFECTIVE INTEGRATION OF PHARMACOVIGILANCE SYSTEMS AT PUBLIC HEALTH FACILITIES IN RESOURCE LIMITED SETTINGS: A QUALITATIVE STUDY

Key Informant interviews

Breakdown of respondents

- 2 Chief Pharmacists
- 1 Medical Doctor
- 1 TIPC staff (Pharmacist)
- 3 Lecturers (Pharmacists)
- 1 Chemonics staff (Pharmacist)

Question – *In your view, what are the ways or how can the pharmacovigilance and adverse drugs reactions reporting system be improved in Namibia?*

Transcription

Participant 1: In regards to pharmacovigilance improvement or motivation of pharmacovigilance my view is that pharmacovigilance needs to be taken up as a national activity. The government of Namibia needs to take full responsibility and by doing so when they do so, they would now require that every healthcare worker employed is required to monitor the safety of patients and therefore ahnn, be, make it an obligation that if any adverse event occurred it is recorded and then are send to the TIPC. Okay so

what this means is that at the moment ahnn, TIPC is operating, it is in charge of pharmacovigilance, and it struggles to promote it, whenever there is a promotion, and it happens say through a training or meeting in a particular facility there is a step up of pharmacovigilance step up of more reports, soon such reports dwindle, the numbers dwindle. But that needs to change, and er, in my view for that to change, the government needs to ahhh, take some critical steps. For example, everyone being employed in government they need to be required to report adverse drug reactions, it needs to be part of the appraisal () of the healthcare worker. They need to know how many adverse drug reactions a doctor was able to detect, and report. Ahhh that should apply to the doctor, should apply to the pharmacist and should also apply at the nurses. But as long as the system is working in tandem and in proper coordination, double reporting will be blocked. Okay, when it comes to the private sector, the private sector also needs to take part in this and that could work through insurance provider. Insurance providers needs to make it a requirement, for the healthcare worker to detect and report these adverse drug reactions and then through insurance service mechanisms they can see how ahh remittances to this kind of activities how it's made. That way pharmacovigilance will improve at a national level. It needs to be a requirement ahh for people to carry out. It shouldn't be looked at as one of those ectopic activities which if apart from says they are very busy they won't be able to report, that now push err err err ensure that the patient to the danger because… The reporting and detecting of this adverse reactions which would be avoided, ammm, this simply a person deciding to or not to report and therefore not seeing it as an obligation. So people need to know that pharmacovigilance is part of health service provision. Yea that is my view on how to improve pharmacovigilance in Namibia. Thank you.

Participant 2: Perfect. From what I know of pharmacovigilance information systems in the US, we have (silence) different ways that information and amm, come together to be able to find (amm) whether there are problems with medicines or side effects. Some of the information come directly from practitioners sending in reports to ammm the, I can't pick up the name of the government agency but I can look it up for you later, amm to send it to them. I think it's through the FDA like ehn they they keep all these information. And they fill one form that you have to fill out. As a pharmacist in the US, I have never filled it out. So emm, I think one of the challenges is uhn, like you said earlier, which thing to report, something ……

Participant 3: Eem, with the ADR reporting system, the main challenge that we have is under reporting, this is basically a common challenge for many pharmacovigilance centers, particularly in the developing countries. Aam, so, definitely there's a need for improved ehn, ADR reporting…. Ahm…..well, I believe there's so many ways to come around it. Ahm, but I will propose ahm, a few

Ahm, one of the areas specially identify that ahm, factors that ahm prevent health workers from reporting.by having such an assessment then help in addressing some of those challenges. So that is an area that needs ehm, to be addressed. Ehm, secondly, ehm, (silence) there is a need for strengthening spontaneous reporting, and although, currently, we have ahm, the paper based reporting system, ahm, it still needs strengthening, however, ahm,I think expanding the system or the mode of reporting will also help, this includes introducing electronic ahm, reporting system. This does not mean

that we have to eliminate the paper based reporting system. Ahm, they can actually work in parallel until we really find a middle ground. So, for now we can have them both parallel, running. Another area that we really need to do a lot of exploration is ahm, patient reporting. We currently don't have ahm, patient reporting system in Namibia; so that will also now ahm, increase the the number of reports that are received. Also, from the patients' perspectives, because not all patients actually report adverse effects to their health workers, although, currently we are relying on health workers to report, so they may, we may need to actually open a platform for health workers to report directly to us at the national pharmacovigilance center. Then, ahm, all that I've mentioned is basically spontaneous reporting, however, active surveillance is also important here is an area that may need strengthening in terms of ahm, maybe sentinel site or active surveillance of selected drugs, that may need to be strengthening it can actually…. that are received from certain areas as well. Yea, I think that answers your first question. Yea.

Interviewer interjection – introducing an electronic system will it be of value to Namibia?

P3 – Definitely. I am, I mean the paper based system is not really ehm, we are mainly using it because of a lack of electronic systems in a .lot of areas, pharmaceutical areas for example in Namibia. So ehm, but there are certain sectors which already have access to electronic systems say for example the private market. They are more, well advanced this might be much more appropriate for them. But not only the private sector, there are those health workers who still prefer electronic reporting system it might be much more convenient, so sort of like eliminate the the logistics of completing the form, fax it, or scan it and email it. Yea, so ehm it might definitely be I believe it will actually be of use

to Namibia. And also in terms of, if we have to say introducing patient reporting system, ehm, it may be paper based but electronic one will also help, yea, may be quick, convenient, store eliminate the issue of bringing reporting form to the pharmacy or take it to the hospital, faxing it or emailing it. Basically, it's just on the go. [Interviewer interjection]. Yea, ahm, perhaps, ahm, in terms of weaknesses in that? [Interviewer interjection – electronic system]. Ok, the weakness could be ahm, not every has a device may actually use ahm, that is friendly to apps, minor things like if it's web based may require internet as well. So this could be a limitation but then the strength is that it's quicker, convenient, yea, but then going back to the basics ahm, it has to be user friendly as well, yea for the patients. If it's not user friendly so that can be a weakness. Ahm, yea, introducing to the patients will generally [increase the] number of reportings, provided that it is well implemented and end users are keen to use it. [Interviewer interjection]. It depends on the purpose, it is triggered by something, triggered by a concern, ahm, of a particular medicine which we just want to actually have; say incidence rate or it could be a new drug in the market which we don't have sufficient information, ahm, safety profile, the the new TB regimens definitely there is a call for active surveillance and it can go on for a period of time as well, yea, it can be shorter or longer; but as long as it helps, it may also help to, ahm, contribute to the culture of note taking as well, something that has been started already.

Interviewer: That is good. Thanks very much.

Participant 3: We're done!

Participant 4: Ok. My name Emmanuel Ugburo, Chief Pharmacist, Intermediate Hospital Katutura. From my experience, in Katutura, in the last 4, 5 years, uhm, I have noted that eh, adverse drug reactions reporting is ehn, is even declining.at a time we were receiving reports especially when we have support on the, from the HIV treatment and management there was a big push for adverse drug reporting, so then in the past 2008, 2010 there were a lot of reports. I can remember very well ahm, I think partially or through reports that ehn they they, we were able to get data on side effects of AZT which I believe prompted the change in the guideline. You know the move from ehn, AZT to TDF, you know, even though it was a global change we had data to support you know ahn the adverse effects experienced by patients on AZT. So then, you know people were motivated to report but as time goes on we were experiencing significant decline. From my experience, I think ahn, there is also lack of awareness, because I think the approach has been training focal persons and the focal persons will now go back, and em, train other people or create awareness. I think that approach has not really worked. Perhaps people we nominate to go for those training are not eh, passionate about er ADR reporting. Like in our setting here, we've trained two of our staff members have been trained and I think a doctor too was trained but that doctor is no longer in the system. And those are the issues, you know you train people after training them either they resign or they are no longer in the system, then because the whole set up is based on individuals running around trying to get reports; once those people are no longer in the system or they are failing, then the whole system you know is like collapsing. So that's why I believe, that we can relook on that approach of you know, we can look at other, other em em, ways in which awareness can be created. Perhaps also, maybe we can ask people why are they not reporting, is it that the form is scary? You

know when people, you know you want a pharmacist assistant to report, what you expect from that report, is it too detailed? You may want to look into that. You know making the form a bit er er, making the form, simplifying aspects in the form that makes it user friendly, let me put it that way. And erh, like the details one can get back to the person making the report but that initial report, can we make it a bit simple and user friendly? Perhaps that will motivate people to report. Like in our setting, really doctors are busy with their clinical work and they've not seen adverse medicine reaction reporting as part of their clinical work. So I think that's another area we need to find a way to integrate adverse medicine reactions reporting as part of a clinical work of the clinician. So when a clinician is seeing a patient or a patient comes to a clinician and complain and say something like when I started using this particular medicine A, I started having this am am side effect, and now because of this side effect I don't think I can continue with this medicine. Immediately, the clinician picks it up and its part of his clinical work to report, but the way it is now, it's like somebody coming to impose an activity on them and it's like no, I have to see more patients, I have to do this. I have to go to the lab I have to do that. Ehn, that is like, that is not part of their job. So I think that is one of the reasons why we are not getting the reports. Even in the pharmacy here, in the pharmacy where I work, I've intervened in some cases, I just stand and see interaction between my colleagues, the pharmacist and erh, and the patients, like a case that is erh, noteworthy to note. Patient is telling the pharmacist that I, I, the doctor changed my medicine and the pharmacist is asking oh, why? Because I was coughing too much, now on this new medication. Pharmacist just go ahead, it doesn't trigger anything in that pharmacist that no, this needs to be reported because there are a lot of patients, filling that form will take time. He doesn't want to waste time, he wants to

finish the patients. So these are some of the issues that comes up, that I feel makes erh, healthcare workers not to report, maybe the workload and they see the filling of those forms as an extra work. And perhaps also, they have not, they have not, we, let me not say they, we have not seen the impact of those reports. When somebody begins to see the impact of his work, then he's encouraged to do more. You know, either you get feedback, timely feedback to say ok based on the reports you made, these are the outcomes. That also is important. You get timely feedback to those that made those reports. It's also important.

Interviewer: So apart from all these, is there any other way we can improve the reporting system? Is there any other way to motivate people to report?

Participant 4: Like I said initially, let's move away from this, training one person, training two people, we can create more, do more enlightenment programs in the hospital, you know, doing things like adverse medicine reactions week, something like that. You know, devote like in a year, like twice in a year or so, you devote erh, you devote you say a week, adverse medicines reactions week. Just to create awareness, not only in the hospital even in the community. Let patients know, they have a right, not a right, a responsibility, you know to report. That even if the doctor is not reporting it, they too they will say I want to report what happened to me. I think it will be…also, I think as part of the enlightenment let people know that it's not going to affect their work, especially, when you shouldn't have given a particular medicine and you gave that medicine and there's an adverse medicine reaction, then the person is, ok I might be sanctioned, could it be anonymous? Could there be that guarantee that we as pharmacovigilance erh, ehm I don't know how to put it now, department we are not

sanctioning you because the patient reacted ok. Or now the HOD got to know then there is a, you know. Those are the things that affect adverse medicines reporting, people feel ok, it might affect their performance rating, yea.

Interviewer: Good

Participant 4: Then another thing, like the world is going digital now, I think there's a place for that also. We have erh, guidelines on our phone, people check references on the phone. So, if it's possible also, but firstly, the reporting, the detail that you need in that report should not be too cumbersome you know. If it's simple then and it's in a digital form then it's easy especially when it's not costing the person any money I think it will improve reporting rate yea.

Interviewer: So any other comment?

Participant 4: No comment. I'm fine.

Interviewer: Do you believe the strategies are going to work?

Participant 4: which strategy?

Interviewer: All of them.

Participant 4: It's worth trying, it's worth trying. Giving it a trial. You can pilot it and see how it goes then you can pilot it.

Interviewer: Thanks very much sir.

Interviewer: So Good morning Mr. Mazibuko.

Participant 5: Good morning.

Interviewer: Thank you for granting me the audience to do this interview. The interview will basically be looking at how we can improve or strengthen the adverse drugs reactions reporting system in Namibia. We know people, I mean the health worker they don't know, and anyway, as in we don't get so much reports at the TIPC. So which probably we don't know whether they don't know how to report or when to report or we don't really know what is there; but how can we improve, how can we make them report. So that is the basic we want to hear from you, your ideas on how to improve the system in Namibia.

Participant 5: Wow, that's a very difficult one, em but still, even though it's a difficult question it can be answered. Uhm, why I say it's difficult is that in Namibia, compared to other countries, we have a sort of a, a fully functional you know, fully functional pharmacovigilance unit (P5 cleared his throat) uhm, that was established by the government, uhm, more than 9 years ago. Uhm, and you have the focal people that can drive activities of erh the pharmacovigilance centre. Of course, em Namibia being a vast country, em having one central point for coordinating all the pharmacovigilance activities which include ADR reporting, product quality, you know, reporting, also giving medicine information may be a very demanding task. So, I'll say ahm, you know, things that can be put in place to increase the reporting or to have you know, people in the facilities have the appetite to document and report on pharmacovigilance, you know they are several, there are several of them and ehm, the first I think is having the centre, and we have a centre. Ahm, secondly, we have the coordinators, that's a plus. Ahm, I think thirdly we need to do is the, we have a coordinated, you know, ahm, awareness raising sort of ahm, you know, you know, intervention amongst our healthcare workers

that there is a system place all they need to do is to just, when they see an adverse reaction in the facility, is to document and you know, send it through this established communication channel. So that is, that can take the form of ehn, you know, trainings, trainings that can be targeted at facilities; trainings that can be targeted at erh, you know, specific people, champions, who we called trainer of trainers, you know, who can go to the facilities and advocate for pharmacovigilance activities. Ahm, they may, ahm, you know, sort of you hold people responsible and those people that are responsible, can actually preach pharmacovigilance in the facilities. And they should be equipped, you don't just train and the people just go to the facilities without anything, they should have the tools, you know for pharmacovigilance. They should have the forms, they should have basic ideas on how, you know, maybe to do a mini analysis of what is happening before sending the report to TIPC, so that people, even in the facilities first hand, ahm, ahm, feedback from their coordinators of what collected from their facilities, so I will say it's not only you know, the relay of the reports to the central centre for it to be put in a database, is analysed from there. People within the facility should be able, also, you know, to do some simple ehm analysis and present. And that should, that should be well structured, you know and standard, right across the country, because people, they say we report [laughter] but we rarely get, we rarely get feedback and that's a fact; because we give them feedback maybe after a quarter, so, the feedback that we give is purely descriptive uhm, how many reports were received; how many facilities reported; by which cadre. Ehm, we rarely go into details, you know, of, you know, so what happened, you know, when they reported, was it something that was resolved internally, something that was, that led to a patient being disabled, patient maybe being hospitalised and so forth. That is one [cleared his throat], and secondly, uhm, uhm, I think it comes back to

feedback still, uhm, intensified central level feedback, you know, to the facilities when they report, you know, we have the bulletin like what we used to have but the bulletin content should contain more of the scientific analysis, you know ahm, ahm, than the descriptive, you know ehm ehm feedback that is normally given. And I think, I think that feedback only comes in quarterly reporting, I don't know if it's included in the medicines newswatch. We may need to find out, but that feedback is very, very important, yea. Uhm, yea, uhm, the other things erh, we talked about having the forms, with the focal people, but the forms also need to be, you know, in every corner where healthcare workers interface with the patient. So it means we have to print as much as possible, forms, have them at the casualty, have them at the you know, the wards, have them, you know, at the pharmacy so that when someone experiences an adverse event they just know where to go pick up the form, they should be clearly labelled ADR reporting form or whatever form, for pharmacovigilance activities. They pick up the form and document and report.

Interviewer: [cleared his throat] the form, do you feel it's adequate? Or the information required is too much?

Participant 5: Well, for spontaneous reporting I think it's a standard form, it's comparable with other forms, countrywide, I mean worldwide. I mean, in the region also, from South Africa, if you look at forms from Swaziland, Ghana, Kenya, and so forth and so forth. They are pretty much standard, they cover the, the, the same, the same thematic areas, the same topics – you need to know about the patient, you need know about the history, the medication that they are taking ahm, you know, the adverse event that is experienced, that drug reaction that is experienced, outcomes and also, the person

that is documenting the ADR. So it's pretty standard information. I will say it's adequate [laughter]. I will say it's adequate.

Interviewer: Alright. So, you mentioned awareness, feedbacks, the forms, are there any other initiative?

Participant 5: Ahm, well I cannot think of any other specific area. We can always expand. Like awareness, goes beyond trainings, eh, it goes beyond just having leaflets and banners, you know, we have to have probably, a midday event as well, where we talk about pharmacovigilance should be a theme for pharmacy week, times where we advocate for pharmacists to, as champions of pharmacovigilance, to encourage each other, healthcare workers to report. But increasingly we can go into the media, TV, radio. We have people talk about the subject, why is it important, why we should we document and send the reports. Ahm, the other thing that we could do, back to the facility level, is to sort of, I know, spontaneous reporting, you report as when you receive a drugs reaction. It's not an active type of pharmacovigilance. If we could set targets, you know, to say, from facilities we need so many reports; from X facility you give us so many reports we'll be happy [laughed], beyond, above and beyond we'll accept. I don't know if that is acceptable, I mean it's one of, it's one of the ways we can look into it.

***I*nterviewer**: Yea, it is good. [Clearing throat]. Ahm, since we are not only dealing with government facilities, in private?

Participant 5: Of course. Chorused [and the patients themselves].

In my submission, when I talk about facilities, I was talking about private themselves. Yea, ahm, we have to also, involve the private sector in this. And ahm, I think the centre is open to, to all facilities. Medicine information, it can be requested by anyone public or the private sector. I have seen in some private sector, uhm, forums, they request the adverse drug reactions forms so which means, there are some health workers who are actually doing, reporting from the private sector. Yea, it increases our base, for, for, for the reports to be filled at facility level and come to national level.

Interviewer: And the patients, will they be also looking for the yellow forms?

Participant 5: Reporting, patient reporting is another level, advanced level or second level of reporting which complements the spontaneous reports from healthcare workers. Ahm, I believe we have the forms but we haven't really implemented it in Namibia.

Interviewer: You mean forms for patients.

Participant 5: For patients. I think they were designed, I stand to be corrected. But definitely it will complement the healthcare worker reporting. Ahm, the thing, the only, it's an advantage, yes because the patient will know what they will experience and they will describe it in a certain way that they understand it. Ahm, ahm, but ahm, sometimes ahn, when we receive such information, it can be very hard to analyse because you know some patients really may not project, or indicate the way, that you know, expected to be acceptable or report that can be analysed. So it needs to have a well-structured system such as the healthcare worker spontaneous reporting.

Interviewer: That is good. So thank you very much.

Participant 5: Alright. I am glad I could be of assistance.

Interviewer: Let me just mention something. For the patients, there are some ideas, maybe mobile phones may be of assistance instead of them reporting papers.

Participant 5: Yes, ahm, yes [laughter], like I said, whether it's mobile phone, whether it's paper, the patients need to understand, they need to be educated on on the report they will produce at the end of the day. Uhm, they can, I mean, I wouldn't know exactly what role the phone will play, whether it's just picking up the phone and call the healthcare worker or calling the TIPC to say I am experiencing this and this and this, ahm, or it is something that is on their phone easily punch, say ok, side effect, medicine, tatatata or a form that they can easily just whatsapp or send by email I am not so sure. But at the end of the day they must have some basic knowledge of what they are doing, so that it can be meaningful. But I think it is a good idea, even for spontaneous reporting, it is high time we put this forms in a pdf kind of format that can be filled and then emailed electronically.

[Laughther]

Interviewer: Thank you very much. This brings us to the end of the first part of my meeting with you.

Participant 6: Recording ADR reporting! Ok. Should I say my name first, it doesn't matter. We said that I will get the approval from the ministry ok. So we can use this recording after the approval. So my point here is to, in general, to create awareness for

the doctors, nurses, pharmacists about the ADR, right, and about the importance of reporting, these adverse drug reactions, because by the end you will use it as a pooled data to add to the erh, what we call post marketing, right. So to create this awareness, maybe, ehn, just to as we are saying CPD points, you can make a session with CPD points to collect nurses, doctors, pharmacists, targeting only ADR. Some previous examples that was reported for example and what is the importance, what is the outcome after reporting these, because people they will not look only on the, they will think that ok, if I report, what is going to happen, uhn, and then they should feel something, something tangible, is not only just a way of reporting. You can see for example, when we get, we report other forms of, now it's not the topic, but other forms of, of erh, of pharmacovigilance …..or whatever, then we see a medicine recall, now there is tangible issues after reporting. For me, it's improving the awareness about ADR and the reporting system and give feedback, what happened after you have reported on these ADR for the doctors and for the nurses. This is a way that people feel if we need something that we should do it and hear what the result. Erh, maybe also you can do some flyers or whatever, to keep them in the wards, or to keep them with the doctor, message with the number just to see this is the importance, this is the way to record, this is the number that you should fax for. Other issues now, as we are saying now I said fax, not everybody has a fax, right, o yea, email also, to be dedicated for adverse drug reaction, right. An easy way of sending the data and retrieving these data and most important as I said in the beginning that erh, repeatedly to give feedback what happened after this reporting, how many was reported; even this feedback if you say for example, this year how many of, was reported, ADR from that medication, was there any report on the same matter from different areas of the country, from different doctors. So,

because this will, for you will, will, will do to stress to the doctor, in the next seminar for example, when you sit again to say, the ADR was reported like this, because we said the first one, you have to give a training later, say after a year there is another one. We don't like, I don't like, we don't just repeating training, we can say this is what happened during the last year; I have got 100 ADR and just for the doctors to know, when you are reporting this from your facility and another one reported from another facility. The importance of ADR, we collate data, we keep it and accordingly we publish the result. They don't feel like you are separate, why I should report because one will say why I should report? You will, they think that because it's a sporadic case, no I will not report. Yes for you it's a sporadic case, so you saw it you don't know about others in the country, maybe they are reporting. So just to encourage each other, to show them you are not alone who is reporting, right. So, this is a big issue in my mind.

Interviewer: So how do you encourage them? Is it just by giving the feedback or are there other ways?

Participant 6: Yea, no I said no. It's part of erh, I don't that, it's part of daily activities of doctors and part of patient care. I consider it part of erh, erh, patients' rights as well, not a patient's right, it's a patients' right as you can say, because when doctor reports and gets feedbacks, then he can inform his patient, this is her, this is what happened with you, I am reporting it and this how it came and something that's concerning the medication or only one sporadic case happened or whatever..

So I see that, the issue erh, the issue is there already. I cannot think about other, for the doctor, except, as I was saying, only the CPD points, seminar, whatever but, I really

don't, I'm not familiar with topic like your erh, to say what are we going to discuss, in, in seminar, talking about ADR only. You want maybe to present, what is the meaning of ADR, then to present some ADR from common medicines.

Interviewer: For CPD, it can be general, maybe pharmacovigilance but with particular mention of ADR.

Participant 6: Yea, it can be. I think also, as I'm saying. This will be, may be the first. But the second meeting you can start mentioning what ADR was reported during the year.

Interviewer: This can be something that is ongoing, not just once off.

Participant 6: Yea, yes. If the doctor knows it's something ongoing, it has, like something like well established, you know, like therapeutic committee meetings for example. ADR meeting in a year, even, to say this is what we have received, this is erh.

Interviewer: ADR meeting like during the pharmacy week.

Participant 6: Ahn, ahn, no it should be not just, even pharmacovigilance centre can organise that. And as we are saying, annual meeting, annual seminar something like those. Sure the CPD points can attract some of the doctors, nurses……..also giving the feedback as I am saying, is considered to be a reward. When the doctor will hear their name, that we got this from dr. who who at central hospital, or the next time, they know that it's valuable towards, when I sent it somebody looked at it and document it and send it on the next meeting. You know like, we all like to hear our names in the meetings. [Laughter]. So this is a kind of reward as well. Yea.

Interviewer: So is there any other way we can improve, make people report, any other way?

Participant 6: Not in my mind now, maybe you can open for me discussion.

Interviewer: You know, patients they are also supposed to be reporting, it's not only pharmacists.

Participant 6: you are right.

Interviewer: Every worker

Participant 6: You are right. So when I am thinking of patient reporting, do we have any way that patient can go, in contact with NMRC and if it's going directly, do you feel "let me take it myself". Do I feel patient can report and understand this is ADR? Ahn, ahn, if I am thinking about patients, I don't think. It has to go to a doctor. Maybe, ok, maybe we encourage the patients to report ADR but he will not know. He goes to the doctor, patient who got the medication, then, he got ADR, right. And then, he will go to the doctor, he will report it. I think patients, anyway any patient who got adverse drug reaction he will go back to the doctor, you understand, will report. Maybe a way of encouraging the patients, they are encouraged already because ADR affects them.

Interviewer: Just mild

Participant 6: Maybe mild ADR,

Interviewer: Patient may not see any need

Participant 6: Yea, the issue is ….if now it's erh, ADR mild, and we need to encourage the patient, looking at the patient as our focus right. So, we will say you, what is, how much is that we should deliver? We should, to make them, to encourage them to report ADR, without being annoying to the system, because sometimes if you say even if it's the same mild issue, you find out the patient they are coming to you they drink alcohol, I got headache from this medication. So you will get a lot of both reports

If we are talking to patients as our target, the message, I don't know what is the message to say for them to report to the doctor proper ADR.

Actually, they will not understand where it is coming from, they will not know the ADRs from the side effects, right. So, yea

Interviewer: That is very good. Thank you very much.

Participant 6: You are welcome.

Interviewer: That is the end of the interview.

Participant 7: Thanks for the opportunity. You want to know what is my thoughts on how to improve the pharmacovigilance system in Namibia. So, you need to tell me, what are the problems you have identified. I don't know, I haven't been in the system for

I:

Paryicipant 7: Erh, obviously we need to do advocacy, but which method of advocacy is going to work, I don't know. But just making sure all people, all healthcare workers

know that adverse drug reactions should be reported and how to report them. When we opened the TIPC, then there was a lot of advocacy efforts going on within the Ministry of Health, I don't know how much was done in the private sector. That was also now more than 10 years ago. Ahm, in the process of pharmacovigilance, what was the importance, why is it done, why Namibia needs to be involved and why every individual health worker to be involved; that needs to be put out there. I mean, and now you have at least one more step, one more asset in the bag of how to address it because we are training pharmacists and doctors in Namibia, so it should be built into the pre-service curriculum but that doesn't help for those who are already out there. So I'm not sure what the best message will be but you need to get the message across to all health workers. As far as I know, there are challenges in getting the private sector on board, they see considerable number of patients, and may also see patients that are on medicines that we don't use in the public sector. Those medicines are, many of them newer medicines, where less information is known about their adverse effects, so, I think that is ah, getting the private sector on board is key, because there could actually be a lot more adverse effects going on in that smaller population in the private sector unlike as the public because of the newer medicines being used in that sector.

[Silence] Ahm, I don't know it, I suppose the other issue is maybe on the legal side. Ahmm, because I believe companies have got legal obligation to report [murmurs – PSUR]. You could also use the companies to push the issue that health workers must report. Because if you are doing advocacy, you can't just follow one route. The more different routes that you follow, the more likely you are to have an effect, maybe you

can look at the companies that represent them in this country what they are doing about ensuring adverse effects are reported.

Interviewer: Yes. Good morning sir.

Participant 8: Good morning.

Interviewer: So, I'm here to talk about pharmacovigilance in Namibia and basically the adverse drug reactions reporting system. You know, what we have realised is that the, most of them they don't report, so we are not getting enough reports so to say. [Phone rang] it's ok.

Participant 8: Ok, to start with, adverse drug reactions reporting is a voluntary reporting system.

Interviewer: Meaning it is not compulsory.

Participant 8: It is not mandatory for someone to report but they have professional obligation to share that information with the TIPC or any regulatory authority. So that is one thing. But ehm, most of the time, the reason why people are not reporting is they don't even consider adverse reaction, in the first place. Meaning [throat clearing], they have difficulty to differentiate it from other clinical presentations. So ehm, if they don't consider it in the first place….possibility when they fail to make the diagnosis for adverse drug reaction. So we need to make them aware that there is a possibility of adverse reactions. So sometimes they will just consider it as part of clinical presentations and that is lost there. They don't have that suspicion; so that is one.

Then, ah! [Murmured about an important meeting] After making the diagnosis, again comes, some may not report even if they consider that it is probably, possibly due to the medicine, then they fail to report. Because one thing, even if they suspected diagnosis, there is no way they can be sure and they are not competent to share something they are not sure, we have to encourage them that the report they are handing doesn't have to be confirmed, should be just a suspicion. So at the first, in the first place, they don't suspect, if they suspect, some people feel like they have to be sure to report.

Then the other reason why people are not reporting is the reporting system. Ahn, sometimes the form is not available, sometimes they have to take it……by trying to complete the form, you know, they have to put additional effort to report. Erh, that way some people feel, let that report pass, so they don't report. Then, other challenge is after, after that, some people complete the form, it may not be complete; then they don't put very important information. So, they send incomplete information. Emm, very important, like the description of the adverse effect may not be incomplete, the time, you know, you really need the time to see if there is an association, probable or possible association between the event and the exposure. Those, those are the challenges in the voluntary reporting. Then, emm, then after reporting, there are other challenges, they don't make use of the report, they don't, they just send it and then, nothing happening there. The information, they don't know that it is useful for them. They don't aggregate, disaggregate, see pattern and take action. So it's like for the sake of reporting. If it is just for the sake of reporting, they don't, they don't sustain it. Even if they report 1, 2. The other thing, is emm, now, there are side effects of medicines and adverse reactions. Some people fail to differentiate the two. So there is a very thin line that differentiate the

two, it's not a clear cut or very gray area. So people have to be encouraged to report any suspected adverse reaction, they don't have to worry about, whether this is ahm, is adverse event or side effect and so on. Even if it is a side effect, it is ……happen, even if it is known, we also need to see the frequency. Sometimes, frequency can change some other environmental or other reasons. So all those challenges.

So, these are the challenges.

Errh, when it comes to the reporting system, the way the report is being collected is one of the challenges. Erh, we have a paper-based reporting, the paper, the clinician ……..clinical practice; it could be a nurse, complete it and then take it to the pharmacist, and then pharmacist, you know, it's not like direct, it's not automatic the information reaches the TIPC, sometimes you lose some reports in the process. Some places when you go support visits, you will find 10 reports 'no I have the reports' and then they have to fax it, you know in that process we can lose a lot. That is the challenge.

So, one area where we can improve, uhm, the pharmaceutical companies, they have responsibility to make their products safe. They have to monitor the safety of their products, so, they should actively monitor the safety of their products, and share the information with the TIPC, that way we can, you know, they have the money, they have the pharmacovigilance unit, so that way it's possible to get more information. That was for, to improve. So the percentage of reports that were coming from the pharmaceutical side was increasing.

Interviewer: In form of the Periodic Safety Updates

Participant 8: No, not Periodic Safety Updates. In-country adverse effect reports on their products. They have products in the market they monitor, they have the pharmacovigilance unit, they have the….you know they go to, from practice to practice to promote their product; at the same time they can ask report and ehm, most private doctors report to the pharmaceutical companies. Yea, so, yea this is how I see the challenges.

We may also talk about ways to improve.

Interviewer: So, within the public health sector, how can we improve?

Participant 8: Within the public health sector, the first thing, the first thing first. The healthcare professional needs to be aware about the existing system, one. And they, they should be, they should know the reason why they need to monitor the safety of the product. There is a very good reason why we need to monitor the safety of the product. So this should be incorporated into the graduate program in the pharmacology and the therapeutic, er, er, what do you call it, in the pharmacology curriculum [cleared his throat]. And when they come out, they should know that there is a need for reporting and there is a system for reporting. That is one.

Then, the second thing is to make the reporting very easy and er, yea, and great. Like you don't need to look for report, you don't need to take any extra minute, that, that may be in the future. If you have an electronic patient management system, the moment you make a diagnosis of adverse event and they, they, their system should populate relevant background information.

Interviewer: An integrated system.

Participant 8: Into the clinical …….. you know for example, for a patient, let's say HIV patient, when they come for follow up, there are two things that you monitor – one is how, whether they are responding for the treatment, the other thing is if they have any adverse reaction. These are, these are the main things. Erh, so that is the two things that you, that you check. If you look at it in general care, then follow up, you already put them on ARV, they are taking their medicines; now when they come for follow up 'are they reacting for the medicines?, are they improving clinically, immunologically? So, this is, this has to be integrated into system.

Interviewer: [Murmuring],

Participant 8: So, it has to be integrated. The general thing that I saw in the field out there in the facilities, when you talk about adverse drug reaction, people think pharmacy. No, it's not a pharmacy thing. Actually, there is, they find it even strange, when they see me doing pharmacovigilance. They think it is a pharmacy thing. If you write a letter and invite, they may say ok, send it to the pharmacy, pharmacist and pharmacist assistant. They don't think that it is their day to day activities. So that it the main, main challenge. So it needs to be integrated into the day to day activities, into the clinical practice, nothing else, patient care. If they see it as something else, it's totally wrong. It's a patient care, you give a medicine for the patient and the patient reacted in an unexpected way, the first thing is to manage the patient and share the event. That sharing or reporting of the event is to prevent similar events from happening in other patients. So it has to be part of clinical practice.

Interviewer: The integration will be of value to Namibia?

Participant 8: The intervention?

Interviewer: Integration of ADR reporting.

Participant 8: Yea, yea. Though, the other thing, I mentioned this earlier. The facility, the team in facility, they should be able to make use of that data, the report. It could be a singular report, they can make use of a singular report. Sometimes, erh, a singular report can be signal. Sometimes you may need to see pattern, to generate signal. So, they should be able to know how to make use of reports and data. If you have data, you look the pattern; if you have a single data and very serious event, that is really, really enough for them to do something. They should be able to know that. That is one. The other thing, erh, drug and therapeutic committees, they should also be involved, in creating awareness, in analysing data, looking into event and trying to make, to come up with some kind of intervention and so on. So the therapeutic committee, should be involved.

Interviewer: So, now you talked about electronic digital, something like EPMS

Participant 8: Yea

Interviewer: So, for general practice so to say, I believe ……will it be successful?

Participant 8: The future is going electronic, you know, there is no other alternative. So, erh, there is a need for us to prepare for electronic reporting system. And definitely, can be successful. The reason I am saying can be successful, like for example if you have to report with the paper, you have, even if you monitor your patient on electronic patient management tool, then you have to pull a paper, write from the demographic variables, from the name, age, all those things. Then adverse events, everything. That is

how you report. But if you are going electronic, you can have a populated form, it can populate uhn, most of the information. Even the, like erh, the current complain, does she come with skin rash, the complaint is skin rash, it can populate even into the form, the presenting complaint, and then finally you may only have to type prescription, additional, erh information. Practically, everything can be populated from the electronic system. So, it can make reporting very easy and a click away. You see, you already collection information to manage a patient, not to report, you collect the information to manage a patient, but it will prompt you to say, ok, when you make a provisional diagnosis of adverse drug reaction, then it will populate and will say 'do you like to submit this report'? A click, then it will, it will submit. If you miss very important information to do the causality assessment, it will ask you, 'please, this is a mandatory field', you'll complete that one and then send it. You have a report. So, it is possible. But erh, how far we are, I am not sure. Yea, and any reporting system, should also be compatible with Vigiflow, with the Vigibase. Erh, so, as we are collecting national data, the WHO centre needs to collect data for the whole world. So we need to share that. We can't have a standalone data and do not share it. Sometimes very, very rare event can be detected at WHO level. You may see patterns at WHO level, you may not be able to have enough, enough exposure at country level. So you may not be able to see some patterns, but if you collect from the whole world you may be able to see some patterns, national level, WHO level. So it has to be compatible, we need to know that. Yea.

Interviewer: So what can make the integration not work?

Participant 8: Change by process. Change, you know, there is resistant to change. There is one, to, to change your behaviour, first you have to have the knowledge and good

attitude towards ……. Change doesn't come because we say, please act like this or behave like this. So we need to be consistent, and other thing, other thing is that pharmacovigilance, should sustain itself. It should be able to sustain itself. Erh, like I said, making sure that their product is safe, is the responsibility of the producer, the pharmaceutical company. So there is a need for them to do big chunk of the work, but there is a need for regulation as well because you can downplay some of the events, if they are not regulated, you know because of erh, business, business principles, they may not be, or I can say, they can downplay the adverse events for the mere reason that they want to lose. It has to be regulated. But at the same time, they have to contribute a lot to the safety of their pharmaceutical product. Erh, so that is, erh, that is one. Erh, the other thing is erh, when we talk of registering a medicine, and keeping them in the register, what we are saying is that we are still convinced that the, that it's safe to be in the market. So we, people are paying, I was arguing on this, registration fee, and what is the other one?

Interviewer: Application fee

Participant 8: To keep the medicine

Interviewer: Retention fee

Participant 8: The retention fee is partly for saying, the product is it still safe? In a way, NMRC or the regulatory authority is saying, it's not the money, it is the information 'we don't have a safety concern to remove it from the register'. That's what we are saying. So we ask them fee, to ensure the safety not to keep it in the register. So we need to see

that the money coming is to ensure the safety of the medicine not to keep it in the register listed.

So that retention fee has a component of including the safety of the medicine as long as it is in the register. So people have to look into sustainability. If the amount the regulatory authority is charging is not enough, it's up to them. They have to improve the ehm, ehm, the cost or the payment. Otherwise, it is not to keep the medicine in the register, it is to say that it is still safe, I'm monitoring it. I'm monitoring the safety and that's how you keep it in the register. This thing has to come also. It's not, it's not like to list it in the …

Interviewer: It's not like they are making money.

Participant 8: Exactly. That is, that is how you can make it sustainable. Generating resource to do safety monitoring. [I: Uhn uhn]. You need to generate resource to monitor the safety of the products.

[Silence]

Participant 8: [On the phone]

End of the interviews.

Appendix 5: A PROFILE OF ADVERSE DRUG REACTIONS OF ATAZANAVIR AND LOPINAVIR BASED SECOND-LINE ANTERETROVIRAL REGIMENS IN NAMIBIA - Published Data Letter

A Profile of Adverse Drug Reactions of Atazanavir- and Lopinavir-Based Antiretroviral Regimens in Namibia

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Drug Safety
The Official Journal of the International Society of Pharmacovigilance [ISoP]

ISSN 0114-5916

Drug Saf
DOI 10.1007/s40264-019-00832-3

Springer

Drug Safety
https://doi.org/10.1007/s40264-019-00832-3

RESEARCH LETTER

A Profile of Adverse Drug Reactions of Atazanavir- and Lopinavir-Based Antiretroviral Regimens in Namibia

Babafunso Aderemi Adenuga[1] · Timothy William Rennie[2]

Dear Editor,

Pharmacovigilance in the area of antiretroviral therapy (ART) is of huge importance, as illustrated by Onoya et al. in a recent issue of *Drug Safety* [1]. In addition, a recent report relating to dolutegravir underpins the need for robust clinical trials and postmarketing surveillance when there is pressure to fast track the development of novel agents [2]. In that report, conducted in Botswana, neural tube defects in infants born to women taking dolutegravir were discovered. This was a new adverse drug reaction (ADR), as picked up during a phase IV clinical trial. As new antiretroviral regimens are being introduced with relative frequency due to the nature of the development of HIV drug resistance and the consequent proliferation of new therapies through drug development, it becomes important to monitor patients and possible ADRs that may develop, especially in areas of high-prevalence HIV. Namibia, a sub-Saharan African country bordering South Africa, endures similar health challenges, particularly in HIV, but with a fraction of the population size of South Africa. HIV prevalence in Namibia in 2017 was reported to be 12.6% in adults (16–64 years), inferring 176,000 cases of people living with HIV (PLHIV) [3]; rates were significantly higher in females compared with males. Most PLHIV seek their care from the public sector facilities—in particular the Ministry of Health and Social Services (MoHSS)—that follow World Health Organization-guided recommendations, including the use of atazanavir boosted with ritonavir (ATV/r) or lopinavir boosted with ritonavir (LPV/r) as a second-line or modified first-line protease inhibitor backbone [4].

We prospectively extracted and analysed the results of ADRs of patients prescribed ATV/r- or LPV/r-based regimens over a 1-year period (August 2017–August 2018) from a database of spontaneously reported ADRs that is in place in Namibia. This is a country-wide, paper-based system of reporting through the MoHSS Therapeutics Information and Pharmacovigilance Centre, which targets the public sector in particular, where most HIV patients are treated.

Seventeen reports were received during this period (Table 1); 58.8% were female, and the mean age was 42.1 years (range 23–53). The majority of reports related to hepatic or gastrointestinal organ systems (55% and 20% of reports, respectively). Most patients (82.3%) were taking ATV/r-based regimens at the time of ADR occurrence, which represents approximately 8 incidents per 100,000 HIV patients in Namibia.

Onoya et al. [1] reported a substantial dataset of ADRs experienced by patients taking second-line ARTs over a 12-year period in a resource-constrained setting, i.e. South Africa, greatly impacted by the HIV epidemic. In light of these findings, we consider that ADRs relating to ATV/r and LPV/r are underreported in Namibia. Possible reasons for this may relate to the nature of a spontaneous reporting system, the logistical challenges of submitting reports, human resources and expertise both to support the system of reporting and to submit quality reports, and general healthcare professional awareness and willingness to report. We suggest that the reporting system in Namibia can be improved to overcome the barriers in reporting—a reporting system that is responsive to the frequent changes relating to ART in particular and is sensitive enough to identify emergent issues. This could include mobile applications, such as those recommended in Europe by Pierce et al. [5], not dependent on continuous internet access, as well as training to underpin the technology and raise awareness and competence of healthcare providers in

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Published online: 08 May 2019

Table 1 Summary of the individual case reports

Case	Sex	Age (years)	Weight (kg)	Regimen	Presenting features	Drug suspect[a]	Action taken	Outcome (if any)
1	Female	23	53	ABC/3TC/AZT/ATV/r	Yellow eyes (jaundice)	ATV/r (6)	Regimen stopped	Recovering
2	Female	51	80	TDF/3TC/AZT/ATV/r	Yellow eye sclera (jaundice)	ATV/r (4)	Regimen stopped	NI
3	Male	42	NI	TDF/3TC/AZT/ATV/r	Jaundice	ATV/r (4)	Regimen stopped	Recovering
4	Male	46	65	TDF/FTC/AZT/ATV/r	Jaundice	ATV/r (4)	Regimen stopped	Recovered
5	Male	51	62.7	TDF/FTC/AZT/ATV/r	Indirect hyperbilirubinaemia (Jaundice)	ATV/r (4)	Regimen was not stopped	Did not recover
6	Female	35	59.2	TDF/FTC/AZT/ATV/r	Jaundice	ATV/r (4)	Regimen stopped	Recovering
7	Female	29	71	TDF/FTC/AZT/ATV/r	Jaundice	ATV/r (4)	Regimen stopped	NI
8	Female	38	NI	TDF/FTC/AZT/ATV/r	Jaundice	ATV/r (3)	Regimen stopped	Did not recover
9	Male	52	58	TDF/FTC/ATV/r	Indirect hyperbilirubinaemia (jaundice)	ATV/r (5)	Regimen stopped	Did not recover
10	Male	29	85	TDF/FTC/ATV/r	Yellow eye sclera (jaundice)	ATV/r (3)	Regimen discontinued	NI
11	Female	45	NI	TDF/FTC/AZT/ATV/r	Nausea; joint pains	ATV/r (2)	Regimen discontinued	Recovering
12	Male	36	NI	TDF/FTC/AZT/ATV/r	Renal failure	ATV/r or TDF (4)	Regimen substituted	Recovering
13	Female	42	NI	TDF/3TC/ATV/r	Hyphema; generalised body pain	None	Regimen was not discontinued	NI
14	Female	49	NI	TDF/FTC/ATV/r CTX	Hepatitis	ATV/r or CTX (4)	Regimen changed	Recovering
15	Female	53	NI	TDF/FTC/AZT/LPV/r	LPV/r GIT-induced adverse effects (diarrhoea)	LPV/r (4)	Regimen changed	Recovered
16	Female	29	NI	TDF/FTC/LPV/r	Diarrhoea	LPV/r (4)	Regimen changed	Recovering
17	Male	39	64	TDF/FTC/AZT/LPV/r	Severe itchy throat; cough; diarrhoea	LPV/r (4)	Regimen discontinued	NI

[a]Naranjo's score [6] is used to determine the causality of an adverse drug reaction in the presence of a suspected offending drug

NI not indicated, *ABC* abacavir, *3TC* lamivudine, *AZT* zidovudine, *ATV* atazanavir, *LPV* lopinavir, */r* ritonavir, *TDF* tenofovir, *FTC* emtricitabine, *CTX* co-trimoxazole, *GIT* gastro-intestinal tract

reporting ADRs. In low-resource settings, smart, innovative and robust systems are required that include a focus on human resources necessary to deliver these solutions.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this letter.

Conflicts of interest Babafunso Aderemi Adenuga and Timothy Rennie have no conflicts of interest that are directly relevant to the content of this letter.

Ethics The Research Ethics Boards of the MoHSS (reference no. 17/3/3) and Ethics Committee of the University of Namibia (reference no. SOPHA/209/2017) approved the study. Secondary data were used in this study and the need for written informed consent was waived by the Research Ethics Committee.

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Appendix 6: OPTIMIZING SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN PUBLIC HEALTHCARE SETTING IN NAMIBIA

Received: 23 July 2019 | Accepted: 11 September 2019

DOI: 10.1111/bcpt.13325

ORIGINAL ARTICLE

Optimizing spontaneous adverse drug reaction reporting in public healthcare setting in Namibia

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Abstract

Despite the universal scale-up of pharmacovigilance systems globally, adverse drug reaction (ADR) reporting remains suboptimal among resource-limited countries. Few studies in sub-Saharan Africa evaluate the effectiveness of adverse drug reaction (ADR) reporting programmes. A cross-sectional survey using a self-administered questionnaire to assess ADR reporting knowledge, attitude and practices among healthcare workers in Namibia's public sector was conducted between September and December 2018. The primary outcome were practices, knowledge and attitude of the respondents towards ADR reporting. Quantitative and qualitative data were analysed using descriptive statistics and thematic analysis, respectively. Of the 197 healthcare workers surveyed, 43.1% were nurses, 63.4% of the respondents knew about the ADR reporting system in Namibia, 76.7% knew the pharmacovigilance/ADR reporting centre in Namibia, while 37.3% had reported an ADR before. Nurses were less likely to be knowledgeable and report ADRs. The independent predictor of ADR reporting was the nursing cadre; adjusted odds ratio (aOR) = 0.17 (95% CI: 0.07, 0.401, $P < .01$). Pre- and in-service trainings including introduction of electronic reporting platforms were some of the identified ways of optimizing the pharmacovigilance and ADR reporting systems by the respondents. As pharmacovigilance in Namibia relies on spontaneous reporting of ADRs, there is a need for advocacy and workforce strengthening for ADR reporting in the public health sector.

KEYWORDS

adverse drugs reactions, namibia, public health care, reporting

1 | INTRODUCTION

The HIV/AIDS epidemic among other communicable and non-communicable diseases has devastated public health in sub-Saharan Africa (SSA), necessitating the scale-up of pharmacovigilance systems for surveillance of safety of standard treatment, which change frequently.[1] For instance, the retrospective study among patients on second-line antiretroviral therapy in South Africa underscored the importance of optimal pharmacovigilance systems.[2]

Adverse drug reactions (ADRs) are a public health challenge associated with high morbidity and mortality.[3] ADRs are a major cause of hospital admissions and treatment interruptions; it was estimated that approximately 6.5% of hospital admissions were due to ADRs in the United Kingdom.[4] As sub-Saharan Africa (SSA) is worst hit by the HIV epidemic, it is important that systems are in place to monitor new and ongoing antiretroviral therapies (ART).[5] As newer medicines are increasingly integrated into standard treatment guidelines for public health care in SSA, the strengthening of adverse drug reaction reporting becomes critical to improve quality of care.[6,7]

In addition, this integration of new essential medicines into standard treatment guidelines not only demands improved

pharmacovigilance but also raises the need for training and awareness of healthcare workers concerning ADRs and ADR reporting. Dealing with ADRs requires a multi-professional approach by healthcare workers—including medical practitioners, pharmacists and nurses—both in public and in private healthcare settings to safeguard population health.[8]

Namibia, a country in southern Africa with a population of about 2.5 million people, has a high burden of infectious diseases such as HIV, tuberculosis and malaria as well as a growing burden of non-communicable diseases. The HIV prevalence in Namibia was estimated at 12.6% in 2017 among adults aged 15-64;[9] the burden of the disease has reduced dramatically in the last two decades largely as a result of effective roll-out of efficacious ARVs and other essential medicines. Nevertheless, the establishment of the Therapeutics Information and Pharmacovigilance Centre (TIPC) in 2007, in the Ministry of Health and Social Services (MoHSS), has improved the access to pharmacovigilance services in public health care in Namibia.[10] Most healthcare workers at public health facilities mainly report ADRs by use of a paper-based spontaneous reporting system (ie voluntary adverse drug reaction reporting by healthcare workers or patients on suspected improper effect of a medicine). The reports can be faxed, scanned and emailed or hand-delivered to the TIPC office, depending on the proximity of the facility and resources available at the reporting facility.

In a recent audit carried out between August 2017 and August 2018, using the Individual Case Safety Report (ICSR) submitted by healthcare workers to TIPC, it was found that, although patients may be experiencing ADRs due to atazanavir- and lopinavir-containing regimens, cases were under-reported.[11]

Studies have elsewhere been carried out to assess the knowledge, attitudes, awareness, practices and perceptions of healthcare workers in different settings in Africa. In Nigeria, for example, the knowledge and perception of pharmacy students of pharmacovigilance activities in three Nigerian universities were assessed.[12] It was found that the knowledge of pharmacovigilance activities was low among students. In another study in Nigeria among healthcare workers, factors associated with under-reporting of ADRs included the lack of availability of reporting forms and lack of awareness of how to report ADRs.[13] Introduction of an electronic reporting platform was suggested to improve and encourage ADR reporting. Furthermore, in western Ethiopia, a lack of awareness and knowledge of pharmacovigilance and pharmacovigilance systems were reported to contribute to under-reporting of ADRs among healthcare professionals.[1]

The current study aimed to better understand the reasons for under-reporting of ADRs in the Namibian context and from the perspective of the healthcare workers empowered to report through the existing pharmacovigilance system.

2 | METHODS

2.1 | Design and settings

Between September and December 2018, a cross-sectional survey was carried out among healthcare workers working in the public healthcare facilities in Namibia. A self-administered questionnaire was adapted from previous studies that assessed the knowledge, attitude and practices of healthcare workers in Nigeria.[11,12] There are 14 geographical regions in Namibia. The study respondents were stratified by 7 regions; the 7 regions were purposively selected with varying settings and populations, that is 2 coastal towns (Karas and Erongo regions), 2 border towns (Caprivi and Omaheke regions), 1 centrally located town (Otjozondjupa region) and 2 central business districts (Khomas and Oshana regions). Healthcare workers at the respective state/regional referral hospital were included in the study.

2.1.1 | Population

Public healthcare workers from different cadres (medical doctors, nurses, midwives, pharmacists, dentists, radiographers, etc) participated in the study. They were invited by the researcher to voluntarily complete an anonymous questionnaire (online or paper-based). Target number of respondents was estimated at 200 respondents using the Kish Leslie method for a one-sample cross-sectional study with the power set at 80% and level of significance at 0.05; 197 respondents participated in the study; thus, the response rate was 98.5%.

2.1.2 | Pharmacovigilance programme in Namibia

TIPC co-ordinates pharmacovigilance activities in Namibia. Namibia is a full member of the World Health Organization Programme for International Drug Monitoring. ICSR from healthcare facilities submitted to the TIPC is collated, aggregated and sent to the WHO-UMC through VigiBase, a database for reporting ADRs.

2.2 | Procedure

The research instrument comprised of 5 sections: (1) demographics of the respondents; (2) knowledge of health workers about pharmacovigilance/ADR reporting, attitude of health workers to pharmacovigilance and ADR reporting measuring separately (3) positive and (4) negative attitudes; and (5) practice of pharmacovigilance and ADR reporting among healthcare workers. To measure knowledge, four multiple-choice question responses were used and scored; a summed

score was generated for analyses. A Likert scale rating system was used to measure the negative and positive attitudinal item responses (strongly agree = 5, agree = 4, neutral = 3, disagree = 2 and strongly disagree = 1); negatively worded items were reverse coded so that higher scores represented more negative attitudes. Respondents were asked to report on their actual pharmacovigilance practice in response to two questions relating to whether they had reported ADRs to the centralized pharmacovigilance reporting system or within their practice setting. Finally, participants were asked to use an open-response question about possible ways of improving the current pharmacovigilance systems in Namibia.

The questionnaire was disseminated using an online platform (ie Google Forms®) as well as paper format. A network sampling method was used in the online questionnaire administration. Index healthcare professionals were identified and asked to request their fellow professionals to complete the questionnaire. A purposive sampling method was used in the paper questionnaire administration, whereby a focal person was identified for seven different health facilities around the country with a high patient turnover. The focal person was sent questionnaires to distribute locally and collect responses to be couriered or hand-delivered back to the main investigator. For responses to the attitudinal scales in the questionnaire, reliability analysis was determined using Cronbach's alpha. Cronbach's alpha for positive and negative intentions was 0.839 and 0.811, respectively, showing acceptable reliability for both scales (Table S1).

The questionnaire was validated through face validity and pilot study. Face validity was carried out by one of the faculty members at the School of Pharmacy, University of Namibia, prior to the pilot phase. Five (5) respondents working with the MoHSS were selected; these completed the paper-based questionnaire in July 2018, and also three (3) academic respondents from the staff of the Faculty of Health Sciences, University of Namibia, completed the online format in August 2018. Feedback was received and incorporated to improve the questionnaire tool.

2.2.1 | Factor analysis

Factor analysis was conducted to determine the construct validity of the questionnaire items for the three domains, knowledge, attitude and practice of ADR reporting. Most questionnaire items loaded onto the common scales that were included in the questionnaire tool (Table S2). The question loading was between 0.42 and 0.89. Three items did not load onto pre-existing scale but did not appear to show any rational commonality. From this analysis, we were reasonably satisfied that the survey tool—including those scales within—was valid for the measurement of perceptions towards pharmacovigilance in Namibia. However, further work can explore why the three items did not load as anticipated including whether this was related to insufficient sample size or whether they were measuring a distinct theme not captured adequately by the questionnaire. A qualitative approach may help in this.

2.3 | Data collection and analysis

SPSS (ver. 25) software was used for data analyses; electronic survey response data were imported, and paper-based questionnaire data were entered manually. Descriptive analyses were performed on responses to the questionnaire including sample characteristics and questionnaire items. Bivariate analysis was conducted to examine the relationships between ADR reporting and willingness or ability to report suspected ADRs and other variables. A multivariate logistic regression model was constructed to explore the independent associations with under-reporting of ADRs. The following variables were entered for regression analysis: professional group, negative intention to report, knowledge of pharmacovigilance and number of years of experience (Table 1).

3 | RESULTS

3.1 | Population characteristics

A total of 197 health workers completed the survey. Of the 145 questionnaires distributed physically, 88.3% (n = 128) were completed. Of the 70 questionnaires completed online, one was a duplicate response which was excluded from the analysis. The majority of the respondents were nursing (43.2%) or pharmaceutical personnel (31.5%). The mean age and years of experience of the respondents were 35.4 (SD 9.1) years and 10.1 (SD 8.3) years, respectively. The majority of the respondents were female (60.9%; Table 2) and worked at either a district hospital (31.5%) or a clinic setting (27.4%) (Table 1).

3.2 | Knowledge, attitude and practice of adverse drug reaction reporting

The majority of respondents (63.4%) knew about the ADR reporting and monitoring system in Namibia, and even more (76.7%) were able to identify the centre responsible for pharmacovigilance activities. Although most respondents (75.1%) acknowledged that every healthcare worker is responsible for ADR reporting, only 64.4% disclosed knowing how to report ADRs. Of the respondents, only 16.5% had attended a pharmacovigilance training while just over one third (37.3%) had reported an ADR before.

Different levels of knowledge were observed among the three professional groups reporting most frequently (Kruskal-Wallis test: $\chi^2 = 11.087$, $P = .004$); about 33% of the nursing

TABLE 1 Demographics of respondents

Demographic variables	Categories	N = 197 (%)
Age, years (mean, SD)		35.38 (9.1)
Age, categorized (n, %)	20-29	60 (30.5)
	30-39	82 (41.5)
	40-49	34 (17.3)
	50-59	19 (9.6)
	60-69	2 (1.0)
Years of experience (mean, SD)		10.11 (8.3)
Years of experience categorized (n, %)	0-9	111 (56.3)
	10-19	55 (27.9)
	20-29	24 (12.2)
	30-39	7 (3.6)
Gender (n, %)	Female	120 (60.9)
	Male	77 (39.1)
Type of facility (n, %)	District Hospital	62 (31.5)
	Clinic	54 (27.4)
	Intermediate Hospital	32 (16.2)
	Health Centre	19 (9.7)
	NMRC	9 (4.6)
	National Referral Hospital	8 (4.1)
	Others	12 (6.0)
	TIPC	1 (0.5)
Professional group (n, %)	Nursing	85 (43.1)
	Medical	31 (15.7)
	Pharmacy	62 (31.5)
	Dental	5 (2.5)
	Allied	5 (2.5)
	Others	9 (4.6)

Abbreviations: NMRC, Namibia Medicines Regulatory Council; TIPC, Therapeutic Information and Pharmacovigilance Centre; Allied, Radiographer.

professionals gave incorrect responses to knowledge of pharmacovigilance questions compared to 31% and 25% of the medical professionals and pharmacy professionals, respectively. Different levels of reporting ADRs between the health professions were also observed with pharmaceutical cadres reporting most frequently, followed by medical personnel and then nursing (Kruskal-Wallis test: $\chi^2 = 19.494$, $P < .001$).

A positive association was observed between training received and ADR reporting ($r = 0.178$, $P = .013$), and negative intention to report ADRs was negatively associated with ADR reporting ($r = -0.202$ $P = .003$) (Table 3).

In logistic regression analysis, only the nursing profession emerged as a potential predictor of ADR reporting such that respondents from the nursing profession were about six times less likely to report ADRs compared with the reference group, pharmacy profession respondents (Table 4: CI 0.070-0.401, $P < .001$).

TABLE 2 Correlations for training and willingness/ability to report ADRs

	ADRs reported ever		ADRs reports in respondent's setting	
Variables (N = 197)	*r*	*P*	*r*	*P*
Negative intention to report (n = 184)	−0.115	.060	−0.202	.003
Positive intention to report (n = 187)	−0.028	.703	0.086	.245
Age of respondents (n = 197)	0.118	.099	0.084	.244
Number of years of experience (n = 184)	0.168	.011	0.135	.034
Ever attended PV training (n = 194)	0.178*	.013	0.274**	.000
Knowledge of pharmacovigilance (n = 185)	0.229	.001	0.189	.005
Professional group (n = 197)	−0.065	.365	0.023	.752
ADRs reported ever	–	–	0.401**	.000

Abbreviations: ADR, adverse drug reaction; *r*, Pearson's coefficient
$P < .05$ level was set to infer statistical significance.
*Number of respondents varies as per the answered paper questionnaire items. Correlation is significant at the .05 level (2-tailed).
**Correlation is significant at the .01 level (2-tailed).

TABLE 3 Predictors of adverse drug reaction under-reporting based on multivariate logistic regression model

			95% CI for OR	
Variables	*P*	OR	Lower	Upper
Profession (reference: Pharmacy)				
Medical	.288	0.595	0.229	1.549
Nursing	.000	0.168	0.070	0.401
Number of years of experience	.248	1.028	0.981	1.078
Ever attended PV training	.997	0.998	0.379	2.629
Negative intention to report	.092	0.659	0.406	1.071
Knowledge of pharmacovigilance	.451	1.804	0.389	8.369

Note: $P < .05$ level was set to infer statistical significance. Odds ratio (OR) and 95% confidence interval (CI) were calculated using multivariate logistic regression, and all variables were entered by forward stepwise method. Wald's test statistic shows the variables that contribute to the logistic regression model (Wald's test statistic was 5.361, $P = .021$), Nagelkerke R square for the model was 0.251.

TABLE 4 Thematic summary of responses for improvement of Pharmacovigilance and ADR reporting system in Namibia

Theme	Subtheme	Respondents' quotes
Training gaps	Training on pharmacovigilance Training on how to complete ADR report forms Training on how to detect ADRs in practice	"Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivates all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects (it is a responsibility for Pharmacists to educate or motivate other health care providers)" "Create awareness about pharmacovigilance and provide relevant information in regard to the centers where adverse reactions can be reported to and the necessary steps that one will need to follow to report adverse drug reactions." "Educate all pharmacists and other healthcare workers on the importance of drug safety and post marketing surveillance" "Health workers and health care providers should be regularly trained and appraised on the importance of Adverse Drug Reactions reporting" "Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivate all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects Continuous professional development on pharmacovigilance should be strengthened in all state hospitals. District hospital's therapeutic committee meetings should be educative and it should motivate all health care providers to report any adverse drug effects. This will help most health care providers to differentiate between side effects and adverse effects." "Training of all healthcare workers, especially nurse, on ADR reporting and pharmacovigilance because they are the first to be seen by the patients. In-service training on what should be reported."
Electronic ADR reporting system	Use of a mobile or cell phone application Digital reporting system	"Electronic/online options eg TIPC mobile application" "electronically reporting, like data base" "Digitalization of the ADR reporting and pharmacy vigilance system"
Decentralization of pharmacovigilance/ADR reporting system	Creation of reporting hubs at district/facility level	"Each hospital must have a specific staff responsible giving awareness assessing, detecting and receiving and reporting to TIPC." "Get a focal person to deal with ADR reporting"
Community engagement	Awareness creation in the community	"Encourage patient/user of medicine to report directly all the adverse reactions in writing to the pharmacy/clinic near him/her"
Feedback	Communication between TIPC and ADR reporters	"Feedbacks and should come back to the person or the organization who report the ADR report" "Provision of feedback on reports and regular feedback to stakeholders on the TIPCs ADR related activities and country status. Pre and post training field visits to health facilities to maximize impacts of trainings and to motivate reporting by professionals - raising public/patients awareness on ADR identification and reporting using various platforms including TV, MOHSS website, social media platforms, etc (I wonder if there exist any report from patients so far)."

3.3 | Responses to open-ended question

Out of 197 respondents who participated in the survey, 168 (85.3%) respondents answered the open-ended question "What other ways would you propose/suggest to improve adverse drug reactions reporting and pharmacovigilance system in Namibia?" Five (5) themes were identified such as training gaps, electronic reporting, Feedback from TIPC and community engagement; subthemes identified included training on pharmacovigilance, awareness creation in the community and digital/electronic reporting (Table 4).

5 | DISCUSSION

This is the first study in Namibia to explore knowledge, attitudes and practices of healthcare workers concerning ADR reporting. Findings suggest that pharmacovigilance practice among healthcare workers in Namibia could be substantially improved, given that a minority have undergone pharmacovigilance training before. Training also appeared to be an important factor that may be related to ADR reporting practices.[13] In a recent audit carried out between August 2017 and August 2018, using the Individual Case Safety Report (ICSR) submitted by healthcare workers to TIPC, it was

found that, although patients may be experiencing ADRs due to atazanavir- and lopinavir-containing regimens, cases were under-reported,[14] though; the under-reporting may not be limited to these regimens.

Respondents themselves suggested that training and education around pharmacovigilance could empower current systems of reporting. Strengthening the communication channel between TIPC and healthcare workers through Therapeutics Committees at the facility level as well as the provision of analytical feedback on TIPC reports could serve as an incentive for the reporters.

Studies have elsewhere been carried out to assess the knowledge, attitudes, awareness, practices and perceptions of healthcare workers in different settings in Africa. In Nigeria, for example, the knowledge and perception of pharmacy students of pharmacovigilance activities in three Nigerian universities were assessed.[15] It was found that the knowledge of pharmacovigilance activities was low among the students. In another study in Nigeria among healthcare workers, factors associated with under-reporting of ADRs included the lack of availability of reporting forms and lack of awareness of how to report ADRs.[16] Other studies have reported that not knowing how to report can be a barrier to ADR report among clinicians.[11,17] Introduction of an electronic reporting platform was suggested by the respondents as a way to improve and encourage ADR reporting in Namibia. Furthermore, in western Ethiopia, a lack of awareness and knowledge of pharmacovigilance and pharmacovigilance systems was reported to contribute to under-reporting of ADRs among healthcare professionals.[16]

The level of awareness of ADR reporting among the respondents was found to be 37.1%. The result is similar to other studies conducted in Nigeria and India which estimated the awareness of the Yellow Card ADR reporting scheme and/or had reported an ADR at 32% and 37%, respectively.[18,19]

More reports were received from the nursing cadre, these are more in number within the health system and the pharmacy cadre which is more involved with pharmacovigilance activities, and this raises questions relating to representation of the sample. However, in general, the survey was inclusive and able to distinguish subtle differences between the professional groups, for example, knowledge levels. Indeed, the only emerging variable that may serve to predict ADR reporting through regression analysis was found to be respondents belonging to the nursing profession.

Further research in this area needs to focus on how to strengthen the pharmacovigilance systems through engagement with stakeholders and development of innovative ways of reporting ADRs in Namibia. Specifically, a better focus on the nursing profession—who are often at the frontline of patient care where they will be administering medicines and observing the effects—in terms of improving competence in recognizing and reporting ADRs may be necessary. As the largest health profession worldwide and in Namibia, this also stands to have significant public health impact especially following any introduction of new standard treatment guidelines incorporating new treatment regimens such as the antimalarials, antituberculosis drugs or antiretroviral medicines or other drug classes.[9]

This study relied on voluntary participation and purposive sampling of healthcare workers. This type of study has the potential of selection bias and limited generalizability. However, the survey of healthcare workers in Namibia was regionally stratified focussing on locations with high number of healthcare workers or locus of activity. The current study did not focus on independent patient-reported ADRs which remains a limitation of the study but can be further investigated through future research.

Depending on the setting, centralized, national reporting systems may not always be the solution to pharmacovigilance but if they are adopted—as is the case in Namibia—there is a need to continually support their function and improvement. This may include ongoing training and education at pre-service and in-service levels, involvement of Therapeutic Committees at facility and regional levels and introduction, for example, of innovative electronic reporting to improve efficiency and boost the response rate among healthcare workers.[19-22]

In conclusion, the study revealed a high level of knowledge of pharmacovigilance and ADR reporting system among the healthcare workers, though this has informed neither their attitude nor their practice of ADR reporting as seen in their reported attitude and practice. In other to optimize the current system, there is a need for effective communications between TIPC and the healthcare workers; this may be in the form of feedback, continuing professional development (CPD) lectures, advocacy within the health sector and community engagement.

CONFLICT OF INTEREST

The three authors, Babafunso Aderemi Adenuga, Dan Kibuule and Timothy William Rennie, have no conflict of interests that are directly relevant to the content of this study.

ETHICAL APPROVAL

Research ethics approvals were obtained from the Research and Ethics Division of the MoHSS (Reference No. 17/3/3) and Ethics Committee of the University of Namibia (Reference No. SOPHA/209/2017).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Adenuga BA, Kibuule D, Rennie TW. Optimizing spontaneous adverse drug reaction reporting in public healthcare setting in Namibia. *Basic Clin Pharmacol Toxicol*. 2019;00:1–7. https://doi.org/10.1111/bcpt.13325

Appendix 7: A case for strengthening pharmacovigilance systems in Namibia

GLOBAL JOURNAL OF MEDICINE AND PUBLIC HEALTH

A case for strengthening pharmacovigilance systems in Namibia

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ABSTRACT

The paper seeks to highlight the problems posed by under-reporting of adverse drug reactions encountered by healthcare workers. It emphasized the importance of strengthening pharmacovigilance systems in different settings. It recommended that a cross sectional study focusing on the knowledge, attitude and practices of healthcare workers should be conducted in Namibia. The conclusion was to emphasize the need to report and document ADRs observed by both patients and healthcare workers and the inclusion of PV training into the curriculum of medical doctors, nurses, pharmacists and all allied healthcare professions.

Keywords: Pharmacovigilance, Healthcare Workers, Adverse Drug Reactions, Training, Under Reporting, Patients

GJMEDPH 2018; Vol. 7, issue 1

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Conflict of Interest—none

Funding—none

INTRODUCTION

Pharmacovigilance (PV), the practice of the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem has grown over the past decade in Low and Medium Income Countries (LMIC) such as Namibia.[1] Nonetheless, the goals for robust systems and coordinated efforts to report Adverse Drug Reactions (ADRs) remain suboptimal in these countries. For example, since the inception of the Therapeutic Information and Pharmacovigilance Centre by the Ministry of Health and Social Services, the quantitative and qualitative impact of the centre on informing policy on safety and effectiveness of medicines Namibia remains underutilized.

The public and private health facilities in Namibia under-report ADRs; this is partly due to a poor acceptance and implementation PV systems at health facility level. In most LMIC such as India and Zimbabwe, among the factors that promote under-reporting of ADRs, is lack of awareness of ADRs Monitoring Centres (AMC) and pharmacovigilance program in the settings, complacency , lack of training to identify ADRs, fear factor, lethargy, lack of risk perception.[2,3]

In addition about half of the health workers do not know how to report ADRs and/or are not aware of the existence of a formal ADR reporting schemes.

The most reported ADRs in Namibia are associated with ARVs; particularly Efavirenz,[4] and Nevirapine[5] and Zidovudine.[6] Gynaecomastia, an ADR associated with Efavirenz is one of the most reported ADRs in Namibia. Protease Inhibitors (PI) are believed to be milder compared to the NRTI/NNRTIs, this may contribute to under-reporting of observed ADRs in Namibia.

Some of the contributing factors to under-reporting have been outlined by Khan and Khoza.[2,3]

Factors that are believed to contribute to ADRs under-reporting can be grouped into two:

1) Provider influenced
2) Patient influenced

Provider Influenced

1) Insignificance of particular ADRs – In a study carried out by Aziz et al,[7] some of the respondents considered some ADRs to be too trivial or too well known to be reported. Jaundice associated to Atazanavir in Atazanavir/Ritonavir combination, has been reported by word of mouth by some health workers in Namibia; however, no account of such ADR has been reported officially. Impact of some activity on the general overview of the PV system in the country is being undermined and the expected outcomes may not be achieved.
2) Okezie and Olufunmilayo,[8] commented that awareness or knowledge about how ADRs should be reported or what should be reported may not encourage some health workers to report ADRs whenever they detect any.
3) Some may deem the ADR form too complex to complete, thus, neglect the activity. According to Kamtane et al,[9] and Oshikoya and Awobusuyi,[10] lack of electronic reporting system may be a hindrance to ADR reporting, thus, leading to under-reporting.
4) Availability of means to communicate compiled report to a central point for collation may discourage health workers from reporting and the possibility of overlooking the importance of the observed ADR over time, considering the possible remission of the ADR.
5) Incentives as a tool to motivate health workers to report observed ADRs was highlighted as a reason for under reporting by Bäckström and Mjörndal.[11]
6) Time spent in attending to patients and the perceived workload.

Patient Influenced

1) According to Sales et al,[12] minimal knowledge of patients about ADRs i.e. the meaning, implications and what to do whenever it occurs, contributes to under reporting of ADRs in a system.

RECOMMENDATION

A cross-sectional research has to be conducted in Namibia in the public and private settings to know the level of knowledge of healthcare providers. Results of such research will inform the type of intervention necessary to improve the PV system in Namibia.

CONCLUSION

It is important for the providers and patients to know the importance of ADR reporting. Training of health workers should not be limited to after they have graduated from school but PV should be incorporated into medical doctors, pharmacists, nurses and other health care trainees' academic structure so as to enhance appreciation of the subject and improve the PV system in the country.

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Appendix 8: Effective integration of pharmacovigilance systems at public health facilities in resource-limited settings: A qualitative study

Research in Social and Administrative Pharmacy xxx (xxxx) xxx-xxx

Contents lists available at ScienceDirect

Research in Social and Administrative Pharmacy

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Effective integration of pharmacovigilance systems at public health facilities in resource-limited settings: A qualitative study

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ABSTRACT

Background: Pharmacovigilance systems increase access to safe medicines and healthcare, but their integration in public healthcare remains a challenge in many countries. The main barriers to pharmacovigilance integration are attributed to high patient load and limited capacities.
Objective: To explore the challenges associated with the effective integration of pharmacovigilance systems in public healthcare in a developing country such as Namibia.
Methods: A nationwide qualitative assessment of integration of pharmacovigilance systems particularly spontaneous adverse drug reaction (ADR) reporting at public health facility level was conducted. Key informant interviews were conducted among pivotal healthcare professionals involved in pharmacovigilance. The main outcomes were themes on challenges and strategies for effective integration of PV services at the facility level. Qualitative data were collected over a one-month period (i.e., March 2019), and thematically analysed.
Results: Eight (8) key informants were recruited; the majority were pharmacists (n = 7) and male (n = 5). The main challenges affecting the effective integration of pharmacovigilance systems reporting at public health facilities were *"weak pharmacovigilance policies and structures"*, *"negative attitude of healthcare workers towards pharmacovigilance"*, and *"limited capacity and support for implementation of pharmacovigilance activities"*. The main strategies for effective integration of PV systems at facilities included local capacity-building through continuing profession education and support, advocacy, stakeholder engagement, facility/region based pharmacovigilance champions, and facility-based policies for universal and inclusive reporting, (i.e. patients and health workers at all levels) as well as development of workable standard operational procedures.
Conclusions: The pharmacovigilance systems at healthcare facilities in Namibia were observed to have sub-optimal policies, structures and support systems, and lack health care worker buy-in. There is a need for a policy framework to ensure effective and sustainable integration of pharmacovigilance activities at public healthcare facilities.

Background

The need for monitoring the safety of medicines became apparent after the use of thalidomide in the early 1960s led to more than 10,000 children developing phocomelia, a birth defect affecting the limbs of new-borns; thalidomide had been used as a sedative and treatment of nausea in pregnant women.[1] This prompted rigorous toxicity testing of new drug candidates by manufacturers and improved post marketing surveillance monitoring of newly approved drugs. Since then, the World Health Organisation (WHO) mandated national governments to incorporate medicines safety programs into their public healthcare; this led to scale-up of pharmacovigilance activities globally.[2]

Pharmacovigilance activities are commonly carried out by National Medicines Regulatory Authorities (NMRA) housed within the Ministries of Health in most sub-Saharan African (SSA) countries; and has become the norm in an era of donor-funded public health programmes such as for antiretroviral therapy (ART), Tuberculosis and malaria programmes.[3–5] Subsequently, most NMRAs in SSA, including

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https://doi.org/10.1016/j.sapharm.2019.11.010
Received 12 November 2019; Accepted 13 November 2019
Available online xxx
1551-7411/

Namibia, have incorporated pharmacovigilance activities in public healthcare to support and promote the safe use of medicines.

During the recent decade, SSA has seen an unprecedented surge in the number of manufacturers and marketers involved in medicines distribution within the sub-continent.[6] SSA, being the global region hardest hit by the HIV pandemic, has prevalence of HIV infection in some countries such as Namibia above 10% in 2017.[7] This has required the integration of novel regimens in public healthcare with the parallel implementation of pharmacovigilance programs.

Some of the challenges facing the integration of a comprehensive and effective pharmacovigilance system in SSA include over-reliance on donor funding to execute critical public health programs, low human capacity and expertise required to implement programs, and the lack of integration of such programs into the existing public health strategies in place.[8]

In Namibia, the Therapeutics Information and Pharmacovigilance Centre (TIPC), which was implemented through the assistance of donor funding, within the Ministry of Health and Social Services (MoHSS), is the largest publicly funded provider of healthcare. A paper-based spontaneous adverse drug reaction (ADR) reporting system has been in use in Namibia since the inception of TIPC; however, there are challenges associated with such a reporting modality; the need for printed material (paper), storage of returned reports, relaying or faxing the report to the central coordinating unit, and eventual collation of and action on the reports. The time between identifying a suspected ADR and possible action to be taken by the coordinating centre may limit the usefulness of some of the reports, rendering pharmacovigilance activities unreliable and risking patient care by not being responsive to hazards that may arise. Identified areas of need in the Namibian healthcare setting that are necessary to close the human and financial capacity gaps created by the donor funders' exit include in-country training of healthcare workers (HCW) and health scientists which might be achieved by the commencement of the School of Pharmacy, Faculty of Health Sciences, which provides a local needs-based curriculum.[9–11]

Evidence suggests[12] that ADRs developed or experienced by patients may be under-reported; this has a direct link to the pharmacovigilance systems in place, both at the central coordinating unit and facility level. However, under-reporting of ADRs is a common phenomenon among low and middle income countries (LMICs).[13,14] The continued digitalisation of healthcare services and programmes has necessitated the development of solutions to bridge the gap between effective reporting and available tools to achieve the goal of improved patient safety. Notable interventions using the digital platform in Namibia included the introduction of a pharmacist's intervention tool through the use of smartphones.[11] It is important to conceptualise the prevailing circumstances within the healthcare system, optimise and develop locally appropriate ways in which the challenges identified within the pharmacovigilance system can be mitigated.

This study aimed to better understand the problems within the Namibian healthcare sector with regard to integrating pharmacovigilance activities and routine clinical practice as perceived by key informants in various settings/sectors, to strengthen and optimise the pharmacovigilance systems, thus improving ADR reporting amongst the healthcare workers.

Methods

Design and setting

A descriptive qualitative study was conducted through key informant interviews using an investigator-administered, semi-structured interview schedule involving strategic healthcare professionals from different sectors in Namibia. Only personnel conversant with the pharmacovigilance system in Namibia and beyond were targeted for the study.

Population

Eight (8) key informants were purposely selected taking into consideration their understanding of pharmacovigilance and the systems to support pharmacovigilance in Namibia, and previous positions within the healthcare sector. These included healthcare professionals – seven pharmacists and one medical doctor – working in the medicines regulatory authority, public sector hospitals, non-governmental organisations (NGO), or academia. The interviews were conducted sequentially until saturation of themes was attained.

Procedure

Key informant interviews were conducted over a one-month period, March 2019. The framing question for the interview was:

> *'In your view, what are the ways or how can the pharmacovigilance and adverse drugs reactions reporting system be improved in Namibia?'*

Subsequently, participants were presented pertinent areas for discussion including subjects around current practices of pharmacovigilance in Namibia, barriers to reporting ADRs from the healthcare workers' perspectives, and possible ways of strengthening the existing pharmacovigilance and ADR reporting systems. Further, participant responses were probed for clarification or to provide more depth. The responses were audio-recorded on an electronic device and later transcribed. The principal researcher (BAA) moderated all the interviews, which were conducted in English Language. Permission to conduct the study was obtained from the ethics committees of the Ministry of Health and Social Services (MoHSS) and University of Namibia.

Data analysis

Audio-recorded responses were transcribed verbatim and double-coded by two researchers (BAA and DK) in the research team using thematic content analysis; a third researcher (TWR) reviewed the coding to identify inconsistencies that were clarified between the three researchers. Confidentiality of the participants was ensured.

Results

Participant characteristics

Eight eligible participants were recruited and all of them agreed to be part of the key informant interviews. The participants included chief pharmacists (2), a medical doctor (1), a TIPC pharmacist (1), academic pharmacists (3), and a pharmacist working in an NGO (1). Of the 8 participants, there were 5 males and 3 females, all of whom were resident in the capital city except one regular visiting academic.

Thematic analyses

Through analyses, a total of 3 themes related to challenges faced by healthcare workers (Table 1) and 7 themes related to ways of improving the pharmacovigilance and ADR reporting systems were derived (Table 2). There were a total of 43 identified challenges and 80 identified improvements derived. A number of challenges limiting the healthcare workers to report ADRs were similar in both public and private healthcare settings.

Challenges faced by healthcare workers to report ADRs in Namibia

In relation to challenges faced by healthcare workers in reporting ADRs, three emergent themes were identified: (1) Weak pharmacovigilance policies and structures, (2) Limited capacity and support for im-

Table 1
Challenges faced by healthcare workers to report ADRs.

Themes	Sub-themes	Quotes
Systems-related challenges limiting ADR reporting	Outdated mode of reporting	*"But not only the private sector, there are those health workers who still prefer electronic reporting system it might be much more convenient, so sort of like eliminate the logistics of completing the form, fax it, or scan it and email it"*
		"And erh, like the details one can get back to the person making the report but that initial report, can we make it a bit simple and user friendly?"
	Reporting by patients	*"Maybe, ok, maybe we encourage the patients to report ADR but he will not know. He goes to the doctor, patient who got the medication, then, he got ADR, right. And then, he will go to the doctor, he will report it"*
	Trained staff attrition	*"Like in our setting here, we've trained two of our staff members have been trained and I think a doctor too was trained but that doctor is no longer in the system. And those are the issues, you know you train people after training them either they resign or they are no longer in the system"*
	Centralised pharmacovigilance centre	*"Of course, em Namibia being a vast country, em having one central point for coordinating all the pharmacovigilance activities which include ADR reporting, product quality, you know, reporting, also giving medicine information may be a very demanding task"*
	Feedback (TIPC)	*"And that should, that should be well structured, you know and standard, right across the country, because people, they say we report [laughter] but we rarely get, we rarely get feedback and that's a fact;"*
		"I think it comes back to feedback still, uhm, intensified central level feedback, you know, to the facilities when they report, you know, we have the bulletin like what we used to have but the bulletin content should contain more of the scientific analysis, you know ahm, ahm, than the descriptive, you know ehm ehm feedback that is normally given"
Limited Capacity	Capability at TIPC	*"Okay so what this means is that at the moment ahm, TIPC is operating, it is in charge of pharmacovigilance, and it struggles to promote it"*

Table 1 (*Continued*)

Themes	Sub-themes	Quotes
	Competence (Healthcare workers)	*"You know when people, you know you want a pharmacist assistant to report, what you expect from that report, is it too detailed? You may want to look into that. You know making the form a bit er er, making the form, simplifying aspects in the form that makes it user friendly, let me put it that way"*
		"Patient is telling the pharmacist that I, I, the doctor changed my medicine and the pharmacist is asking oh, why? Because I was coughing too much, now on this new medication. Pharmacist just go ahead, it doesn't trigger anything in that pharmacist that no, this needs to be reported because there are a lot of patients, filling that form will take time. He doesn't want to waste time, he wants to finish the patients"
	Workload	*"It shouldn't be looked at as one of those ectopic activities which if apart from says they are very busy they won't be able to report"*
		"Like in our setting, really doctors are busy with their clinical work and they've not seen adverse medicine reaction reporting as part of their clinical work."

Table 1 (*Continued*)

Themes	Sub-themes	Quotes
Healthcare worker attitude	Resistance to change	*"Change, you know, there is resistant to change. There is one, to, to change your behaviour, first you have to have the knowledge and good attitude towards … …. Change doesn't come because we say, please act like this or behave like this. So we need to be consistent, and other thing, other thing is that pharmacovigilance"*
	Willingness to report	*"Those are the things that affect adverse medicines reporting, people feel ok, it might affect their performance rating, yea"*
	Sense of responsibility	*"Perhaps people we nominate to go for those training are not eh, passionate about er ADR reporting. Like in our setting here, we've trained two of our staff members have been trained and I think a doctor too was trained but that doctor is no longer in the system"*

plementation of pharmacovigilance activities, and (3) Negative attitude of healthcare workers towards pharmacovigilance.

Of the 8 key informants, the challenges on reporting ADRs among the healthcare workers were related to systems issues with subthemes such as outdated reporting modalities, reporting by patients and feedbacks from TIPC. Limited capacity of both the healthcare workers and TIPC staff and competency of health workers to identify, record and report suspected ADRs was the second identified theme. Attitude of healthcare workers to report identified ADR was the third identified theme with subthemes such as resistance to change, willingness to report and sense of responsibility (Table 1).

Theme 1: weak pharmacovigilance policies and structures

The respondents described the challenges that government institutions such as the MoHSS and the TIPC have to address in order to strengthen the pharmacovigilance systems and improve ADR reporting by healthcare workers. Respondents commented on the unsuitability of the paper-based reporting system, which they suggested was outdated and that there was a need to come up with a more versatile and responsive system to ensure prompt transmission of reports from the healthcare worker to TIPC. The need to decentralise the coordination centre by involving the Therapeutic Committees at the facility/regional level was highlighted by one of the participants.

Table 2
Improving the pharmacovigilance and ADR reporting systems dynamics.

Themes	Sub-themes	Quotes
Policy	Integrating PV activities into routine clinical work	*".So I think that's another area we need to find a way to integrate adverse medicine reactions reporting as part of a clinical work of the clinician"*
		"You see, you already collection information to manage a patient, not to report, you collect the information to manage a patient, but it will prompt you to say, ok, when you make a provisional diagnosis of adverse drug reaction, then it will populate and will say 'do you like to submit this report'? A click, then it will, it will submit. If you miss very important information to do the causality assessment, it will ask you, 'please, this is a mandatory field', you'll complete that one and then send it. You have a report. So, it is possible. But erh, how far we are, I am not sure. Yea, and any reporting system, should also be compatible with Vigiflow, with the Vigibase"
	Facility level involvement	*"The other thing, erh, drug and therapeutic committees, they should also be involved, in creating awareness, in analysing data, looking into event and trying to make, to come up with some kind of intervention and so on. So the therapeutic committee, should be involved."*
Advocacy	Insurance providers/ Private practice involvement	*"the private sector also needs to take part in this and that could work through insurance provider"*
	Patient reporting	*"Another area that we really need to do a lot of exploration is ahm, patient reporting. We currently don't have ahm, patient reporting system in Namibia"*
	Awareness	*"So my point here is to, in general, to create awareness for the doctors, nurses, pharmacists about the ADR, right, and about the importance of reporting"*
	Manufacturers/ Marketing Authorisation Holder	*"Erh, like I said, making sure that their product is safe, is the responsibility of the producer, the pharmaceutical company. So there is a need for them to do big chunk of the work, but there is a need for regulation as well because you can downplay some of the events, if they are not regulated"*
Systems-related ways of improving pharmacovigilance and ADR-reporting systems	Performance appraisal	*"For example, everyone being employed in government they need to be required to report adverse drug reactions, it needs to be part of the appraisal () of the healthcare worker"*

Table 2 (*Continued*)

Themes	Sub-themes	Quotes
	Competence	*"They should have the forms, they should have basic ideas on how, you know, maybe to do a mini analysis of what is happening before sending the report to TIPC, so that people, even in the facilities first hand, ahm, ahm, feedback from their coordinators of what collected from their facilities, so I will say it's not only you know, the relay of the reports to the central centre for it to be put in a database, is analysed from there"*
		"The facility, the team in facility, they should be able to make use of that data, the report"
	Insurance providers	*"Insurance providers needs to make it a requirement, for the healthcare worker to detect and report these adverse drug reactions and then through insurance service mechanisms they can see how ahh remittances to this kind of activities how it's made."*
	Electronic reporting	*"The future is going electronic, you know, there is no other alternative. So, erh, there is a need for us to prepare for electronic reporting system"*

Table 2 (*Continued*)

Themes	Sub-themes	Quotes
	HCW assurance of absolution from reprimand	*"I think it will be … also, I think as part of the enlightenment let people know that it's not going to affect their work, especially, when you shouldn't have given a particular medicine and you gave that medicine and there's an adverse medicine reaction, then the person is, ok I might be sanctioned, could it be anonymous?"*
		"I don't know how to put it now, department we are not sanctioning you because the patient reacted ok. Or now the HOD got to know then there is a, you know."
Training	Pre-registration curricula/Incorporating PV training into pre-service health professionals' curriculum	*"There is a very good reason why we need to monitor the safety of the product. So this should be incorporated into the graduate program in the pharmacology and the therapeutic, er, er, what do you call it, in the pharmacology curriculum [cleared his throat]. And when they come out, they should know that there is a need for reporting and there is a system for reporting. That is one."*
	In-service professional/ personal development	*"it goes beyond just having leaflets and banners, you know, we have to have probably, a midday event as well, where we talk about pharmacovigilance should be a theme for pharmacy week, times where we advocate for pharmacists to, as champions of pharmacovigilance, to encourage each other, healthcare workers to report."*

Table 2 (*Continued*)

Themes	Sub-themes	Quotes
	Data analysis at facility	*"they should have basic ideas on how, you know, maybe to do a mini analysis of what is happening before sending the report to TIPC, so that people, even in the facilities first hand, ahm, ahm, feedback from their coordinators of what collected from their facilities, so I will say it's not only you know, the relay of the reports to the central centre for it to be put in a database, is analysed from there"*

Table 2 (*Continued*)

Themes	Sub-themes	Quotes
Incentivisation	Feedback from TIPC	*"When somebody begins to see the impact of his work, then he's encouraged to do more. You know, either you get feedback, timely feedback to say ok based on the reports you made, these are the outcomes. That also is important. You get timely feedback to those that made those reports. It's also important"* *"I think it comes back to feedback still, uhm, intensified central level feedback, you know, to the facilities when they report, you know, we have the bulletin like what we used to have but the bulletin content should contain more of the scientific analysis, you know ahm, ahm, than the descriptive, you know ehm ehm feedback that is normally given."* *"For me, it's improving the awareness about ADR and the reporting system and give feedback, what happened after you have reported on these ADR for the doctors and for the nurses."*
	CPD points	*"Sure the CPD points can attract some of the doctors, nurses … … … …..also giving the feedback as I am saying, is considered to be a reward."*

Table 2 (*Continued*)

Themes	Sub-themes	Quotes
	Recognition at professional meetings	*"When the doctor will hear their name, that we got this from dr. who who at central hospital, or the next time, they know that it's valuable towards, when I sent it somebody looked at it and document it and send it on the next meeting. You know like, we all like to hear our names in the meetings. [Laughter]."*
Inclusive reporting	Integrated electronic reporting/Introducing electronic data capturing system/ Integrating	*"They don't think that it is their day to day activities. So that it the main, main challenge. So it needs to be integrated into the day to day activities, into the clinical practice, nothing else, patient care. If they see it as something else, it's totally wrong"*
Stakeholder engagement	Private sector/MAH engagement	*"you know because of erh, business, business principles, they may not be, or I can say, they can downplay the adverse events for the mere reason that they want to lose. It has to be regulated. But at the same time, they have to contribute a lot to the safety of their pharmaceutical product"*

Table 2 (*Continued*)

Themes	Sub-themes	Quotes
	Community enlightenment/ engagement	*"You know, devote like in a year, like twice in a year or so, you devote erh, you devote you say a week, adverse medicines reactions week. Just to create awareness, not only in the hospital even in the community. Let patients know, they have a right, not a right, a responsibility, you know to report. That even if the doctor is not reporting it, they too they will say I want to report what happened to me."* *"But increasingly we can go into the media, TV, radio. We have people talk about the subject, why is it important, why we should we document and send the reports."*

Theme 2: limited capacity and support for implementation of pharmacovigilance activities

It was suggested by one of the participants that limited capacities, including human and financial resources, at the TIPC did not allow for proper follow-up and coordination of pharmacovigilance activities within the country. This reportedly has an impact on the promotion of pharmacovigilance among healthcare workers as highlighted by the participants concerning the competence, willingness to report, and workload of medical doctors. It was further suggested that healthcare workers cannot appropriately identify ADRs or differentiate side-effects from ADRs, which undermines accurate reporting.

Theme 3: negative attitude of healthcare workers towards pharmacovigilance

Participants suggested resistance to change as a barrier to reporting. It was emphasised that after trainings there can be an increase in ADR reports, however, over time the number of reports decline which, according to participants, may be due to the way pharmacovigilance activities are being promoted currently.

Improving the pharmacovigilance and ADR-reporting systems dynamics

In relation to improving pharmacovigilance reporting, seven emergent themes were identified: (1) Systems-related ways of improving pharmacovigilance and ADR-reporting, (2) policy, (3) advocacy, (4) training, (5) incentives, (6) inclusive reporting, and (7) stakeholder engagement. (Table 2).

Theme 1: systems-related ways of improving pharmacovigilance and ADR-reporting systems

Participants identified making pharmacovigilance a national activity as part of the daily routine medical personnel attending to patients and linked to the performance appraisal of healthcare workers. Other reported ways of improving the system included the implementation of an electronic reporting system, constant feedback from TIPC, and integration of ADR reporting into the clinical work of healthcare workers.

Theme 2: policy

Establishment of policies addressing pharmacovigilance activities was suggested as a measure that can help in integrating the pharmacovigilance systems and, invariably, ADR reporting within the healthcare system.

Theme 3: advocacy

Participants reported that creating awareness of pharmacovigilance activities among healthcare workers and the community at large was a possible way to improve ADR reporting. Also, involvement of marketing authorisation holders (MAH) or holder of certificate of registration (HCR) of registered pharmaceutical products, medical aid insurance firms, initiating pharmacovigilance week or incorporating such into pharmacy week could be mechanisms to promote pharmacovigilance. Political will on the part of policy makers in embracing pharmacovigilance activities, was seen as a means to encourage healthcare workers.

Theme 4: training

Inclusion of pharmacovigilance into undergraduate healthcare trainees' curricula such as medicine, nursing, and pharmacy was identified as a way of optimising the system. Continuing Profession Development (CPD) or in-service training/lectures was suggested as another training avenue for healthcare workers.

Theme 5: incentivisation

Provision of feedback to healthcare workers individually and in a group setting such as pharmacy week was identified as a reporting incentive. Recognition of best performers in specific settings was deemed to be an incentive for healthcare workers to report identified ADRs. Another incentive identified by the participants was the provision of CPD credit as CPD is a requirement for practicing medical doctors, pharmacists and dentists, for example.

Theme 6: inclusive reporting

As there is no platform for patients to report ADRs in Namibia, provision of user-friendly ways such as the use of mobile phones and other digital platforms may be warranted.

Theme 7: stakeholder engagement

Involving the community through the provision of information on mass media such as national radio and television or through newspapers, and other avenues was mentioned as a way to create awareness and improve patient reporting. Marketing authorisation holders were believed to be vital in extending the frontiers of pharmacovigilance within the country, engaging such pharmaceutical companies and mandating them to liaise with the private practitioners/entities they serve was suggested as a way of improving the pharmacovigilance within the private healthcare sector in Namibia.

Discussion

A qualitative study of key informants was conducted among healthcare workers from different sectors within Namibia to explore the ways that challenges faced by healthcare workers with respect to integration of ADR reporting and pharmacovigilance with routine clinical practice can be mitigated with the focus of integrating pharmacovigilance activities into routine clinical practice. Challenges related to the pharmacovigilance centre included awareness of the system in place, feedback from the centre to healthcare workers, and training of healthcare workers. Provision of incentives, prompt and appropriate feedbacks from TIPC, pre-service training of healthcare workers on pharmacovigilance and CPD training have been identified as ways of bridging the gap of under-reporting of ADRs in our study[14,15]

Knowledge, diagnosis and reporting of suspected ADR by healthcare workers are some of the challenges contributing to the under-reporting of ADRs within the healthcare delivery system.[16] Workload and the amount of time needed to identify and report an ADR were suggested reasons for under-reporting, since healthcare workers want to 'move the queue'. Similar findings have been reported by some studies.[17,18] Lack of feedback contributes to under-reporting as reported in our study and this is similar to other studies carried out elsewhere.[19,20]

It is necessary for the Namibian government to take responsibility of the pharmacovigilance activities, thus providing the necessary political will that will drive the pharmacovigilance system itself. Electronic or digital reporting system incorporated into an Electronic Patient Monitoring System (EPMS) has been suggested as a way forward, though not doing away with the paper-based ADR reporting system currently in place.[20] This will enhance the submission of reports of suspected ADRs and it will reduce the duplication of medical records as it is today. Encouraging the Therapeutic Committees at different levels of the healthcare system, to take over pharmacovigilance activities within their setting will give more credence to the importance of ADR and ADR reporting in the country.

Although patient reporting seems a bit far-fetched in the Namibian context, educating the population about basic pharmacovigilance and the necessity for reporting whatever reaction occurred after the administration of a medicine will assist in strengthening the system and creating a knowledgeable population.[13,21] Also, an enabling environment is needed to achieve a workable patient-reporting system; this may be achieved through the introduction of a mobile telephonic system which may be at no cost to the reporter and feeds directly into the TIPC database.

The regulatory authority in conjunction with the MoHSS have to make a concerted effort in carrying the healthcare workers along with the pharmacovigilance issues, creating awareness and advocating for incorporating pharmacovigilance training into the pre-service curricula of healthcare professionals-in-training.[7]

Conclusion

Key informants from this study identified challenges facing the pharmacovigilance system in Namibia and suggested ways to mitigate the challenges so as to improve the system. The suggestions might be useful for the regulatory authority to enhance spontaneous ADR reporting and promote a culture of pharmacovigilance in the country. Also, integrating pharmacovigilance activities into the existing electronic patient monitoring and reporting system and routine clinical work of healthcare workers will minimise the loss of information, thus, improving the reporting of adverse events in general.

Compliance with ethical standards

Conflict of interest (COI) – BAA, DK, KDSB and TWR have no conflicts of interest that are directly relevant to the content of this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

BAA and TWR conceived and designed the study. BAA conducted the study, data collection and analysis. TWR and DK helped with the data analysis. TWR supervised the study. BAA, TWR and DK contributed to interpretation of results and writing the manuscript. BKDS reviewed the final manuscript. All authors approved the final version of the manuscript.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethical approval and consent to participate

Research ethics approvals were obtained from the Research and Ethics Division of the MoHSS (Reference No. 17/3/3) and Ethics Committee of the University of Namibia (Reference No. SOPHA/209/2017).

Acknowledgement

We wish to thank all the participants who took part in this study for their invaluable time and contributions.

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Appendix 9: Ethical Approval by the Ethics Committee of Ministry of Health and Social Services

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

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OFFICE OF THE PERMANENT SECRETARY

Ref: 17/3/3
Enquiries: Dr. H. Nangombe

Date: 28 April 2017

Mr. Adenuga B. Aderemi
University of Namibia
School of Pharmacy
Namibia

Dear Mr. Aderemi

Re: Safety, Tolerability and outcomes of Lopinavir/Ritonavir and Atzanavir/Ritonavir based second line regimens in Namibia

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

3.4 A quarterly report to be submitted to the Ministry's Research Unit.

3.5 Preliminary findings to be submitted upon completion of the study.

3.6 Final report to be submitted upon completion of the study.

3.7 Separate permission should be sought from the Ministry for the publication of the findings.

Yours sincerely,

Andreas Mwoombola (Dr)
Permanent Secretary

PERMANENT SECRETARY
MINISTRY OF HEALTH & SOCIAL SERVICES

"Health for All"

Appendix 10: Ethical Approval from the UREC, University of Namibia

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOPHA /209/2017 **Date: 24 April, 2017**

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: Safety, Tolerability and Outcomes of Atazanavir /Ritonavir and Lopinavir/Ritonavir Second Line Regimes in Namibia

Nature/Level of Project: Doctorate

Researcher: Adenuga Babafunso Aderemi

Student Number: 201301305

Faculty: School of Pharmacy

Supervisors: Prof. Timothy Rennie (Main) Dr. DKS Bamitale (Co)

Take note of the following:

(a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the UREC. An application to make amendments may be necessary.

(b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the UREC.

(c) The Principal Researcher must report issues of ethical compliance to the UREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by UREC.

(d) The UREC retains the right to:

(i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,

(ii) Request for an ethical compliance report at any point during the course of the research.

UREC wishes you the best in your research.

Prof. P. Odonkor: UREC Chairperson

Ms. P. Claassen: UREC Secretary

Appendix 11: Data collection tool

Knowledge, attitude, awareness and practices of public healthcare workers regarding Pharmacovigilance (PV) and Adverse Drug Reactions (ADR) reporting in Namibia

I invite you to complete the following questionnaire.

This is a part of the PhD contribution of Mr. Ademuga Babaflinzo Aderemi, a student at the School of Pharmacy, University of Namibia. The study seeks to know the reasons for under-reporting of adverse drug reactions and the factors associated with such reasons in Namibia. In particular, the researcher seeks to identify the reasons/determinants for non-reporting of ADRs associated with atazanavir/ritonavir and lopinavir/ritonavir based second line regimens. This research is undertaken to improve service delivery in Namibia.

This questionnaire is anonymous and no personal information will be collected that can be used to identify you. We hope to report the findings of this research nationally and internationally and if you wish to follow up on the findings of the study you can contact the researcher via the email below.

Completed questionnaires can be mailed to: ademuga11@gmail.com or P.O. Box 99551, Windhoek, Namibia. You can call me at +264818659993 for any enquiry concerning this questionnaire.

Section I: Demographics

1. Age (years): .....
2. Gender (Tick the correct response)

☐ Male

☐ Female

3. What is/are your registered qualification(s) in Namibia? (Tick the correct response(s))

☐ Medical specialist

☐ Medical doctor

☐ Medical House officer

☐ Dental Surgeon

☐ Intern Dental Surgeon

☐ Registered nurse

☐ Midwife

☐ Enrolled nurse

☐ Pharmacist

☐ Pharmacist Intern

☐ Pharmacist Technician

☐ Pharmacist Specialist

☐ Pharmacist assistant

☐ Allied Health Practitioner. Other .....

4. Number of years of experience: .....

5. What is the type of facility you are currently working in?

☐ Clinic
☐ Health center
☐ Intermediate hospital
☐ District hospital
☐ National Referral hospital
☐ Other.

Section II: Public health workers' knowledge about Pharmacovigilance/Adverse Drug Reaction reporting

1. Which of the following BEST defines Pharmacovigilance? (Tick the correct answer(s))

i. The science and activities of detecting, assessing, understanding & preventing adverse effects.

ii. The science of detecting the type & incidence of Adverse Drug Reactions after a drug is marketed.

iii. The process of improving the safety of drugs

iv. The science of monitoring Adverse Drug Reactions happening in a Hospital

v. Don't know

2. The purpose of Pharmacovigilance is (Tick the correct answer(s))

i. To enhance patients' safety in relation to use of drugs

ii. To identify predisposing factors to Adverse Drug Reactions

iii. To identify unrecognized Adverse Drug Reactions

iv. To calculate incidence of Adverse Drug Reactions

v. Don't know

3. Which of the following defines an Adverse Drug Reactions correctly? (Tick the correct answer(s))

i. Any noxious/harmful or undesired effect of a drug occurring at normal doses, during normal use

ii. Adverse health outcomes associated with inappropriate drug use

iii. Harm resulting from the use of substandard/counterfeit drugs

iv. Harm caused by drug overdose

v. Adverse outcomes associated with drug impurity

vi. Other health problems associated with drug use

vii. Don't know

4. Which Adverse Drug Reactions should be reported? (Tick the appropriate answer(s))

i. All serious Adverse Drug Reactions

ii. Adverse Drug Reactions to herbal and non-allopathic drugs

iii. Adverse Drug Reactions to new drugs

iv. Adverse Drug Reactions to vaccines

v. Unknown Adverse Drug Reactions to old drugs

vi. All of the above

vii. Don't know

5. Do you know about the adverse drug reactions (ADRs) reporting and monitoring system (National Pharmacovigilance Centre) in Namibia? (Tick the correct answer)

- ☐ Yes
- ☐ No
- ☐ Don't know

Section III: Attitude of health workers to Pharmacovigilance and Adverse Drug Reactions reporting

1. Adverse Drug Reactions reporting is necessary.

- ☐ Strongly agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly disagree

2. Adverse Drug Reactions reporting is a professional obligation

- ☐ Strongly agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly disagree

3. Adverse Drugs Reactions reporting should be voluntary

- ☐ Strongly agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly disagree

4. Adverse Drug Reactions reporting should be compulsory

- ☐ Strongly agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly disagree

5. Adverse Drug Reactions reporting should be remunerated or offered incentives

- ☐ Strongly agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly disagree

6. Inclination or urge to report an event

Question	Strongly agree	Agree	Neutral	Disagree	Strongly disagree

I would report an instance where a patient had an adverse reaction to a new drug					
I would report a serious event					
I would report an unusual event experienced by a patient					
I would report a well recognised adverse drug reaction of a drug					

7. What are the discouraging factors from reporting Adverse Drug Reaction? (Tick the appropriate response)

Strongly agree – 5, Agree – 4, Neutral – 3, Disagree – 2 and strongly disagree - 1

Factor	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I would not report an event out of concern that the report may be wrong					
I do not know how to report					
I do not know where to report					

I do not know when to report					
I do not have enough time to fill in a report					
I think a single unreported case may not affect Adverse Drug Reaction database					
There are no incentives for reporting					
I have no concern that reporting may generate extra work for me					
I do not have time to actively look for ADRs while at work					
My level of clinical knowledge makes it difficult to decide whether or not an Adverse Drug Reaction has occurred					
I do not have confidence to discuss the Adverse Drug Reaction I identified with other colleagues					

Section IV: Awareness of Pharmacovigilance and Adverse Drug Reactions reporting systems

1. Can you identify the office responsible for Pharmacovigilance monitoring and Adverse Drug Reactions reports collation in Namibia? Tick the correct answer.

- ☐ Ministry of Health and Social Services
- ☐ Therapeutics Information and Pharmacovigilance Center
- ☐ Central Medical Stores
- ☐ National Medicine Policy Coordination

2. Who should report Adverse Drug Reactions? (Tick the correct answer(s))

   a. Medical doctor

   b. Registered Nurse

   c. Enrolled Nurse

   d. Pharmacist

   e. Pharmacist assistant

   f. Other healthcare workers

   g. Patients

   h. All of the above

   i. I am not sure

Section V: Practice of Pharmacovigilance and Adverse Drugs Reactions reporting

1. Have you attended Pharmacovigilance training before? (Tick the correct answer)

- ☐ Yes
- ☐ No
- ☐ Don't know

2. Have you reported any suspected adverse drug reactions to any of the Adverse Drug Reactions reporting and monitoring centres? Tick the correct answer.

- ☐ Yes
- ☐ No
- ☐ Don't know

3. Did you report any suspected adverse drug reactions to ADR reporting and monitoring system existing at your hospital? Tick the correct response.

- ☐ Yes
- ☐ No
- ☐ Don't know

4. Would you report any of these adverse drug reactions that may be due to atazanavir/ritonavir? (Tick the correct response(s))

- ☐ Jaundice
- ☐ Nausea
- ☐ Diarrhoea
- ☐ Chronic kidney disease
- ☐ All of the above

5. Would you report any of these adverse drug reactions that may be due to lopinavir/ritonavir? (Tick the correct response(s))

- ☐ Diarrhoea
- ☐ Nausea
- ☐ Vomiting
- ☐ Hypertriglyceridaemia
- ☐ Hypercholesterolemia
- ☐ All of the above

Miscellaneous

What other ways would you propose/suggest to improve Adverse Drug Reactions reporting and Pharmacovigilance system in Namibia?

Any other comments you might have: ….

Thank you for completing this questionnaire!

Appendix 12: Consent form for KAP study (Study 2)

INFORMED CONSENT

Introduction and Purpose:

My name is Adenuga Babafunso Aderemi. I am a PhD candidate at the School of Pharmacy, University of Namibia. I am hereby inviting you to participate in my research study. The study seeks to know the reasons for under-reporting of adverse drug reactions (ADR) by healthcare workers and the factors associated with such reasons in Namibia. This research is undertaken to improve healthcare service delivery in Namibia.

The findings from the study will document the current knowledge, attitude and practices, highlight the gaps in practice (if any) and provide necessary background to design appropriate recommendations expected to improve pharmacovigilance in Namibia. This questionnaire is anonymous and no personal information will be collected that can be used to identify you. We hope to report the findings of this research nationally and internationally and if you wish to follow up on the findings of the study you can contact the researcher via the email below.

Procedures:

Please answer the following questions about your knowledge, attitudes and practice of pharmacovigilance and ADR reporting in the spaces provided. Your genuine responses will be greatly appreciated. Your participation is absolutely voluntary and there is no penalty for refusing to take part.

Confidentiality:

All information recorded will be kept strictly confidential; your name and address will not be used and you will not be identified in any way, they shall remain anonymous.

Risks/discomfort and Benefits:

There is no serious risk to you if you agree to participate in this survey activity. I want to assure you that all information collected will be kept confidential. This study will help the Ministry of Health and Social Services to better understand the current state of pharmacovigilance among healthcare workers and thus, be able to develop policies to mitigate the gaps in service delivery.

Persons to contact:

If you have any questions you would like to ask about the purpose or procedure of this questionnaire, I can be contacted on the following number: 081 865 9993

Are you able to proceed with the questionnaire? Yes _____ No_____

Sign _____ Date _____ /_____/2018

Please Contact me for any further question
Mr. Adenuga Babafunso A. (Principle Investigator)
Email: adenuga11@gmail.com
Box 99551, Windhoek, Namibia.
Mobile: +264 81 865 9993

Appendix 13: Consent form for key informants (Study 3)

INFORMED CONSENT

Introduction and Purpose:

My name is Adenuga Babafunso Aderemi. I am a PhD candidate at the School of Pharmacy, University of Namibia. I am hereby inviting you to participate in my research study. The study seeks to know the reasons for under-reporting of adverse drug reactions (ADR) by healthcare workers and the factors associated with such reasons in Namibia. This research is undertaken to improve healthcare service delivery in Namibia.

The findings from the study will document the current knowledge, attitude and practices, highlight the gaps in practice (if any) and provide necessary background to design appropriate recommendations expected to improve pharmacovigilance in Namibia. This interview is anonymous and no personal information will be collected that can be used to identify you. We hope to report the findings of this research nationally and internationally and if you wish to follow up on the findings of the study you can contact the researcher via the email below.

Procedures:

Please answer the following questions about the current state of pharmacovigilance and ADR reporting system in Namibia. Your genuine responses will be greatly appreciated. Your participation is absolutely voluntary and there is no penalty for refusing to take part.

Confidentiality:

All information recorded will be kept strictly confidential; your name and address will not be used and you will not be identified in any way, they shall remain anonymous.

Risks/discomfort and Benefits:

There is no serious risk to you if you agree to participate in this survey activity. I want to assure you that all information collected will be kept confidential. This study will help the Ministry of Health and Social Services to better understand the current state of pharmacovigilance among healthcare workers and thus, be able to develop policies to mitigate the gaps in service delivery.

Persons to contact:

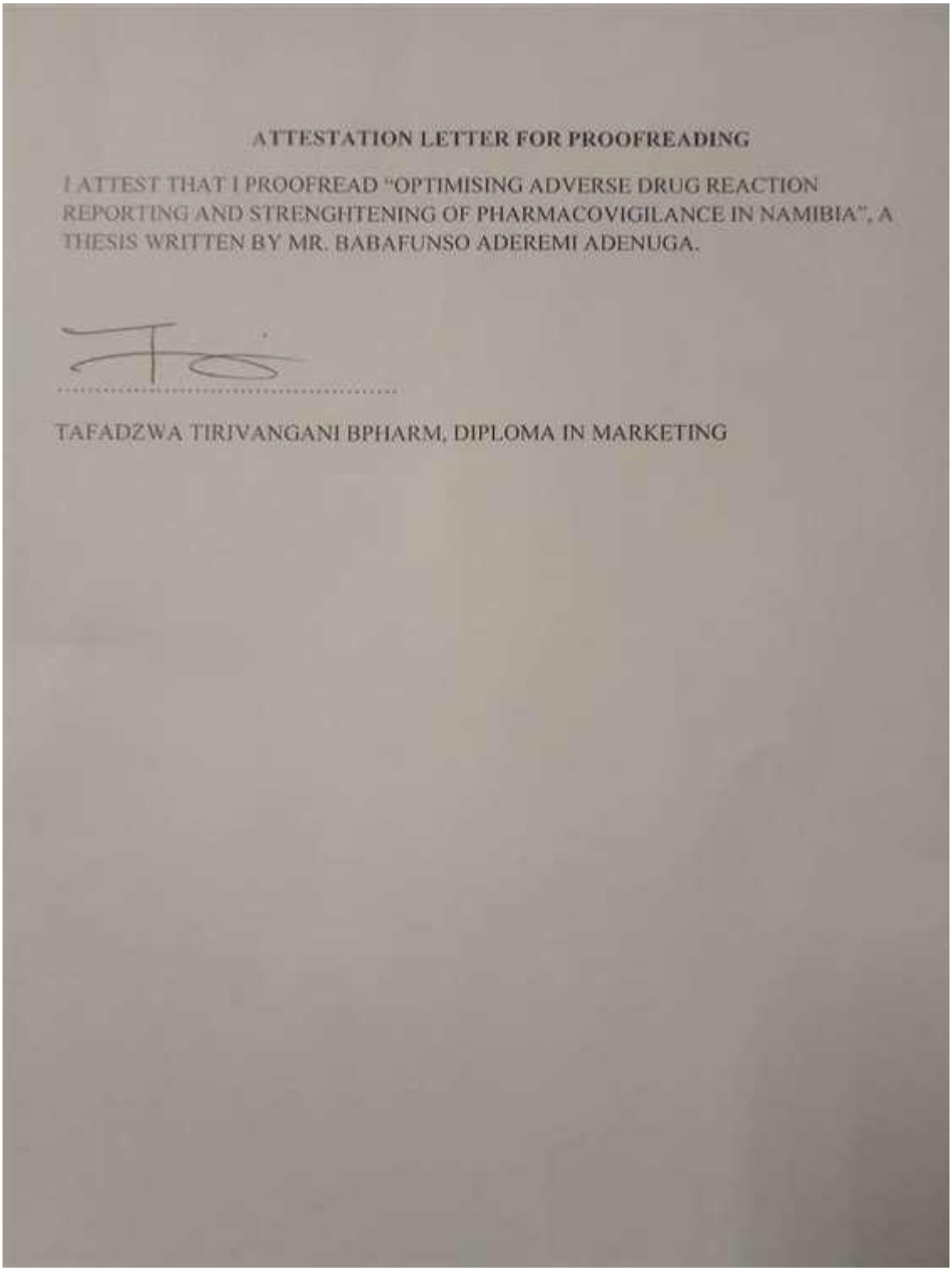
If you have any questions you would like to ask about the purpose or procedure of this questionnaire, I can be contacted on the following number: 081 865 9993

Are you able to proceed with the questionnaire? Yes _____ No_____

Please Contact me for any further question

Mr. Adenuga Babafunso A. (Principle Investigator)
Email: adenuga11@gmail.com
Box 99551, Windhoek, Namibia.
Mobile: +264 81 865 9993

Appendix 14: Attestation letter for proofreading



ATTESTATION LETTER FOR PROOFREADING

I ATTEST THAT I PROOFREAD "OPTIMISING ADVERSE DRUG REACTION REPORTING AND STRENGHTENING OF PHARMACOVIGILANCE IN NAMIBIA", A THESIS WRITTEN BY MR. BABAFUNSO ADEREMI ADENUGA.

.....

TAFADZWA TIRIVANGANI BPHARM, DIPLOMA IN MARKETING