

# Awareness of pharmacovigilance and experience with reporting of adverse drug events by adults in South Africa

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Pharmacy Practice with Pharmacovigilance and  
Pharmacoepidemiology at the North-West University

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Examination: November 2023

# DECLARATION

## DECLARATION

I, Nokukhanya Ncube, hereby declare that the dissertation entitled: Awareness of pharmacovigilance and experience with reporting of adverse drug events by adults in South Africa, which I herewith submit to the North-West University in fulfilment with the requirements set for the degree Master of Pharmacy in Pharmacy Practice with Pharmacovigilance and Pharmacoepidemiology, is my own work, has been language edited and has not been submitted to any other university.

Nokukhanya Ncube  
  
Signature

Nokukhanya Ncube

44459564

## **DEDICATION**

In loving remembrance of my late father Lawrence Paundi Mkhabela, my late sister Nombuso Ngwane, my late maternal grandparents Nomhlangano and Dabula Ngwane and my late paternal grandparents Gertrude and Alpheus Mkhabela, who all believed in the importance of education, and who, I'm sure, would have been pleased to see me achieve academic success.

## PREFACE

This research dissertation was written in article format according to the standards provided by the North-West University (NWU).

The dissertation is presented in four chapters. Chapter 1 presents the study's background, aims and objectives as well as the research methods used to conduct the study. Chapter 2 presents a comprehensive literature review which focuses on describing what is known about pharmacovigilance, including attitudes, practices, and experiences of medicine users with ADE reporting, as well as the barriers and enablers that affect ADE reporting globally. Chapter 3 contains the results of the empirical study, presented as two manuscripts that answer the empirical objectives of the study. The two manuscripts will be submitted for peer review and possible publishing in two journals: *Pharmacoepidemiology and Drug Safety*, and *BMC Public Health*. The two manuscripts were prepared according to the author guidelines of the respective journals (included in Annexures E and F). The final chapter concludes this study, providing future recommendation,s and discusses the study's strengths and limitations.

The reference list contains all the references used in this dissertation and is presented according to the NWU Harvard referencing style as stipulated by the NWU. The reference list in both manuscripts has been prepared according to the journal's reference style as specified in the author guidelines for the selected journal (included in Annexures E and F).

The layout of the dissertation is as follows:

Chapter 1: Introduction and study overview

Chapter 2: Literature review

Chapter 3: Results and discussion

Chapter 4: Conclusions, strengths, limitations and recommendations

Reference list and annexures follow after Chapter 4.

The co-authors of the two manuscripts were the supervisor and co-supervisors of this study and they revised and approved the final manuscripts before submission for examination. The roles of each author are outlined in Chapter 3.

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My gratitude also extends to my friends, whose unwavering encouragement and support have helped me get through some of my hardest moments.

Above all, I give thanks to the Lord for his love, protection and guidance.

## **ABSTRACT**

**Study title: Awareness of pharmacovigilance and experience with reporting of adverse drug events by adults in South Africa**

### **Background:**

Individuals who use medication have first-hand knowledge of their experiences with adverse drug events (ADEs); however, under-reporting of ADEs has been identified as a leading shortcoming of pharmacovigilance programmes in South Africa and around the world. When patients are encouraged to report ADEs, it is more likely that the events that could influence medicine usage or result in injury are quickly identified and managed appropriately. It is important to understand the experiences of consumers, the enablers, and the barriers they encounter when reporting ADEs, to improve ADE reporting in South Africa.

### **Objective:**

The aim of this study was to explore adults' awareness of pharmacovigilance and ADEs, attitudes regarding their perceived role in reporting ADEs, and the practice of and experience with ADEs reporting in South Africa. In accordance with the study's aim, the first objective was to assess adults' awareness about pharmacovigilance, ADEs and attitudes regarding their perceived role in reporting ADEs in South Africa, and the second objective was to describe adults' practices and previous experience with reporting ADEs, including the barriers and enablers to reporting ADEs in South Africa

### **Methods:**

For this study, a cross-sectional, quantitative, analytical design was used. Data were collected using an online study questionnaire which contained 32 questions arranged in five sections as follows: Section A: Socio-demographic information; Section B: Awareness of adverse drug events; Section C: Attitudes regarding adverse drug events and adverse drug events reporting; Section D: Practices and experience with reporting adverse drug events; Section E: Barriers to reporting adverse drug events. Participants were recruited via a news article published on the 18th of April 2023 on the News24 online platform in English, translated to Afrikaans and published on Netwerk24. The article contained a link that directed readers to SurveyMonkey® to complete the survey. The survey was launched on 18th of April 2023 and data were collected until 18th of June 2023. The data obtained was analysed using both descriptive and inferential statistics.

## Results:

The first objective of this study was addressed in manuscript 1. The majority of participants (86.2%,  $n = 302$ ;  $N = 350$ ) had heard about ADEs and most (94.8%,  $n = 276$ ;  $N = 291$ ) knew that ADEs can affect people of any age. Participants knew that ADEs had to be reported (87.4%,  $n = 264$ ;  $N = 302$ ) and 84.9% ( $n = 247$ ;  $N = 291$ ) correctly indicated that anyone can report ADEs. Most participants (94.4%,  $n = 301$ ;  $N = 319$ ) indicated that reporting of ADEs was important. For non-healthcare professionals (non-HCPs) and healthcare professionals (HCPs) this importance was related to ensuring that the healthcare professional is made aware of what the medicine has caused, avoiding the repeat of the reaction in other people and ensuring that the report reaches the medicine's manufacturer. Less than one in five respondents knew about the Med Safety App, (17.3%,  $n = 58$ ;  $N = 336$ ) while the South African Health Products Regulatory Authority (SAHPRA) was well known (77.4%,  $n = 260$ ;  $N = 336$ ). Healthcare providers only educated 55.7% ( $n = 180$ ;  $N = 323$ ) of the participants about ADEs and only 50.5% ( $n = 163$ ;  $N = 323$ ) of the participants asked the healthcare providers about ADEs.

The second objective of this study was addressed in manuscript 2. The majority of participants (70.5%  $n = 203$ ;  $N = 288$ ) indicated they had experienced ADEs in the past and 77.0% ( $n = 181$ ;  $N = 235$ ) of these events occurred after the use of medication. Only 59.1% ( $n = 120$ ;  $N = 203$ ) of participants who experienced ADEs reported them. In terms of reporting frequencies there were no discernible variations between the HCP and non-HCPs ( $p > 0.9$ ); furthermore 78.3% ( $n = 94$ ;  $N = 120$ ) reported these ADEs to their doctor.

As indicated by both HCP and non-HCPs, the three main enablers for reporting ADES were that reporting could help to keep others safe, being worried about what was happening and wanting to share their experience. The most cited barrier to ADE reporting for both HCP and non-HCPs was assuming that once the medication was stopped, the side effects would go away and reading from the medicine leaflet that the event they had was a side effect. The third most cited barrier for non-HCPs was lack of knowledge on where to report ADEs, whereas HCPs indicated that it was the belief that all medications have side effects so it is not necessary to report .

**Conclusion:**

The results of this study indicate that there is awareness regarding ADEs and ADE reporting among adult South Africans. Healthcare professionals were more aware regarding this aspect than non-HCPs. There is a positive attitude regarding the reporting of ADEs with participants agreeing on the importance of reporting ADEs. High reporting rates for ADEs were observed among participants, and doctors were the preferred recipients of these reports. This study found that HCP acted similarly to non-HCPs when they are users of medicine, with the same percentages of each group reporting ADEs and similar reasons for doing so. We identified several barriers to reporting, and one of them is awareness of the anticipated ADEs. The optimistic outlook seen in this study should be leveraged to support initiatives that encourage the reporting of ADEs in South Africa. Both HCPs and non-HCPs must be the target of these activities. To ensure that awareness-raising campaigns aimed at enhancing ADE reporting in South Africa are successful, the information on the barriers and facilitators to reporting ADEs presented in this study can be used.

**Key terms:** Adverse drug events, awareness, experience, pharmacovigilance

## AUTHORS' CONTRIBUTION TO MANUSCRIPT 1

The contributions of each of the authors to manuscript 1, Awareness and attitudes regarding adverse drug events and reporting in South Africa, were as follows:

Author	Role in the study
Ms N Ncube (Researcher)	Concept of research Interpretation of results Manuscript planning, design and writing Writing up of results
Prof NV Motaze (Supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript and final approval
Prof MS Lubbe (Co-supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript and final approval
Mrs H Steyn (Co-supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript and final approval

The following statement provided by the co-authors confirms their roles in the study and sanctions the inclusion of the manuscripts in the dissertation.

*I declare that I have approved the above-mentioned manuscripts and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of N Ncube.*

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## AUTHORS' CONTRIBUTION TO MANUSCRIPT 2

The contributions of each of the authors to manuscript 2, Barriers and enablers of adverse drug event reporting in South Africa: a cross-sectional survey of medicine users, were as follows:

Author	Role in the study
Ms N Ncube (Researcher)	Concept of research Interpretation of results Manuscript planning, design and writing Writing up of results
Prof NV Motaze (Supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript and final approval
Prof MS Lubbe (Co-supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript and final approval
Mrs H Steyn (Co-supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript and final approval

The following statement provided by the co-authors confirms their roles in the study and sanctions the inclusion of the manuscripts in the dissertation.

*I declare that I have approved the above-mentioned manuscripts and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of N Ncube.*

  
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## LIST OF DEFINITIONS

Adult	In the context of this study, adult refers to any person who is 18 years or older
Adverse drug event (ADE)	<p>An ADE is any untoward medical occurrence that may present during treatment with a medicine, but does not necessarily have a causal relationship with this treatment. An ADE can be any unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicine, whether considered related to the medicine or not (SAHPRA, 2022c:4).</p> <p>For the purposes of this study, ADEs are incidents connected to the use of medicine, whether prescribed or purchased without a prescription, a vaccine, or a medical device.</p>
Adverse drug reaction (ADR)	<p>“An adverse drug reaction (ADR) is a noxious and unintended response to a medicine, including lack of efficacy, and which occurs at doses normally used in man and which can also result from overdose, misuse or abuse of a medicine. The reaction may be a known side effect of the medicine, or it may be new and previously unrecognised. An ADR can be caused by any therapeutic agent, including prescribed, over-the-counter (OTC) medicines and vaccines” (SAHPRA, 2022c:4)</p> <p>“A reaction, contrary to an event, is characterised by the occurrence of a suspected causal relationship between the medicine and the reaction, as determined by the reporter” (SAHPRA, 2022c:4).</p>
Adverse effect	“An adverse effect is a negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all” (SAHPRA, 2022c:4)
Adverse event(s) following immunisation (AEFI)	“An AEFI is defined as any untoward medical occurrence which follows immunisation; does not necessarily have a causal relationship with the usage of the vaccine; may be any unfavourable symptom about which a vaccine recipient complains; and may be an abnormal laboratory finding, sign or disease found by medical staff” (SAHPRA, 2022c:4)
Attitudes	In this study, attitudes refer to a line of thinking, belief systems, and personal convictions about pharmacovigilance, ADEs, and reporting of ADEs.

Prior experience	In the context of this study, prior experience refers to what participants or the people they care for, have personally experienced during the reporting of adverse drug events in the past, as well as any barriers or enablers that they encountered.
Healthcare professional (HCP)	A person who is qualified and trained to provide healthcare to humans. This includes doctors, nurses, dentists, pharmacists, midwives, and any medically qualified persons otherwise specified by local regulations (CIOMS, 2021:26).
Knowledge	Knowledge refers to information that is comprehensive and fact-based to varying degrees. In contrast, awareness refers to personally relevant information (Trevethan, 2017:1). This study uses knowledge and awareness interchangeably to refer to what is known or perceived through any means of gaining insight.
Medicine user	In this study, a medicine user is any person who has used medicines to treat or prevent a health condition, or who has administered medications to those they care for. Therefore, this study uses the terms patients, consumers and medicine users interchangeably
Pharmacovigilance	Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine-related problem (WHO, 2023c)
Practices	In the context of this study, practices refer to actions taken in relation to pharmacovigilance, ADEs, and reporting of ADEs.

## LIST OF ABBREVIATIONS

ADE (ADEs)	Adverse drug event (Adverse drug events)
ADR	Adverse drug reaction
AEFI	Adverse events following immunisation
APP	Application
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease of 2019
EBSCO	Elton B. Stephens Company
HCP (HCPs)	Healthcare professional (Healthcare professionals)
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IP	Internet protocol
MCC	Medicines Control Council
ME	Medication errors
MUSA	Medicine Usage in South Africa
NADEMC	National Adverse Drug Events Monitoring Centre
NDoH	National Department of Health
NMRA	National Medicines Regulatory Authority
NWU-HREC	North-West University Health Research Ethics Committee
NWU	North-West University
OTC	Over the counter

PADR	Preventable adverse drug reactions
PV	Pharmacovigilance
SAHPRA	South African Health Products Regulatory Authority
UK	United Kingdom
UMC	Uppsala Monitoring Centre
USA	United States of America
WHO	World Health Organization
WHO PIDM	WHO Programme for International Drug Monitoring

# TABLE OF CONTENTS

<b>CHAPTER 1</b>	<b>INTRODUCTION AND STUDY OVERVIEW</b>	<b>1</b>
<b>1.1</b>	<b>Introduction</b>	<b>1</b>
<b>1.2</b>	<b>Background</b>	<b>1</b>
<b>1.3</b>	<b>Problem statement</b>	<b>4</b>
<b>1.4</b>	<b>Research aim and objectives</b>	<b>5</b>
1.4.1	Research aim	5
1.4.2	Specific research objectives	5
1.4.2.1	Literature review	5
1.4.2.2	Empirical investigation	5
<b>1.5</b>	<b>Research methodology</b>	<b>6</b>
1.5.1	Literature review	6
1.5.2	Empirical investigation	7
1.5.2.1	Study setting	7
1.5.2.2	Target population	7
1.5.2.3	Study design	8
<b>1.6</b>	<b>Data source</b>	<b>8</b>
1.6.1	Data collection	8
1.6.1.1	Recruitment of participants	9
1.6.1.2	Data collection tool	9
1.6.1.3	Data collection process	11
<b>1.7</b>	<b>Statistical analysis</b>	<b>12</b>

<b>1.8</b>	<b>Ethical considerations .....</b>	<b>16</b>
1.8.1	Anticipated risks and precautions .....	17
1.8.1.1	Anticipated risks to the participants and precautions taken .....	17
1.8.1.2	Anticipated risks to the researcher and the precautions taken .....	17
1.8.2	Data management .....	18
1.8.2.1	Data management during the study .....	18
1.8.2.2	Data management after completion of the study .....	18
1.8.3	Conflict of interest .....	19
<b>1.9</b>	<b>Chapter summary .....</b>	<b>19</b>
 <b>CHAPTER 2 LITERATURE REVIEW .....</b>		<b>20</b>
<b>2.1</b>	<b>Introduction .....</b>	<b>20</b>
<b>2.2</b>	<b>Key pharmacovigilance organisations.....</b>	<b>20</b>
2.2.1	South African Health Products Regulatory Authority (SAHPRA) .....	20
2.2.2	Council for International Organizations of Medical Sciences (CIOMS) .....	21
2.2.3	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) .....	21
2.2.4	World Health Organization (WHO) .....	21
<b>2.2.5</b>	<b>Uppsala Monitoring Centre (UMC).....</b>	<b>22</b>
<b>2.3</b>	<b>Definitions.....</b>	<b>22</b>
2.3.1	Pharmacovigilance .....	22
2.3.2	Adverse drug event (ADE) and adverse drug reaction (ADR) .....	23
2.3.3	The connection between ADE and ADR .....	24

2.3.4	Spontaneous reporting .....	24
2.3.5	Active surveillance .....	24
<b>2.4</b>	<b>Pharmacovigilance and experiences with adverse drug event reporting.....</b>	<b>25</b>
2.4.1	History of pharmacovigilance.....	25
2.4.2	Aim of pharmacovigilance.....	25
2.4.3	Pharmacovigilance cycle .....	26
2.4.4	Pharmacovigilance systems .....	27
2.4.5	Spontaneous reporting in pharmacovigilance .....	29
2.4.6	Consumer reporting in pharmacovigilance.....	30
2.4.7	Importance of consumer involvement .....	31
<b>2.5</b>	<b>Attitudes and practices of consumers regarding ADE reporting.....</b>	<b>33</b>
2.5.1	Awareness, attitudes and practices. ....	33
2.5.1.1	Consumer awareness.....	35
2.5.1.2	Consumer attitudes and practice regarding ADEs and ADE reporting .....	36
2.5.2	Healthcare Professional (HCP) awareness and attitudes towards ADE reporting .....	37
2.5.3	Influence of severity of ADE on consumer reporting of ADEs .....	38
<b>2.6</b>	<b>Barriers and enablers of adverse drug event reporting.....</b>	<b>38</b>
2.6.1	Barriers to adverse drug event reporting.....	40
2.6.1.1	Lack of awareness.....	40
2.6.1.2	Reporting processes that are difficult to follow .....	41
2.6.1.3	The expectation that ADEs will resolve .....	41

2.6.1.4	Apprehension of harmful consequences from HCP .....	41
2.6.2	Enablers of adverse drug event reporting .....	42
2.6.2.1	Noble motives.....	42
2.6.2.2	Severity of ADE .....	42
<b>2.7</b>	<b>Regulatory requirements for ADE reporting in South Africa.....</b>	<b>43</b>
2.7.1	WHO Programme for International Drug Monitoring (WHO PIDM).....	43
2.7.2	Legislation in South Africa .....	44
2.7.3	Oversight of pharmaceutical industry.....	45
2.7.4	Tools for reporting ADEs in South Africa.....	46
<b>2.8</b>	<b>Chapter Summary.....</b>	<b>47</b>
<b>CHAPTER 3 RESULTS AND DISCUSSION .....</b>		<b>49</b>
<b>3.1</b>	<b>Manuscript 1 .....</b>	<b>52</b>
<b>3.2</b>	<b>Manuscript 2 .....</b>	<b>76</b>
<b>3.3</b>	<b>Chapter summary .....</b>	<b>98</b>
<b>CHAPTER 4 CONCLUSIONS, STRENGTHS, LIMITATIONS AND RECOMMENDATIONS .....</b>		<b>99</b>
<b>4.1</b>	<b>Introduction .....</b>	<b>99</b>
<b>4.2</b>	<b>Study outline.....</b>	<b>99</b>
<b>4.3</b>	<b>Study conclusion.....</b>	<b>99</b>
4.3.1	Literature review conclusions.....	100
4.3.1.1	Objective 1: What is currently known about pharmacovigilance and experiences with ADE reporting by users of medicines globally?.....	100

4.3.1.2	Objective 2: Attitudes and practices of medicine users regarding ADE reporting .....	101
4.3.1.3	Objective 3: Barriers and enablers that affect ADE reporting globally .....	102
4.3.1.4	Objective 4: Regulatory requirements for ADE reporting in South Africa and how they support ADE reporting .....	104
4.3.2	Conclusions following empirical investigation .....	105
4.3.2.1	Objective 1: Assess adults' awareness about pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa .....	105
4.3.2.2	Objective 2: Describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa.....	106
<b>4.4</b>	<b>Study limitations.....</b>	<b>107</b>
<b>4.5</b>	<b>Recommendations.....</b>	<b>108</b>
<b>4.6</b>	<b>Chapter summary .....</b>	<b>108</b>

**LIST OF TABLES**

Table 1-1: Inclusion criteria ..... 8

Table 1-2: Exclusion criteria ..... 8

Table 1-3: Articles used to develop the questionnaire ..... 10

Table 1-4: Summary of data analysis ..... 13

Table 1-5: Anticipated risks to participants and precautions taken..... 17

Table 1-6: Anticipated risks to the researcher and the precautions taken ..... 17

Table 2-1: PV Cycle, stages and associated actions ..... 26

Table 2-2: Characteristics of included studies ..... 34

Table 2-3: Studies used to determine barriers and enablers..... 39

Table 2-4: WHO PIDM criteria ..... 44

Table 2-5: Tools for ADE reporting in South Africa ..... 46

Table 3-1: Manuscript details..... 50

**LIST OF FIGURES**

Figure 1-1: Top 10 most frequently reported AEFIs, 17 May 2021-18 March 2022 ..... 3

Figure 2-1: Professional groups or associations and their functions ..... 28

# CHAPTER 1 INTRODUCTION AND STUDY OVERVIEW

## 1.1 Introduction

Individuals who use medications have first-hand knowledge of their experiences with adverse drug events (ADE); however, under-reporting of ADEs has been identified as a leading shortcoming of pharmacovigilance programmes in South Africa and around the world (Pillay *et al.*, 2021:2). This study focussed on adults' awareness of ADEs and their experiences in reporting ADEs related to the use of a medicine, whether prescribed or purchased without a prescription, a vaccine, or a medical device in South Africa.

The background of the study, the problem statement, the research aim and objectives, the research methodology, the ethical considerations, and the limitations are presented in this chapter.

## 1.2 Background

The World Health Organization (WHO) estimates that patient harm due to ADEs is one of the top ten causes of death and disability in the world (WHO, 2019). Furthermore, involving patients and families is one of the key strategic areas that should be prioritised to improve patient safety (WHO, 2019). According to Smith and Benattia (2016:782), regulatory authorities worldwide increasingly recognise the importance of acquiring the patient perspective on pharmaceutical products' benefit-risk profile.

Joubert and Naidoo (2016:239) emphasised spontaneous ADE reporting as the most frequently used method of medicine monitoring globally, with the main limitation of this method of reporting being a failure to do so by affected parties, as reporting is often voluntary and without compensation. Alomar *et al.* (2020:5) attribute this underreporting of cases to, among other things, a low level of awareness about pharmacovigilance, a lack of understanding of what constitutes an adverse drug event, and a lack of understanding of the actionable information.

The most basic form of pharmacovigilance is spontaneous reporting systems that gather information on adverse effects of drugs after they have been approved for use (Jones *et al.*, 2020:1226). The biggest constraint of spontaneous reporting, according to (Varallo *et al.*, 2014:740), is underreporting. They estimate that only around 5% to 10% of ADEs are reported.

According to Regulation 40 of the Medicines and Related Substances Act 101 of 1965 as amended, a healthcare provider, veterinarian or any other person should notify the South African

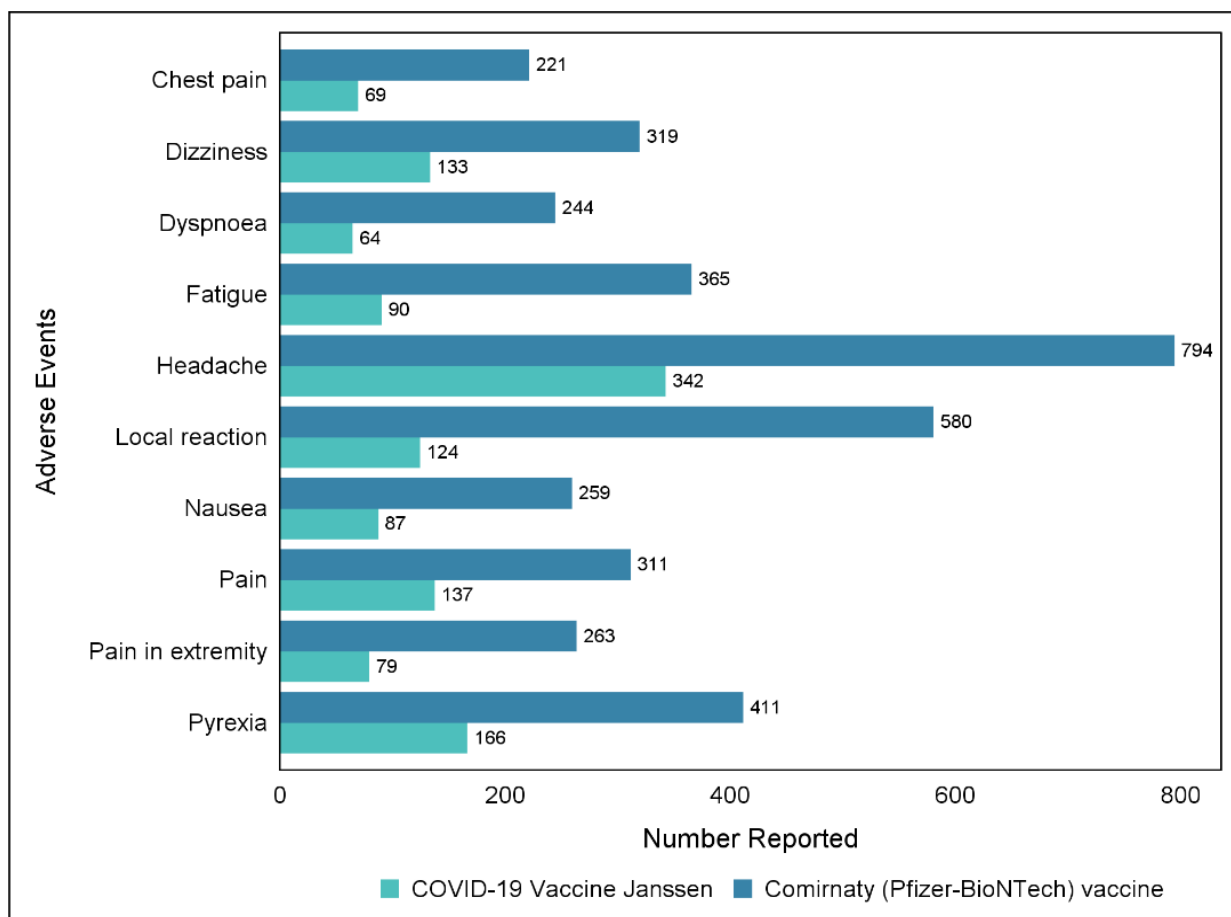
Health Products Regulatory Authority (SAHPRA) of any suspected adverse drug reactions (ADRs), or new or existing safety, quality or effectiveness concerns arising from the use of any medicine or scheduled substance.

The reference above to "any other person" indicates that everyone is required to participate in the reporting of ADEs in South Africa. This is supported by the SAHPRA's recent launch of the Med Safety App, a mobile application designed to simplify and promote the reporting of suspected ADEs, including adverse events following immunisation (AEFIs), by both the public and healthcare professionals. This app was created as part of SAHPRA's efforts to increase adverse event reporting (SAHPRA, 2021b).

The dearth of ADE reporting in South Africa is evidenced by SAHPRA's current statistics on reported AEFIs associated with Coronavirus disease of 2019 (COVID-19) vaccine administration (SAHPRA, 2022a). According to these data, as on 17 April 2022, only 5,566 cumulative AEFI reports had been received out of 32 246 926 cumulative vaccine doses administered, meaning that reported AEFIs account for 0.0173% of all doses administered. In a survey performed in Spain by Pares-Badell *et al.* (2021:4), 37.2% of respondents reported having experienced pain at the injection site. This contrasts with the lower reporting rates (0.002%) in South Africa for similar reactions (SAHPRA, 2022a).

According to the current standard treatment guidelines (DoH, 2019:10), Tenofovir is one of the first-line antiretroviral therapies, and with Africa being home to more than two-thirds of the world's HIV population (WHO, 2021), it is unexpected that VigiAccess reports from Africa on Tenofovir account for only 9% of all reports received globally. This could be because Africa, including South Africa, underreports cases of ADEs (VigiAccess, 2022).

Figure 1-1 depicts the top ten most frequently reported AEFIs with the Jansen and Comirnaty (Pfizer BioNTech) Covid-19 Vaccines , from 7 May 2021 to 18 March 2022 (SAHPRA, 2022a).



**Figure 1-1: Top 10 most frequently reported AEFIs, 17 May 2021-18 March 2022**

Several studies have found that the attitudes of certain healthcare professionals (HCPs), for example complacency, causative evaluations, procrastination, apathy to report, fear of the legal implications of reporting, guilt, a lack of training, lack of interest, or a lack of time, have a negative impact on spontaneous reporting (Asiamah *et al.*, 2022:2; Le *et al.*, 2020:124-125; Varallo *et al.*, 2014:740). This finding was echoed in a study undertaken in South Africa, which found similar attitudes acting as barriers to HCP reporting in South Africa (Bogolubova *et al.*, 2018:5).

While only HCPs have previously been permitted to report ADEs, a global shift has seen the formal inclusion of medicine users as reporters, allowing patients to report their experience of ADEs directly to regulators. Getting data from users may help combat low ADE reporting rates (Inacio *et al.*, 2017:228)

Inadequate ADE reporting can increase patient suffering by delaying the detection of ADRs; acquiring ADE reports directly from patients may therefore be crucial for discovering new ADRs (Pillay *et al.*, 2021:2). When patients are encouraged to report any ADEs, this guarantees that these events that might influence medicine usage or result in injury are quickly identified and

managed appropriately (Mehta, 2011:247). In fact, Kruger and Gasperini (2020:2) predict that in the coming years, regulatory authorities may use data on consumer experience, gathered through direct consumer reporting, to help decide whether to approve or withdraw medicines from the market.

The factors that affect medication users' direct reporting of ADE have not been studied extensively. However, lack of knowledge about pharmacovigilance and ADEs, as well as the lack of knowledge about reporting systems, and insufficient knowledge about their role in reporting ADEs, are some of the factors that lead to non-reporting of ADEs by medication users globally (Adisa *et al.*, 2019:1072; Kim *et al.*, 2020:9; Sales *et al.*, 2017:871). Sales *et al.* (2017:871) suggested that HCP complacency regarding adverse event reporting also negatively influences direct reporting by medicine users. Similarly, a study in South Africa found that anticipating a complex reporting process and having insufficient knowledge about the ADE reporting process are some of the factors that contribute to underreporting by patients in South Africa (Pillay *et al.*, 2021:7).

Investigating what adults in South Africa know about pharmacovigilance and their perceptions of their role in reporting ADEs, including their prior experiences of reporting ADEs, may provide insights that can enhance medicine safety in South Africa through:

- review of legislation to support direct reporting by medicine users;
- knowledge and awareness campaigns directed at the medicine users; and
- development or enhancement of reporting tools.

### **1.3 Problem statement**

Low rates of ADE reporting in South Africa may be due to the lack of knowledge about pharmacovigilance and ADE reporting, thus restricting involvement in the voluntary ADE reporting procedures aimed at improving medicine safety. The following questions were addressed by this study, which focussed on the knowledge about ADEs and characteristics that influence ADE reporting:

- What is known about pharmacovigilance and ADEs?
- What is the medication users' experience with reporting ADEs?
- What is known about the individual's responsibilities in reporting ADEs?

- What is known about when to report ADEs?
- What is known about whom to contact if an ADE occurs?

## **1.4 Research aim and objectives**

The study's aim and objectives are discussed in sections 1.4.1 and 1.4.2.

### **1.4.1 Research aim**

The aim of this study was to explore adults' awareness about pharmacovigilance and ADEs, attitudes regarding their perceived role in reporting ADEs, and the practice of and experience with ADE reporting in South Africa.

### **1.4.2 Specific research objectives**

The specific research objectives included objectives for the literature review as well as the empirical investigation.

#### **1.4.2.1 Literature review**

The literature review aimed to determine how thoroughly the current issue has been explored and documented in prior studies.

The literature review objectives were to:

- describe what is currently known about pharmacovigilance and experiences with ADE reporting by users of medicines globally,
- review the attitudes and practices of medicine users regarding ADE reporting globally.
- describe the barriers and enablers that affect ADE reporting globally and
- examine the current regulatory requirements for ADE reporting in South Africa and how they support ADE reporting.

#### **1.4.2.2 Empirical investigation**

Based on the aim of the study, the following objectives were developed:

- To assess adults' awareness about pharmacovigilance, ADEs and attitudes regarding their perceived role in reporting ADEs in South Africa

- To describe adults' practices and previous experience with reporting ADEs, including the barriers and enablers to reporting ADEs in South Africa

## **1.5 Research methodology**

The following methodology was used to conduct this study:

### **1.5.1 Literature review**

The literature search was conducted by using databases such as Academic Journal, Google Scholar<sup>®</sup>, Scopus<sup>®</sup>, Science Direct<sup>®</sup>, EBSCO Discovery Service<sup>®</sup>, and Web of Science<sup>®</sup>. The following keywords were used in different combinations to conduct a literature search across databases for all relevant literature:

- “Pharmacovigilance”
- “Adverse drug events”
- “Knowledge”
- “Experience“
- “Spontaneous reporting”
- “World Health Organization”
- “Factors“
- “Enablers”
- “Barriers”
- “South Africa”
- “International”
- “Patients”
- “Consumers”
- “Health care professionals”

The material acquired from the literature review was used to generate the questionnaire, write the introduction, background, and literature chapter, and compare the findings of similar studies.

## **1.5.2 Empirical investigation**

### **1.5.2.1 Study setting**

The setting for the study was both the private and public healthcare sector in all nine provinces of South Africa.

South Africa is a country in Southern Africa with a land surface area of 1 220 813 km<sup>2</sup>. It is split into nine provinces and is home to 59.62 million people with 11 official languages(South African Government, 2022).

The nine provinces of South Africa are the following:

- Eastern Cape
- Free State
- Gauteng
- KwaZulu-Natal
- Limpopo
- Mpumalanga
- Northern Cape
- North West
- Western Cape

### **1.5.2.2 Target population**

The target population for this study included all adults currently residing in South Africa.

#### **1.5.2.2.1 Inclusion criteria**

Participants who fulfilled the criteria presented in Table 1-1 were eligible to participate in this study.

**Table 1-1: Inclusion criteria**

<b>Criteria</b>	<b>Justification/Motivation</b>
All adults 18 years of age and older.	The planned study methodology, including the recruitment of participants, did not allow for the process of obtaining parental consent for minors to participate, because anyone under the age of 18 is considered a minor in South Africa.
Adults currently residing in South Africa.	As the study's aim was to investigate the awareness attitudes, and practices of adults in South Africa, participants must live in the country.
Adults who were able to respond to the questionnaire in English.	The study questionnaire was only available in English, as discussed in section 1.6.1.2.

#### 1.5.2.2.2 Exclusion criteria

Participants who fulfil the criteria presented in Table 1-2 could not participate in this study.

**Table 1-2: Exclusion criteria**

<b>Criteria</b>	<b>Justification/Motivation</b>
Members of the research team	They were involved in the development and approval of the data collection tool; their involvement may lead to bias.
Members of the Medicine Usage in South Africa (MUSA) Scientific Committee	They were involved in the development and approval of the data collection tool; their involvement may lead to bias.
Individuals who were involved in the data collection tool development	They were involved in the development and approval of the data collection tool; their involvement may lead to bias.

#### 1.5.2.3 Study design

A quantitative, analytical, non-experimental, cross-sectional study design was used for this study.

### 1.6 Data source

This study used primary data collected as described in the following sections.

#### 1.6.1 Data collection

During this study, data were collected via a self-administered, online, structured questionnaire distributed via SurveyMonkey®. This online platform allows users to create questions that can be shared online and answered by participants, as well as collect feedback from them. The survey was launched on 18 April 2023 and data was collected until 18 June 2023. Details on the recruitment of participants, the data collection tool and the data collection process are further described below.

### **1.6.1.1 Recruitment of participants**

Participants were recruited via a paid-for advertisement in the form of a news article published on the News24 online platform in English and translated to Afrikaans and published on Netwerk24 (see Annexure C). The news article was published on 18 April 2023. The article (News24, 2023) was also posted on the Netwerk24 and News24 Facebook® and Instagram® pages and was visible to all people who visited these platforms regardless of whether they were subscribers or not. Individuals who were interested in the study could click on the link provided in the article which took them to the study's cover page on SurveyMonkey® (SurveyMonkey Inc, 2023), which contained the informed consent information.

People who read the cover page and decided to participate in the study had to click "I accept" to the line "I voluntarily consent to participate in the study" and were directed to SurveyMonkey® to complete the questionnaire. If a person read the study's cover page and chose not to participate, they could discontinue their involvement by clicking "I do not wish to participate". The link to the study questionnaire could be shared by participants to other platforms.

### **1.6.1.2 Data collection tool**

A structured online questionnaire was utilised to collect data. When a questionnaire is used, the respondent provides answers in response to a set of questions. A well-designed questionnaire should meet the study's objectives, be linked to the research problem, and be user-friendly while still being able to obtain accurate and complete information (Brink et al., 2006:145-146).

#### **1.6.1.2.1 Development of the data collection tool**

The questionnaire (see Annexure D) for this study was developed by using validated questionnaires of previous studies that had similar objectives. The questions from these studies were adapted and the questionnaire was developed in English.

During the development of data collection instruments, a review of relevant literature can aid the researcher in identifying existing tools that can be used just as they are or changed to fit the investigator's needs (Worley, 2011:162).

The questionnaire contained 32 questions, arranged in the following five sections:

- Section A: Socio-demographic information
- Section B: Awareness of adverse drug events

- Section C: Attitudes regarding adverse drug events and adverse drug events reporting
- Section D: Practices and experience with reporting adverse drug events
- Section E: Barriers to reporting adverse drug events

The following articles (as shown in Table 1-3) were used during the development of the questionnaire:

**Table 1-3: Articles used to develop the questionnaire**

Study objective	Questionnaire section	Articles
Biographical information	Section A	N/A
Objective 1 To assess adults' awareness about pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa	Section B Section C	Adisa <i>et al.</i> (2019); Kim <i>et al.</i> (2020); Sabblah <i>et al.</i> (2017); Sales <i>et al.</i> (2017); Wang <i>et al.</i> (2022)
Objective 2 To describe adults' practices and previous experience with reporting ADEs, including the barriers and enablers to reporting ADEs in South Africa	Section D Section E	Adisa <i>et al.</i> (2019); Kim <i>et al.</i> (2020); Sabblah <i>et al.</i> (2017); Sales <i>et al.</i> (2017); Wang <i>et al.</i> (2022)

#### 1.6.1.2.2 Validity and reliability of data collection tool

Instrument validity is concerned with determining whether the designed instrument accurately measures what it intends to measure, as interpreting the results might be difficult unless the researcher is certain that the instruments are measuring what they are supposed to be measuring (Brink *et al.*, 2006:159).

- Content validity

The content validity of an instrument is a measure of how effectively it represents all the elements of the variable being evaluated. In this study, the questionnaire was assessed by experts from the MUSA Scientific Committee to evaluate how it is linked to the study objectives.

- Face validity

The instrument's face validity determines whether it appears to measure what it claims to measure. In this study, the questionnaire was assessed by a statistician to evaluate face validity.

- Reliability

The consistency with which the collecting tool will deliver the same or a similar value for an unchanging variable is determined by reliability (Aparasu, 2011:61). In this study all the participants were given the same questionnaire to complete.

### **1.6.1.3 Data collection process**

Data collection began after ethical permission from the NWU-Health Research Ethics Committee (NWU-HREC) had been obtained. Participants were recruited as described in section 1.6.1.1. The survey was launched on 18 April 2023 and data were collected until 18 June 2023.

A study mediator (independent person) was responsible for the following:

- Creating the online structured questionnaire in SurveyMonkey®
- Sharing the link to the online questionnaire with Netwerk24 and News24 (via the study supervisor) to post on the platform of Netwerk24/News24.
- Receiving completed questionnaires from participants and exporting the data into an anonymised Excel spreadsheet before sharing with the research team.

## 1.7 Statistical analysis

The data gathered for this study was analysed following a statistical analysis plan designed with input from a statistician from the NWU statistical consultancy services. We performed both descriptive and inferential statistics. All categorical variables were summarised as frequencies and percentages. Pearson's chi-square test or Fischer's test was used, when appropriate, to test for an association between two categorical variables. The Wilcoxon rank sum test was used to compare median ages between groups of participants. All statistical tests were two-tailed, and the type-I error rate set at 5% ( $\alpha = 0.05$ ). Statistical analyses were performed using the statistical software package R statistical software version 4.3.1 (R Foundation, 2023). Table 1-4 outlines the data analysis plan's executive summary.

**Table 1-4: Summary of data analysis**

Objectives	Measurements	Variables		Statistical Analysis	
		Independent	Dependant	Descriptive	Inferential
<b>Objective 1</b> To assess adults' awareness of pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa.	To assess adults' awareness of pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa	<b>Section A</b> <ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Province of residence</li> <li>• Residing in rural or urban area</li> <li>• Level of education</li> <li>• Preferred health care provider</li> </ul>	<b>Section A</b> Qualification as a healthcare provider	Measure of Frequency (number or percentage)	Chi-square test or Fisher's exact test if appropriate
			<b>Related questions:</b> <b>Section B-</b> <ul style="list-style-type: none"> <li>• Have you heard about the term adverse drug events?</li> <li>• Do adverse drug events have to be reported?</li> <li>• Where did you hear about the reporting of adverse drug events?</li> <li>• Which age groups can experience adverse drug events?</li> <li>• Who can report adverse drug events?</li> <li>• Have you heard of Med Safety App, a mobile application that can be used to report suspected adverse drug events?</li> <li>• Have you heard of the South African Health Products Regulatory Authority (SAHPRA)</li> </ul> <b>Section C</b> <ul style="list-style-type: none"> <li>• Have you or anyone you look after ever used medication?</li> </ul>	Measure of Frequency (number or percentage)	Chi-square test or Fisher's exact test if appropriate

			<ul style="list-style-type: none"> <li>• Did you ask your healthcare professional about the potential adverse effects of your medication?</li> <li>• Did your healthcare professional inform you about the potential adverse effects of your medication?</li> <li>• I did not get the medicine from a healthcare professional.</li> <li>• Do you ever read the patient information leaflet that comes with your prescription medication?</li> <li>• Do you believe it is important or necessary to report adverse events that you may experience after taking medication?</li> <li>• Why is it important to report adverse drug events?</li> <li>• Do you feel well informed about the adverse effects that your medication may cause?</li> <li>• Do you wish you could get more information about the adverse effects of your medication?</li> <li>• Have you ever experienced adverse drug events after taking medicine?</li> <li>• Did this occur after using or taking medicine; vaccination /immunisation, using a medical device?</li> <li>• Was this reported to anyone?</li> </ul>		
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<p><b>Objective 2</b> To describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa.</p>	<p>To describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa.</p>	<p><b>Section A</b></p> <ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Province of residence</li> <li>• Residing in rural or urban area</li> <li>• Level of education</li> <li>• Preferred health care provider</li> </ul>	<p><b>Section A</b> Qualification as healthcare provider</p> <hr/> <p><b>Section D</b></p> <ul style="list-style-type: none"> <li>• When was the adverse drug event reported?</li> <li>• To whom did you report the adverse drug event?</li> <li>• To what extent did the below motivate your decision to report?</li> </ul> <p><b>Section E</b></p> <ul style="list-style-type: none"> <li>• To what extent did the below influence your decision not to report?</li> <li>• Are you likely to report any adverse drug events you may have in the future?</li> </ul>	<p>Measure of Frequency (number or percentage)</p>	<p>Chi-square test or Fisher's exact test if appropriate</p>
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## 1.8 Ethical considerations

A researcher is accountable for carrying out research ethically. Inability to do so jeopardises the methodological approach and may lead to detrimental outcomes (Brink *et al.*, 2006:30). The following was performed while conducting the research project, as guided by the principles outlined in Brink *et al.* (2006:30-43), to ensure an ethically sound research project.

Permission to conduct the study was obtained from the NWU-Health Research Ethics Committee of the Faculty of Health Sciences of the North-West University (NWU-00223-22-A1; refer to Annexure A). Recruitment of participants started once ethical clearance for the study had been issued. Informed consent was obtained from participants to ensure voluntary participation. The purpose of the study and the nature of their participation was explained to the study participants as part of the process of obtaining consent (see Annexure B).

A study mediator was appointed to receive the completed questionnaires from the participants. These questionnaires were exported into an Excel spreadsheet before the anonymised data was shared with the research team. All study participants remained anonymous because no identifying information was collected.

Participants' right to privacy, confidentiality, and anonymity were honoured to ensure that their dignity is maintained. All participants have a right to privacy and their responses were kept confidentially in access-controlled electronic storage. There is no link between the Netwerk24/News24 platform, their Facebook® or Instagram® accounts and the SurveyMonkey® platform. When the participant clicked on the study link, the participant was directed out of the Netwerk24/News24 platform and into SurveyMonkey®. To respect the participants' right to self-determination, participation in this study was voluntary and participants were free to withdraw at any moment during the study without experiencing any consequences. There was no monetary compensation for taking part in the study.

There were no direct benefits for taking part in the study, as there was no direct contact between the participant and the researchers. The indirect benefit to participants was that knowing the public's current level of awareness of pharmacovigilance and adverse drug events may inform interventions that can lead to improved reporting of ADEs by medicine users, thus improving public health safety in South Africa.

During the study, the study supervisors and MUSA Scientific Committee ensured, through close monitoring, that the research protocol was followed.

### 1.8.1 Anticipated risks and precautions

Possible anticipated risks and precautionary measures are presented below:

#### 1.8.1.1 Anticipated risks to the participants and precautions taken

In Table 1-5 below, the anticipated risks to participants and precautions that were taken, are presented.

**Table 1-5: Anticipated risks to participants and precautions taken**

<b>Risks</b>	<b>Precautions</b>
Discomfort and loss of time associated with answering the research questions	The researcher made sure that the questionnaire was short and well structured so that it was easy to complete.
Questions were not clearly understood by the respondents	All questions were written in simple English.
Identification of study participants	A study mediator was appointed to receive completed questionnaires from participants. The research team did not know the identities of the participants.

#### 1.8.1.2 Anticipated risks to the researcher and the precautions taken

Table 1-6 below presents the anticipated risks to the researcher and precautions to be taken.

**Table 1-6: Anticipated risks to the researcher and the precautions taken**

<b>Risks</b>	<b>Precautions</b>
The questionnaire is too long and not fully completed by respondents, resulting in partially completed questionnaires.	<ul style="list-style-type: none"><li>-The researcher made the questionnaire short and well structured so that it was easy to complete.</li><li>-SurveyMonkey® was set up to allow participants to start the questionnaire, stop at any given point, and complete the questionnaire at a convenient time, if the participant completed the questionnaire from the same location and device (Internet protocol (IP) address).</li></ul>
Participants refuse to provide their permission, but can proceed to the questionnaire, resulting in participation without documented consent.	<ul style="list-style-type: none"><li>-The questionnaire was only available to those participants who gave their consent to participate.</li><li>-The procedure for ensuring anonymity was explained clearly in the informed consent form.</li></ul>

Based on the anticipated benefits and risks, as well as the precautions that can be put into place, the benefits of the study outweigh the associated risks. This study posed a minimal, low or negligible risk.

### **1.8.2 Data management**

During the research, the following data management principles as per the MUSA research data management plan were observed:

#### **1.8.2.1 Data management during the study**

During the study, the following was in place:

- Electronic questionnaires were completed by using SurveyMonkey®.
- NWU has a SurveyMonkey® account, and the study data was stored on the SurveyMonkey® servers as long as NWU owns an account. The current SurveyMonkey® data management policy indicates that the data associated with an account is deleted permanently 60 days after the account is closed.
- An independent person extracted the final data at the end of the gathering period; the data was shared with the research team in a password-protected Excel spreadsheet.
- The extracted data will be kept on the researcher's, supervisor's and statistician's password-protected laptops/desktops (with an anti-virus program installed and an external password-protected hard drive on each) for the duration of the study.
- After the data analysis has been completed, the raw (electronic) and analysed data will be stored on the dedicated MUSA research data site on Nextcloud.

#### **1.8.2.2 Data management after completion of the study**

After completion of the study, the following will take place:

- Access to the electronic data will be limited to the Director and administrative assistant of MUSA.
- The data will be stored on an external hard drive, locked in the safe at MUSA's office, and on a MUSA-dedicated Nextcloud space.

- The raw data sets and analysed data will be kept for five years.
- All electronic data sets will be stored and kept until the study has been completed, the five years have expired, and the data are no longer used.
- After five years, MUSA will delete all the data from all stored sites.

### **1.8.3 Conflict of interest**

There were no conflicts of interest to declare.

### **1.9 Chapter summary**

In this first chapter, the need to study adults' awareness about pharmacovigilance and ADEs, attitudes regarding their perceived role in reporting ADEs, and the practice of and experience with adverse drug event reporting in South Africa has been established.

This chapter presented the background information, problem statement, aims and objectives of this research. This chapter also covers the ethical considerations for the study, the planned data analysis, the research methodology, and the data collection tool. The next chapter entails a comprehensive literature review that answers the objectives as listed in section 1.4.2.1.

## **CHAPTER 2      LITERATURE REVIEW**

### **2.1    Introduction**

The findings from the literature review are presented in this chapter under six sections: (1) key pharmacovigilance organisations, (2) definitions, (3) pharmacovigilance and experiences with adverse drug event reporting, (4) attitudes and practices of consumers regarding ADE reporting, (5) barriers and enablers of adverse drug event reporting and (6) regulatory requirements for ADE reporting in South Africa.

This chapter seeks to fulfil the following objectives for the literature review that were established in chapter 1:

- Describe what is currently known about pharmacovigilance and experiences with ADE reporting by users of medicines globally.
- Review the attitudes and practices of medicine users regarding ADE reporting globally.
- Describe the barriers and enablers that affect ADE reporting globally.
- Examine the current regulatory requirements for ADE reporting in South Africa and how they support ADE reporting.

### **2.2    Key pharmacovigilance organisations**

Pharmacovigilance relies on international cooperation to increase the safety of medicines, as this can result in early risk identification and assessment of data on risk. Through this partnership, risk data from a wider range of patients can be pooled, enabling the identification of even the rarer and delayed adverse events. This information can then be used to create and implement risk management strategies aimed at lowering identified risks (Salimi, 2023:1). In South Africa, the SAHPRA's pharmacovigilance mandate is carried out through international collaboration and the key organisations active in pharmacovigilance on a local and international level are listed below.

#### **2.2.1    South African Health Products Regulatory Authority (SAHPRA)**

The SAHPRA is the body that regulates health products for use in people and animals through the licensing and regulation of the pharmaceutical industry in South Africa. The SAHPRA must conduct post-marketing surveillance to collect evidence of ADEs. Subsequently, these ADEs

should be analysed to identify relevant signals and ensure appropriate actions to safeguard public health (SAHPRA, 2023a).

### **2.2.2 Council for International Organizations of Medical Sciences (CIOMS)**

The Council for International Organizations of Medical Sciences (CIOMS) is a global organisation that was created to promote public health by providing scientific guidance on research and policies covering the ethical, safety and drug product development domains (CIOMS, 2023a). A number of resources have been developed by the CIOMS through its working group on pharmacovigilance with the aim of standardising procedures worldwide. One of these resources is the CIOMS reporting form, which is used by the pharmaceutical industry to notify the authorities of possible adverse drug reactions (CIOMS, 2023b). In South Africa, the pharmaceutical industry can submit ADE reports to SAHPRA on the CIOMS form, which is available from the SAHPRA website (SAHPRA, 2022f:11).

### **2.2.3 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is an official global group of regulatory agencies and pharmaceutical industry representatives concerned with ensuring effective and safe medication during the development, registration and post-marketing maintenance of medicines to guarantee high-quality medicines. The ICH has developed safety guidelines to aid in the identification of potential risks associated with the use of medications. These standards have been successfully utilised to pinpoint some drug toxicities, such as carcinogenicity (ICH, 2023). Stakeholders in the South African pharmaceutical industry can submit reports on ADEs electronically to SAHPRA in E2B format (SAHPRA, 2022f:11).

### **2.2.4 World Health Organization (WHO)**

The World Health Organization (WHO) is a United Nations agency that brings together individuals, partners, and states to promote health and assist the most vulnerable people to guarantee that everyone everywhere can achieve the highest possible standard of health (WHO, 2023a). Regarding pharmacovigilance, the WHO provides reliable data gathered globally as part of the WHO Programme for International Drug Monitoring (WHO PIDM) to improve patient care and patient safety. South Africa is a full member of the WHO PIDM, so SAHPRA is required to send

all suspected ADE reports to VigiBase®, the global database of individual case safety reports (ICSRs) (WHO, 2023d).

### **2.2.5 Uppsala Monitoring Centre (UMC)**

The Uppsala Monitoring Centre (UMC) is the WHO Collaborating Centre for International Drug Monitoring, which provides tools for quick access to the global database of reported possible ADEs and assists WHO in the identification, evaluation, comprehension, and prevention of ADEs or any other drug-related problem (UMC, 2022). The UMC maintains VigiBase®, the global database of suspected ADEs that provide a pool of ADEs that may be analysed to find signs of possible harm caused by medicines worldwide (UMC, 2022).

## **2.3 Definitions**

The essential terms used in pharmacovigilance will be defined in the context of this study in this section of the dissertation. These terms will include "pharmacovigilance," "adverse drug events," "connection between adverse drug events and adverse drug reactions," "spontaneous reporting," and "active surveillance."

### **2.3.1 Pharmacovigilance**

The word "pharmacovigilance" originates from "Pharmakon" which is Greek for "medicinal ingredient," and "Vigilia" which in Latin means "to keep a watch" and this emphasises in a nutshell the primary concern of pharmacovigilance (Fornasier *et al.*, 2018:744).

The WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine-related problem" (WHO, 2023c). This definition of pharmacovigilance appears consistently throughout the pharmacovigilance literature, demonstrating that the phrase is used comparably around the world and that the understanding of pharmacovigilance is the same worldwide (Fornasier *et al.*, 2018:744; Garashi *et al.*, 2022:717; Kiguba *et al.*, 2022:1; Potts *et al.*, 2020:521; Santoro *et al.*, 2017:856).

### **2.3.2 Adverse drug event (ADE) and adverse drug reaction (ADR)**

The SAHPRA defines an ADE as "any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicine, whether considered related to the medicine or not" (SAHPRA, 2022c:4).

The CIOMS defines an ADE as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (CIOMS, 2021:7).

The ICH expands on the above definitions by pointing out that an ADE can be any undesirable and undesired symptom, sign, or condition that is temporally linked to the use of a medical product, whether or not it is connected to the medicinal product, including any abnormal laboratory findings (ICH, 2016:2).

The SAHPRA defines ADR as "a noxious and unintended response to a medicine, including lack of efficacy, and which occurs at doses normally used in man and which can result from overdose, misuse or abuse of medicine. The reaction may be a known side effect of the medicine, or may be new and previously unrecognised. An ADR can be caused by any therapeutic agent, including prescribed and over-the-counter (OTC) medicines" (SAHPRA, 2022c:4).

According to the CIOMS, the response in this setting signifies at least a likelihood that a medicine product and an ADE are causally related (CIOMS, 2021:7).

Adverse drug events are inclusive of ADRs, which can be described as unwanted effects to drugs happening within the normal drug therapeutic levels, drug interactions, sub-optimal doses, overdosing events due to failure to adhere or premature medicine withdrawal, and lack of efficacy (Woo *et al.*, 2020:293).

The definitions of ADEs in the literature are consistent, and it is emphasised throughout the literature that it is not necessary to establish a connection between a reported ADE and the medication taken for the event to be reportable.

### **2.3.3 The connection between ADE and ADR**

Adverse drug events occur after a medicine is administered at any dose and might or might not harm the patient. Adverse drug reactions are a subgroup of ADEs as they occur when a medicine is administered within the normal dose range and have "noxious and unintended" effects on the patient (Wolfe *et al.*, 2018:2). There must be an established causal link between the medicine and the noted reaction (SAHPRA, 2022c:4).

A subgroup of ADRs called preventable adverse drug reactions can occur as a result of medication errors (MEs) when a patient receives the wrong prescription, dose, or dose schedule, or when a medication is given to someone who is already known to be allergic to it (Wolfe *et al.*, 2018:2).

The terms "adverse drug event" and "adverse drug reaction" will be used interchangeably in this study because, from the perspective of the medicine user, it is difficult to distinguish between the two terms, as causality assessments that determine whether an ADE is causally related to the medication that was used, are not done at their level.

### **2.3.4 Spontaneous reporting**

Spontaneous reporting, a passive pharmacovigilance surveillance method, involves healthcare providers or consumers voluntarily sharing information about ADE experiences while taking one or more medicines, with a company, regulatory authority, or other organisation. This information is not the result of a study or other planned data collection program (ICH, 2004).

### **2.3.5 Active surveillance**

The WHO defines active surveillance as “ the collection of case study information as a continuous pre-organised process (WHO, 2023b).” Active surveillance is divided into three categories (CIOMS, 2021:5):

- medicine-based, which focuses on recognising adverse events that affect users of specific medications.
- healthcare location based, which focuses on identifying adverse events that occur at the facility level, and
- event-based, which focuses on identifying adverse events connected to specific medications.

## **2.4 Pharmacovigilance and experiences with adverse drug event reporting**

The sections that follow will present what is currently known about pharmacovigilance and experiences with ADE reporting by consumers of medicines globally. The topics include the history and aim of pharmacovigilance, the pharmacovigilance cycle, pharmacovigilance systems and spontaneous reporting.

### **2.4.1 History of pharmacovigilance**

The history of pharmacovigilance dates back to 170 years ago when a little girl from the north of England named Hannah Greener died on 29 January 1848, following the administration of chloroform anaesthesia prior to the excision of an infected toenail (Fornasier *et al.*, 2018:744).

When thalidomide was used to treat morning sickness in pregnant women in the late 1950s and early 1960s, it led to birth abnormalities in babies who were exposed to this medicine as foetuses (CIOMS, 2022:130). The thalidomide catastrophe taught us, among other things, that medications must be extensively evaluated before being marketed, that governments must control pharmaceuticals, that there must be systems in place to detect ADEs, and that it is possible to reduce certain risks associated with the use of medicine (Waller, 2010:3).

It is in the wake of this tragedy that the WHO Programme for International Drug Monitoring (WHO PIDM) was established in 1968 to develop the practice of pharmacovigilance in nations around the world and ensure that information regarding patient harm was gathered from a wide range of sources (UMC, 2023b).

### **2.4.2 Aim of pharmacovigilance**

Pharmacovigilance aims to improve patient care and patient safety related to the use of medicines and promote public health initiatives by offering trustworthy, impartial information to evaluate the risk-benefit profile of medication (WHO, 2023d).

Before any medication is approved for use, the only available proof of its efficacy and safety comes from testing in carefully chosen patients who are monitored under controlled clinical trials. Following approval, the medication may be administered to a large number of patients, continuously and in conjunction with other medicines. In such cases, uncommon and previously unidentified side effects may manifest (SAHPRA, 2022e:6).

Therefore, pharmacovigilance practice promotes the safe and effective use of medications by providing trustworthy information for evaluating the medicine's benefit-risk profile, taking into consideration knowledge acquired in 'real-world' settings (Santoro *et al.*, 2017:856).

### 2.4.3 Pharmacovigilance cycle

To ensure that the information relating to drug safety is found, processed and necessary steps are made to prevent further risks, the pharmacovigilance cycle necessitates coordination between many stakeholders. Table 2-1 details each stage (UMC, 2023a).

**Table 2-1: PV Cycle, stages and associated actions**

<b>Cycle stage</b>	<b>Actions</b>
Treat	Healthcare professionals must ensure that the proposed treatment's advantages outweigh its risks while the patient is receiving treatment.
Recognise	All stakeholders must be able to identify ADEs during therapy to flag them for reporting.
Report	Adverse drug events must be reported to the national pharmacovigilance centre or healthcare practitioners, who must then report the situation to the national pharmacovigilance centre to inform regulators and healthcare professionals of any new safety concerns.
Collect	Structures must be in place to guarantee the collection of reports at the facility, national, and international levels.
Analyse	This phase is crucial for determining whether a connection between the reported event and the medication being used can be detected.
Act	The findings of the analysis must guide the steps that must be followed to limit any additional harm to the patients resulting from ongoing drug usage. The following are some possible courses of action: <ul style="list-style-type: none"> <li>• Issuing safety alerts.</li> <li>• Modifying product labelling, including professional information and patient literature.</li> <li>• Product removal from the marketplace.</li> </ul>
Communicate	The findings must be shared with everyone concerned to ensure they know the new emergent risks.
Prevent	Measures must be taken to lessen the effects of ADEs, and the knowledge acquired must be applied for the benefit of all patients to improve patient safety.

Adapted from (UMC, 2023a)

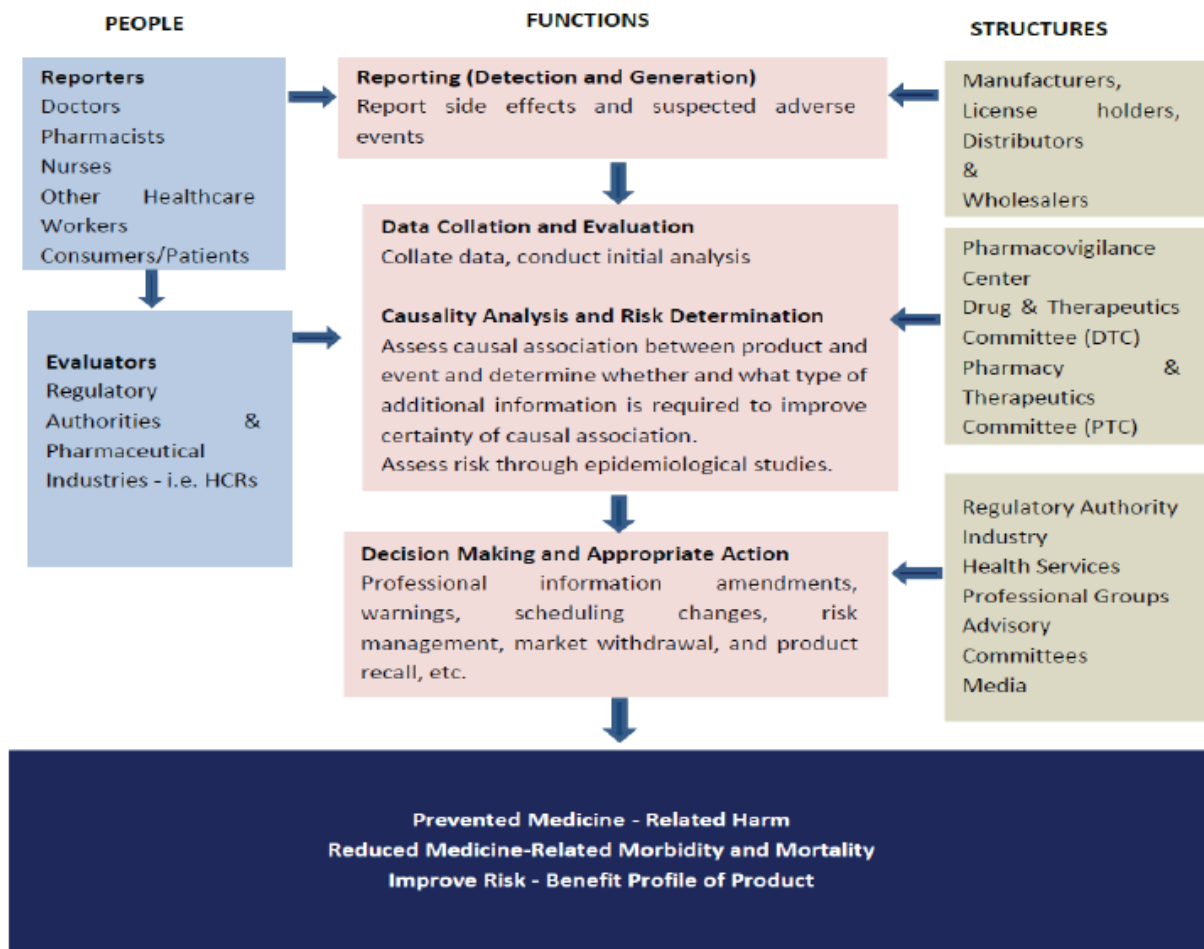
#### **2.4.4 Pharmacovigilance systems**

Pharmacovigilance systems provide a regulatory framework that allows for the monitoring of medicine safety in a particular setting; however, the level of maturity of these systems can differ from country to country (Kiguba *et al.*, 2022:3).

Although many organisations, people, and agencies may engage in pharmacovigilance efforts, the National Medicines Regulatory Authority (NMRA) typically organises and coordinates the national pharmacovigilance system. At a minimum, each national pharmacovigilance system should have a country pharmacovigilance centre, a national system for spontaneous reporting, a national reporting database that compiles and manages reports, and an advisory panel for pharmacovigilance and communication strategies (WHO, 2018). The requirement that each national pharmacovigilance system must have a national system for spontaneous reporting, as stated above, alludes to the fact that spontaneous reporting is essential to pharmacovigilance because it is one of the systems that allows for reporting of ADEs, including reporting by patients.

Pharmacovigilance was initially established in South Africa in 1987 as the National Adverse Drug Events Monitoring Centre (NADEMC) at the Faculty of Health Sciences of the University of Cape Town, and advanced as a division of the Medicines Control Council (MCC). Since its creation in 2018, SAHPRA has been tasked with monitoring the safety of health products and helping to understand the potential adverse effects of medications better when used outside of the tightly controlled conditions of clinical trials. The pharmacovigilance unit is in charge of SAHPRA's pharmacovigilance activities. These are carried out in collaboration with various stakeholders, including the pharmaceutical industry, healthcare professionals and patients (SAHPRA, 2022f:2).

The relationship between the various pharmacovigilance stakeholders is depicted in Figure 2-1 (SAHPRA, 2022f:8)



**Figure 2-1: Professional groups or associations and their functions**

Note. This figure has been used with permission from SAHPRA (South African Health Products Regulatory Authority). VigiGuardian newsletter. 2022.

The following tools serve as a framework for the South African pharmacovigilance system, which facilitates reporting of ADEs:

- Vigilance hub, which enables the capturing of paper-based reports, viewing, updating and editing of submitted reports.
- VigiFlow®, which is a management system for case reports.

- VigiBase®, which is a global database used by SAHPRA to contribute to the global database of individual case safety reports.
- VigiLyze®, a search-and-analysis tool to retrieve data from VigiBase®.
- VigiAccess®, which allows the public to access the VigiBase® database of reported ADE.

The tools that are available to report ADEs in South Africa are discussed in section 2.7.4 (Tools for reporting ADEs in South Africa).

#### **2.4.5 Spontaneous reporting in pharmacovigilance**

Spontaneous reporting is the main method for gathering post-marketing data on the safety of medications and identifying safety signals in pharmacovigilance (Hazell *et al.*, 2013:200).

Spontaneous reporting is a low-cost, adaptable, and highly efficient information-gathering technique through which both consumers and HCPs can report ADEs (Asiamah *et al.*, 2022:2). The primary benefits of spontaneous reporting in pharmacovigilance are that reports can be related to any medicines, they can be from any level of healthcare services, they can be focused on specific medicines and observed ADEs, facilitate coding of the reported ADE and they can reveal the timing and progression of the reactions. It can also reveal the existence or absence of additional risk factors and the patient's medical background (ENCePP, 2023).

Spontaneous reporting is vital for monitoring a drug throughout its lifecycle. It involves a diverse group of potential reporters and a wide array of pharmaceuticals. Notably, it is the primary source of drug-safety data, contributing to 52-55% of medicinal label revisions. This underscores its important role in pharmacovigilance operations (Schurer *et al.*, 2017:81).

Worldwide, the practice of reporting ADEs spontaneously is common. Numerous studies have been carried out to enhance our understanding of the various aspects of spontaneous reporting. One such study conducted in the United States of America (USA) that examined the characteristics of voluntary reports found that when compared to reports from HCP, consumer reports varied in terms of patient demographics, results, and suspect medicines (Toki & Ono, 2018:126). However, it is essential to remember that these variations should not be interpreted as a failure of consumer reporting because data from consumers can supplement that from HCPs (Inacio *et al.*, 2017:245).

In a recent study performed to review the completeness of adverse drug reaction reports in South Africa, it was discovered that of 8,438 cases which were reported in VigiBase during a period from 1 January to 1 December 2017, the reporter categories were doctors reporting 38.58% of cases, drug users reporting 28.58% of cases, other HCPs reporting 25.78% of cases, pharmacists reporting 4.33% of cases, and lawyers reporting 0.01% of cases (Matlala *et al.*, 2023:4). According to Ampadu's analysis of the spontaneous reports in VigiBase, less than 1% of all reports were from Africa, and the vast majority of those reports were for items related to HIV/AIDS (Ampadu *et al.*, 2016:337-340).

By examining the study mentioned above, it is evident that spontaneous reports can provide important information about the nation from which they were received. This information can be utilised as a guide when one creates country-specific programs to increase the safety of medications.

#### **2.4.6 Consumer reporting in pharmacovigilance**

Consumer reporting offers perspectives on people's experiences with ADEs that are not otherwise available. With the rise of the Internet and social media, consumers have the potential to play a significant role in pharmacovigilance because their opinions could alter how we currently view the benefit-harm analysis of drugs (Harmark *et al.*, 2015:345).

The Lareb Center, the WHO Collaborating Center for Pharmacovigilance in Education and Patient Reporting in the Netherlands, is dedicated to the analysis of spontaneous patient reporting and helps WHO in educating member nations on patient reports as well as carrying out studies on how patient reports affect pharmacovigilance (UMC, 2015:12-13).

A study, conducted by Lareb Center in collaboration with Uppsala Monitoring Center, investigated the use of patient reports in signal detection within VigiBase<sup>®</sup>. It revealed that the case narratives of ADEs reported directly by patients can provide detailed consumer experiences. Whenever possible, the prioritisation of signal detection from consumer reports is recommended, as it ensures a review of these individual narratives (Watson *et al.*, 2018:210-211).

Researchers have discovered that patient reporting of ADEs can be influenced by individuals such as family members, friends, healthcare providers as well as information found online and on social media (Kitisopee *et al.*, 2022:3). When consumer reporting experiences were examined across 11 countries in a study by van Hunsel *et al.* (2012:54) it was discovered that after media attention, ADE reporting increased in all of the participating countries. Although social media can

be used to promote patient safety, the risk of malevolent, malicious use, including fraudulent reports, might negatively influence pharmacovigilance (Kruger & Gasperini, 2020:6).

Despite having little confidence in the pharmaceutical industry and governmental organisations, consumers typically believe that these institutions are the most accountable for guaranteeing drug safety. This belief contributes to lack of engagement with drug safety (Patel *et al.*, 2019:243). This is supported by a study, which found that although participants were confused regarding where and to whom they should report ADEs, most of them believed that HCPs, rather than consumers, should do so (Sales *et al.*, 2017:871).

Permitting direct consumer reporting to national pharmacovigilance centers has resulted in improvements worldwide and organisations like the WHO recognise the benefits of this practice (Inacio *et al.*, 2017:228). Although there are countries with consumer reporting systems in place, not all of them actively encourage consumer reporting (van Hunsel *et al.*, 2012:55). To allow for consumer involvement in pharmacovigilance, it is important that consumers are aware of what to report, know where to report, have easy access to the reporting systems, and reporting must be meaningful to the consumers (Jacobs *et al.*, 2018:2).

One of the criticisms of permitting consumer reporting has been the issue of incomplete reports submitted by consumers (Kruger & Gasperini, 2020:5); however, a recent study by Matlala *et al.* (2023:7) found that the completeness of reports provided by consumers was comparable to that of reports submitted by HCPs and this affirms the patient's role as an important contributor to pharmacovigilance. The adoption of standard forms can assist in ensuring that all pertinent data is recorded during reporting (Kruger & Gasperini, 2020:5).

Public promotion of patient reporting, including the provision of information on what must be reported, simplifying the reporting procedures and providing feedback to consumers regarding their reports, are some of the suggestions made by Avery *et al.* (2011:129-130) as ways to encourage consumer reporting of ADEs and enhance patients' reporting experiences.

#### **2.4.7 Importance of consumer involvement**

Patients are in a good position to report ADEs and increase medication safety since they know their medical condition and the medications they are using (Al Dweik *et al.*, 2017:876). Patient reporting seems to play a significant role in the pharmacovigilance system, as reports of adverse responses increased by about 30% in a year with the involvement of both patients and those who look after them (Sienkiewicz *et al.*, 2021:13).

Consumers' ability to report drug side effects enhances medication-related risk surveillance, enables the identification of safety signals that are supplementary to those presented by medical professionals, and, ultimately, participation by consumers will eventually contribute in raising public awareness, competency, and understanding of safety (Margraff & Bertram, 2014:418). Because consumers include in their reports, personal information about how ADEs affect their everyday lives, this is valuable in increasing overall knowledge about ADEs (Inacio *et al.*, 2017:244-245).

The results of the first extensive study undertaken (Avery *et al.*, 2011:129) in the United Kingdom (UK) to evaluate the impact of consumer reports on pharmacovigilance in comparison to reports from HCPs, were as follows:

- Reports from patients included in-depth descriptions of potential adverse drug reactions in linking the reaction to a particular medication, which was useful in causality assessment.
- Compared to HCP's reports, patient reports frequently included more detailed narratives with no unrelated information.
- Patient reports frequently provided in-depth information regarding the impact on the patient's life of the suspected adverse drug reactions, revealing insights that were not commonly found in the reports or were comparatively uncommon in HCP's reports.
- Most patients reported clinically meaningful issues that HCPs and the relevant regulatory body had also regarded as serious.
- Patient reports strengthen HCP reports by contributing new, potentially significant signals.

The majority of patient reporters said that reporting was at least "pretty easy" and that they would have welcomed feedback.

This study demonstrates the importance of consumer reporting and supports the continued promotion of consumer reporting. Patients and anticipated medicine users should not just be treated as passive recipients of treatments but also included in the development and usage of new treatments as this is in accordance with the ethical consideration of principles of beneficence and non-maleficence, such exclusion might decrease benefit while heightening harm (CIOMS, 2022:xv).

In a study by Rolfes *et al.* (2018:1523) to determine whether consumers' reports resulted in earlier discovery of drug safety signals, it was found that consumers reported on average later than HCPs did, but that consumers contributed a significant portion of reports on drug-ADR pairs that ultimately became drug safety signals. This highlights the significant role that consumer reports play in pharmacovigilance.

Consumer participation in pharmacovigilance is crucial, and as a result, active promotion of consumer reporting through various tactics directed at both consumers and HCPs is necessary. These tactics may include using internet tools and running awareness campaigns (Matlala *et al.*, 2023:8-9).

Despite the obvious advantages mentioned above, some have noted biased reporting subject to media reports, increasing the reporting system's load with excessive ADEs to the detriment of signal detection and inconsistent quality of consumer reports received. These are some of the disadvantages of adding consumers in reporting of ADEs (Hazell *et al.*, 2013:200). Although some consumers' reports may be incomplete or overstated, a UK study found that overall; they still reflect sound logic (Patel *et al.*, 2018:1777).

## **2.5 Attitudes and practices of consumers regarding ADE reporting**

In order to identify elements that can be targeted in future efforts that can be directed at enhancing ADE reporting, it is necessary to understand the attitudes and practices of medicine users in relation to ADE (Sabblah *et al.*, 2017:913). The following topics present the attitudes and practices of medicine users regarding ADE reporting globally.

### **2.5.1 Awareness, attitudes and practices.**

A growing number of nations support direct consumer reporting, and many institutions concur that these reports can benefit pharmacovigilance; however, despite this, some countries struggle to implement or improve consumer-reporting systems due to a shortage of resources, personnel, and population literacy levels (Matos *et al.*, 2016:1114-1115).

Several studies have been conducted to identify medicine users' attitudes as well as behaviors regarding adverse events and the reporting of adverse events. The characteristics of the studies that were included in this literature review, are presented in Table 2 2.

**Table 2-2: Characteristics of included studies**

<b>Authors</b>	<b>Study Title</b>	<b>Data collection method</b>	<b>Study Setting</b>	<b>Number of participants</b>
Adisa <i>et al.</i> (2019)	Knowledge, awareness, perception and reporting of experienced adverse drug reactions among outpatients in Nigeria	Investigator administered questionnaire	Nigeria	1190
Elkalmi <i>et al.</i> (2013)	Adverse drug reactions reporting: knowledge and opinion of general public in Penang, Malaysia	A self-administered questionnaire	Malaysia	334
Hariraj and Aziz (2018)	Patient reporting of adverse drug reactions (ADRs): survey of public awareness and predictors of confidence to report	Investigator administered questionnaire	Malaysia	860
Jacobs <i>et al.</i> (2018)	The contribution of Ghanaian patients to the reporting of adverse drug reactions: a quantitative and qualitative study	Investigator administered questionnaire and interviews	Ghana	572
Kim <i>et al.</i> (2020)	A cross-sectional survey of knowledge, attitude, and willingness to engage in spontaneous reporting of adverse drug reactions by Korean consumers	A self-administered questionnaire	Korea	1000
Patel <i>et al.</i> (2019)	Knowledge, attitude and practice among consumers about adverse drug reaction reporting	Investigator administered questionnaire-based	India	820
Pillay <i>et al.</i> (2021)	Parental reporting of adverse drug reactions in South Africa: an online survey	A self-administered questionnaire	South Africa	206
Sabblah <i>et al.</i> (2017)	Patients' perspectives on adverse drug reaction reporting in a developing country: a case study from Ghana	Investigator administered questionnaire	Ghana	434
Sales <i>et al.</i> (2017)	Public awareness and perception toward adverse drug reactions reporting in Riyadh, Saudi Arabia	A self-administered questionnaire	Saudi Arabia	204
Wang <i>et al.</i> (2022)	A cross-sectional study: comparison of public perceptions of adverse drug reaction reporting and monitoring in eastern and western China	A self-administered questionnaire	China	869
Zondi and Naidoo (2022)	Perceptions, practices and barriers to reporting of adverse drug reactions among HIV infected patients and their doctors in 3 public sector hospitals of the eThekweni Metropolitan, Kwa-Zulu Natal: a cross-sectional and retrospective analysis	A self-administered questionnaire	South Africa	426

The sections that follow will provide insights into the findings of these studies.

### 2.5.1.1 Consumer awareness

Consumer awareness regarding ADE includes awareness of the phrase "adverse drug event," by users, the requirement to report ADEs, the reporting process, and their national pharmacovigilance centers.

#### 2.5.1.1.1 Awareness regarding the term adverse drug event

There were large variations in participant awareness of ADEs, with some studies (Kim *et al.*, 2020:4; Sales *et al.*, 2017:869; Wang *et al.*, 2022:4), reporting that 25.7% to 51.9% of participants could correctly define an ADE. While in other studies (Jacobs *et al.*, 2018:5; Patel *et al.*, 2019:1779) between 67.8% and 86% of participants were aware of ADE. The study performed in South Africa reported 70.9 % of the participants knew the term (Pillay *et al.*, 2021:6).

#### 2.5.1.1.2 Awareness regarding the requirement to report ADEs

All studies that addressed this topic found that participants were aware that they needed to report ADEs, with awareness rates ranging from 72.9% to 94% of participants indicating this. (Adisa *et al.*, 2019:1067; Kim *et al.*, 2020:4; Patel *et al.*, 2019:1778). Despite this understanding of the reporting obligation, not all ADEs were reported, with the lowest number of reported ADEs being 3.4% in one of the studies (Kim *et al.*, 2020:4).

#### 2.5.1.1.3 Awareness regarding the process of reporting ADEs

There were wide variances in the participants' knowledge of the ADE reporting process, with one study stating that only 3.9% of the participants were aware of the process and another reporting that as high as 86.6% were aware of the reporting process. The study performed in South Africa found that 58.7% of the participants knew the process to report ADEs (Pillay *et al.*, 2021:4). Lack of awareness has been cited as one of the most common barriers to ADE reporting, as discussed in section 2.6.1 Barriers to ADE reporting.

#### 2.5.1.1.4 Awareness of the National Pharmacovigilance Centre

One aspect of the studies was to determine whether the participants were aware of their national pharmacovigilance centres and it was discovered that the majority of participants were unaware of the centre's existence (Elkalmi *et al.*, 2013:226; Hariraj & Aziz, 2018:758; Jacobs *et al.*, 2018:5; Sabblah *et al.*, 2017:915). One study reported that only 1.2% of participants were aware of their centre (Patel *et al.*, 2019:1778). However, this contrasts with a study performed in Ghana which

revealed that 81.6% of participants were aware of their country's national centre (Sabblah *et al.*, 2022:915). Consumer ignorance of the presence of their country's pharmacovigilance center and their role in the collection of ADEs is one of the most common barriers to reporting, as provided in section 2.6.1 Barriers to ADE reporting.

### **2.5.1.2 Consumer attitudes and practice regarding ADEs and ADE reporting**

The necessity of reporting ADEs and whether persons who encountered ADEs did so, as well as to whom these reports are submitted, were among the consumer attitudes and practices on ADEs and ADE reporting that were evaluated.

#### **2.5.1.2.1 Consumer attitudes on the importance of reporting ADEs**

When participants were asked whether they thought it was important or necessary to report ADEs, a significant majority (more than 90%) of them said yes (Adisa *et al.*, 2019:1067; Kim *et al.*, 2020:4; Pillay *et al.*, 2021:5; Sales *et al.*, 2017:870). The study performed in South Africa reported that 99% of the participants believed that reporting ADEs was important (Pillay *et al.*, 2021:5). Some of the motivational factors that participants reported as driving them to report are described in detail in section 2.6.2 Enablers of ADE reporting. Despite knowing of the importance of reporting, this does not always translate into reporting of ADEs, as seen in the study by Kim *et al.* (2020:4) where 93.9% of the participants agreed on the importance of reporting, however only 3.4% of the participants actually reported the experienced ADEs.

#### **2.5.1.2.2 Consumer practices regarding reporting ADEs**

The studies assessed whether participants had previously experienced ADEs. The findings revealed that in the majority of studies, fewer than 50% of participants reported past ADEs (Adisa *et al.*, 2019:1067; Elkalimi *et al.*, 2013:226; Jacobs *et al.*, 2018:5; Patel *et al.*, 2019:1779; Sabblah *et al.*, 2017:917). The study performed in South Africa found that 72% of the participants reported to have experienced ADEs (Zondi & Naidoo, 2022:7).

A high percentages of people who indicated to have encountered ADEs, reported them (Adisa *et al.*, 2019:1067; Elkalimi *et al.*, 2013:226; Jacobs *et al.*, 2018:5; Patel *et al.*, 2019:1779; Sabblah *et al.*, 2017:917), with only 47% of South African participants reporting (Zondi & Naidoo, 2022:7). The high reporting is however in contrast to Malaysia and Korea, where only 18% and 3.4% of participants, respectively, reported their experienced ADEs (Hariraj & Aziz, 2018:758; Kim *et al.*,

2020:4). A variety of factors as discussed in section 2.6 Barriers and enablers of ADE reporting influence the practice of reporting ADEs.

The participants who reported ADEs said they had reported them to their HCPs with the majority reporting to their doctor (Adisa *et al.*, 2019:1067; Elkalmi *et al.*, 2013:226; Hariraj & Aziz, 2018:758; Jacobs *et al.*, 2018:7; Patel *et al.*, 2019:1779; Sabblah *et al.*, 2017:916). Section 2.5.2 discusses the relationship between medicine users and HCPs regarding the reporting of ADEs.

### **2.5.2 Healthcare Professional (HCP) awareness and attitudes towards ADE reporting**

The influence of interactions with HCPs must also be considered when evaluating the experience of consumers reporting ADEs, because the reporting of ADEs by HCPs is fundamental to pharmacovigilance (Asiamah *et al.*, 2022:7). As further reporting the ADEs is largely voluntary from the perspective of a HCP, collaboration and commitment by HCPs is important. This is because reports of ADEs from HCPs often originate from the reports that consumers share with their HCP (Waller, 2010:34).

Knowledge of ADRs and pharmacovigilance is generally strong, and there is agreement across HCP on the need of ADE reporting and the positive role it plays in safeguarding public safety (Bogolubova *et al.*, 2018:5; Gordhan & Bangalee, 2022:81; Hussain *et al.*, 2021:4; Khan *et al.*, 2023:17). However, when it comes to the practice of reporting ADEs, this perceived importance does not translate into actual reporting, with studies indicating that more than 60% of healthcare workers admitted to encountering ADEs but did not report them (Bogolubova *et al.*, 2018:6; Khan *et al.*, 2023:11).

The reporting by HCPs is influenced by a variety of factors. Important factors that have been identified through studies include complacency, procrastination, unavailability of reporting tools, lack of time, deeming the event unrelated, fear of the legal implications of reporting and lack of awareness (Asiamah *et al.*, 2022:2; Bogolubova *et al.*, 2018:5; Le *et al.*, 2020:124-125; Varallo *et al.*, 2014:740). Even though Asiamah *et al.* (2022:9) found that HCPs' knowledge did not influence their attitudes regarding reporting, they contend that making reporting by HCPs mandatory will increase the practice of reporting. However, Waller (2010:34) notes that even in nations where reporting by HCP is mandatory, this did not raise reporting rates due to poor enforcement ability.

Due to the intimate contact that HCPs have with consumers, consumer reporting of ADEs cannot be completely separated from HCPs, hence strategies to encourage HCPs and consumer

collaboration in reporting ADEs are necessary (Inacio *et al.*, 2018:750). This indicates that in conjunction with efforts aimed at consumers to improve reporting of ADEs, equal efforts must be extended to ensure that HCP are aware of the significance of submitting these reports, as only then will the increase in consumer reporting result in an overall increase in ADEs reported to the pharmacovigilance centres (Sabblah *et al.*, 2017:917).

### **2.5.3 Influence of severity of ADE on consumer reporting of ADEs**

When it comes to assigning severity to ADEs, research has found that both HCPs and consumers assess the severity in the same manner (Avery *et al.*, 2011:116). However, consumers, as opposed to HCPs, tend to report on the severity of the ADE and its impact on their daily life rather than casually, which is evident in HCP's reports (Harmark *et al.*, 2015:344).

Studies have shown that consumers tend to report more ADEs that are serious in nature than those that are mild and that the severity of the ADEs is one of the factors that encourages consumers to report ADEs. (Al Dweik *et al.*, 2017:881; Kitisopee *et al.*, 2022:8; Krska *et al.*, 2011:1101; Pillay *et al.*, 2021:5; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147).

In a study by Sales in Saudi Arabia, many respondents said they would not report a non-serious ADE, which suggests that they are unaware of the objectives and purpose of ADE monitoring (Sales *et al.*, 2017:871). Matlala *et al.* (2023:8) discovered that when it came to serious ADEs, the filed reports were more complete, demonstrating the level of effort that is taken while reporting these.

The above observation that patients tend to report more serious ADEs and that consumer perceptions of seriousness are generally consistent with those of HCPs, suggests that researchers' concerns (Hazell *et al.*, 2013:200) regarding a rise in frivolous reporting should be put to rest.

### **2.6 Barriers and enablers of adverse drug event reporting**

Lack of reporting or low levels of reporting of ADEs make it challenging to recognise risks to patient safety; therefore it is critical to comprehend the aspects that act as barriers and enablers to ADE reporting (Archer *et al.*, 2017:1).

In order to identify some of the frequently reported barriers and enablers of consumer reporting of ADEs, several studies that included this as part of their scope were analysed with the findings summarised in the sections below. The research utilised to develop this section is listed in Table 2-3.

**Table 2-3: Studies used to determine barriers and enablers.**

Author	Study Title	Study Setting
Adisa <i>et al.</i> (2019)	Knowledge, awareness, perception and reporting of experienced adverse drug reactions among outpatients in Nigeria	Nigeria
Al Dweik <i>et al.</i> (2017)	Factors affecting patient reporting of adverse drug reactions: a systematic review	International
Arnott <i>et al.</i> (2013)	What can we learn from parents about enhancing participation in pharmacovigilance?	England
Avery <i>et al.</i> (2011)	Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys	United Kingdom
Elkalmi <i>et al.</i> (2013)	Adverse drug reactions reporting: knowledge and opinion of general public in Penang, Malaysia	Malaysia
Hariraj and Aziz (2018)	Patient reporting of adverse drug reactions (ADRs): survey of public awareness and predictors of confidence to report	Malaysia
Jha <i>et al.</i> (2014)	Pharmacovigilance knowledge among patients at a teaching hospital in Lalitpur District, Nepal	Nepal
Kim <i>et al.</i> (2020)	A cross-sectional survey of knowledge, attitude, and willingness to engage in spontaneous reporting of adverse drug reactions by Korean consumers	Korea
Kitisopee <i>et al.</i> (2022)	Consumers' adverse drug event reporting via community pharmacists: three stakeholder perception	Thailand
Krska <i>et al.</i> (2011)	Medicine safety: experiences and perceptions of the public in Liverpool	England
Matos <i>et al.</i> (2016)	Patient reporting of adverse drug reactions: an international survey of National Competent Authorities' views and needs	International
Patel <i>et al.</i> (2019)	Knowledge, attitude and practice among consumers about adverse drug reaction reporting	India
Pillay <i>et al.</i> (2021)	Parental reporting of adverse drug reactions in South Africa: an online survey	South Africa
Sabblah <i>et al.</i> (2017)	Patients' perspectives on adverse drug reaction reporting in a developing country: a case study from Ghana	Ghana
Sales <i>et al.</i> (2017)	Public awareness and perception toward adverse drug reactions reporting in Riyadh, Saudi Arabia	Saudi Arabia
Salvo <i>et al.</i> (2013)	Attitudes and opinion about adverse drug events of women living in a city of south Italy	Italy

Author	Study Title	Study Setting
Adisa <i>et al.</i> (2019)	Knowledge, awareness, perception and reporting of experienced adverse drug reactions among outpatients in Nigeria	Nigeria
Valinciute-Jankauskiene and Loreta (2021)	Qualitative study of public views towards adverse drug reactions in Lithuania	Lithuania
van Hunsel <i>et al.</i> (2012)	Experiences with adverse drug reaction reporting by patients an 11-country survey	International
Wang <i>et al.</i> (2022)	A cross-sectional study: comparison of public perceptions of adverse drug reaction reporting and monitoring in eastern and western China	China
Zondi and Naidoo (2022)	Perceptions, practices and barriers to reporting of adverse drug reactions among HIV infected patients and their doctors in 3 public sector hospitals of the eThekweni Metropolitan, Kwa-Zulu Natal: a cross-sectional and retrospective analysis	South Africa

## 2.6.1 Barriers to adverse drug event reporting

It is critical to identify influential factors that function as obstacles to reporting in order to develop strategies for enhancing the voluntary reporting of ADEs by patients (Al Dweik *et al.*, 2017:876). The four most common reasons why participants said they had experienced ADEs, but did not report them, are as follows:

### 2.6.1.1 Lack of awareness

Lack of awareness was reported as one of the barriers to ADE reporting. This included participants who did not know what ADEs were, what to report, reporting systems that are accessible or their role in reporting (Adisa *et al.*, 2019:1064; Al Dweik *et al.*, 2017:877; Arnott *et al.*, 2013:1115; Elkalmi *et al.*, 2013:227; Hariraj & Aziz, 2018:758; Jha *et al.*, 2014:34; Kim *et al.*, 2020:5; Kitisopee *et al.*, 2022:9; Krska *et al.*, 2011:1101; Patel *et al.*, 2019:1776; Robertson & Newby, 2013:685; Sales *et al.*, 2017:871; Salvo *et al.*, 2013:176; Valinciute-Jankauskiene & Loreta, 2021:6; Wang *et al.*, 2022:6). In the research conducted in South Africa, lack of awareness was also identified as a barrier to consumer reporting (Pillay *et al.*, 2021:5; Zondi & Naidoo, 2022:11).

### **2.6.1.2 Reporting processes that are difficult to follow**

The reporting process was mentioned as a concern. Reporting forms are not easy to complete, and are time-consuming. There is also a lack of resources or time in the consultation room to facilitate consumer reporting to their HCP (Al Dweik *et al.*, 2017:878; Hariraj & Aziz, 2018:758; Kim *et al.*, 2020:8; Kitisopee *et al.*, 2022:9; Matos *et al.*, 2016:1106; Valinciute-Jankauskiene & Loreta, 2021:6). Complicated reporting procedures were also noted as a barrier to consumer reporting in the South African research (Pillay *et al.*, 2021:5; Zondi & Naidoo, 2022:8).

### **2.6.1.3 The expectation that ADEs will resolve**

Knowing about the expected ADE and expecting that the ADE will resolve in time, has been cited as a barrier to reporting ADEs. Research has found that the following groups of people often did not report ADEs (Al Dweik *et al.*, 2017:878; Hariraj & Aziz, 2018:758; Krska *et al.*, 2011:1101; Robertson & Newby, 2013:685; Wang *et al.*, 2022:6):

- people who believed the ADEs would resolve in time without any intervention,
- those who had been told by their HCP to expect the occurrence of the ADE,
- people who had previously experienced the same ADE, and
- people who believed that their experienced ADE was not serious.

In the South African study, this belief that the reported ADEs will resolve and do not need to be reported, was also identified as a barrier to consumer reporting (Zondi & Naidoo, 2022:8).

### **2.6.1.4 Apprehension of harmful consequences from HCP**

One reason given for not reporting ADEs was fear of negative outcomes from HCPs, which included situations in which people feared that they would look as though they were challenging their HCP, those who feared offending the HCP, those who had been dissuaded from reading the brochures and learning more about their medicines by their healthcare providers, and those who were worried that they could cause trouble for the HCP (Al Dweik *et al.*, 2017:877; Arnott *et al.*, 2013:1115; Robertson & Newby, 2013:685; Valinciute-Jankauskiene & Loreta, 2021:6):

Similar worries were voiced by participants in South Africa (Pillay *et al.*, 2021:5):

Other cited barriers include lack of feedback on previously reported ADE, lack of interest from HCPs as well as uncertainty about whether the medicine they had taken had caused the ADE (Al

Dweik *et al.*, 2017:877; Kim *et al.*, 2020:8; Kitisopee *et al.*, 2022:4; Sales *et al.*, 2017:871; Valinciute-Jankauskiene & Loreta, 2021:6; Wang *et al.*, 2022:6).

These noted barriers suggest that patient education initiatives about ADEs, their effects, and consumers' roles in ADE reporting will significantly increase consumer engagement in pharmacovigilance activities. It has been reaffirmed by Kruger and Gasperini (2020:4) that the main aspects to improve direct reporting by consumers is to inform and teach consumers, as well as to develop more effective ways to involve them in the entire pharmacovigilance process.

## **2.6.2 Enablers of adverse drug event reporting**

Participants who said they had previously reported ADEs had some factors in common that they felt encouraged or made it easier for them to report. The most frequent explanations are as follows.

### **2.6.2.1 Noble motives**

The reporting of ADEs was motivated by humanitarian intentions which included persons who wanted to contribute to research and information about medicine by sharing their experiences, those who felt it was their responsibility to report or to promote awareness regarding the ADEs, and those who wished to stop others from experiencing the same ADEs (Al Dweik *et al.*, 2017:877; Hariraj & Aziz, 2018:758; Kim *et al.*, 2020:5; Kitisopee *et al.*, 2022:6; Pillay *et al.*, 2021:5; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147). All of these incentives seem to be more focused on enhancing communal safety than merely benefiting the individual and the study performed in South Africa echoed this sentiment (Pillay *et al.*, 2021:5). However, a study done in Ghana shows that this is not always the case, with self-preservation being the most cited motivational factor for reporting ADEs (Adisa *et al.*, 2019:1067).

### **2.6.2.2 Severity of ADE**

The severity of the experienced ADEs was cited as a motive for participants to report, with the participants who perceived their experienced ADEs to be serious or severe being more likely to report as opposed to those who experienced minor ADEs (Al Dweik *et al.*, 2017:881; Krska *et al.*, 2011:1101; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147). This idea was supported in the South African study (Pillay *et al.*, 2021:5). The impact of ADE severity on consumer reporting of ADEs is described in detail in Section 2.5.3.

Other cited motivators as noted in the research (Al Dweik *et al.*, 2017:882; Avery *et al.*, 2011:122; Pillay *et al.*, 2021:5; Zondi & Naidoo, 2022:5) included:

- participants who wished to tell someone about their experience,
- participants who were interested in learning more about their experience,
- those who received instructions from a HCP, family members, or anybody else to report ADEs if they experienced them, and
- participants who read the information leaflet supplied with their medicine but could not find a mention of their event.

## **2.7 Regulatory requirements for ADE reporting in South Africa**

The function of regulatory authorities is to safeguard the public's health and to promote safe and effective use of medicines. From a pharmacovigilance standpoint, the regulator protects the public's health by taking steps to prevent serious adverse drug reactions and by regulating the industry to ensure compliance with its pharmacovigilance obligations (Waller, 2010:61-65).

The regulatory requirements for ADE reporting in South Africa and the way in which they enable ADE reporting, are described below.

### **2.7.1 WHO Programme for International Drug Monitoring (WHO PIDM)**

South Africa became the first nation in Africa to join the WHO PIDM as a full member in 1992 and as a member state; South Africa is required to comply with several duties related to the conduct of pharmacovigilance activities in the nation (SAHPRA, 2020b:14).

As a member state of WHO PIDM, South Africa is obligated to actively participate in reporting cases and establish nationwide information-sharing mechanisms. The alliance with WHO PIDM has some advantages that include access to combined knowledge from all member nations, software and tools for data collection and analysis with early warnings of recognised safety signals (UMC, 2014:2-7). The South African Health Products Regulatory Authority (SAHPRA), in cooperation with the National Department of Health (NDoH), serves as the central coordinator of surveillance activities (SAHPRA, 2020b:12).

Table 2-4 summarises some of the essential criteria for national pharmacovigilance systems as set by WHO and indicates whether or not South Africa satisfies these criteria.

**Table 2-4: WHO PIDM criteria**

<b>Criteria</b>	<b>South Africa</b>
Presence of a facility for handling pharmacovigilance activities	South African Health Products Regulatory Authority (SAHPRA) Pharmacovigilance unit, handles pharmacovigilance activities
Are pharmacovigilance activities endorsed by legislation?	Regulation 40 of the <i>Medicines and Related Substances Act</i> 101 of 1965
Presence of regulatory authority	South African Health Products Regulatory Authority (SAHPRA) is the medicines regulatory authority.
Funding for pharmacovigilance centre is available	SAHPRA is funded by the National Department of Health, Industry fees charged and grant income from donors.
Personnel to carry out PV functions available	Yes
Standard ADR reporting form present?	Adverse drug reactions and quality problem reporting form
Is there a system in place to collect, document, and evaluate ADR reports?	National Vigilance Policy for Health Technologies in SA”
Is pharmacovigilance taught in national curriculum for different healthcare professions?	Yes
Is there a communication tool for sharing information on pharmacovigilance	VigiGuardian Newsletter
Presence of pharmacovigilance advisory committee	The Pharmacovigilance Committee (PVC)

Adapted from (SAHPRA, 2020b:14,20,25; SAHPRA, 2022b:83-87, 98; SAHPRA, 2022f)

Considering the aforementioned, it can be said that South Africa, due to its membership in the WHO PIDM and in compliance with the WHO PIDM requirements, has minimal processes in place that permit reporting of ADEs.

### **2.7.2 Legislation in South Africa**

Pharmacovigilance is one of the requirements for medicine registration, according to Regulation 40 of the *Medicines and Related Substances Act* 101 of 1965, as amended (SAHPRA, 2020b:13).

The existence of a pharmacovigilance-related legal provision demonstrates the government's commitment to ensuring the safe use of medications, and it permits pharmacovigilance centres to effectively carry out their duties with confidence (WHO, 2015:19).

Regulation 40 of South Africa's *Medicines and Related Substances Act* 101 of 1965, as amended, contains the following requirements to encourage the reporting of ADEs.

*“(1) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C (1) (b) must inform the Authority, in the manner and within the time frame as determined by the Authority, of any –*

- (a) new or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to adverse drug reactions; and*
- (b) risk management activities associated with paragraph (a).”*

*“(2) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C(1)(b) must maintain or have access to records of the reports and case reports referred to in sub regulation (1) above.”*

*“(3) A healthcare provider, veterinarian or any other person should inform the Authority, in the manner as determined by the Authority, of any-*

- (a) suspected adverse drug reactions; or*
- (b) new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance.”*

The abovementioned regulations clearly create the tone that supports reporting of ADEs by anybody and holds medicine manufacturers accountable when it comes to fulfilling their role in ensuring medicine safety in South Africa.

### **2.7.3 Oversight of pharmaceutical industry**

The pharmaceutical industry is subject to regulatory requirements on how pharmacovigilance is handled within their organisations; those requirements that underpin ADE reporting can be summed up as follows (Waller, 2010:65-66):

- The ADR reporting process must be outlined in writing.
- Within 15 days, notify the authorities of any serious safety incidents.
- Alert regulatory agencies to information that could alter the risk/benefit ratio.
- Systematically scan the medical literature to find case reports of reported adverse drug reactions.

The Pharmacovigilance Systems Guideline developed by SAHPRA outlines the procedures in South Africa to provide oversight of the pharmaceutical industry and enables ADE reporting in South Africa. Every pharmaceutical company must have the following in place(SAHPRA, 2022e):

- Adhere to the pharmacovigilance requirements of the revised *Medicines and Related Substances Act* 101 of 1965, as amended.
- In general, pharmaceutical companies should make sure that the necessary systems and procedures are in place for them to adequately carry out their duties.
- ADEs from any source are collected, managed, quality-controlled, followed up on for missing data, coded, classified, looked for duplicates, evaluated, and promptly transmitted electronically .
- Pharmaceutical companies should communicate with the authority about safety issues, especially when it comes to alerting the authority to changes in the risk-benefit ratio of pharmaceuticals.
- To ensure the safe and effective use of medications, information concerning changes to the risk-benefit ratio of products must be shared with consumers and HCP.
- The regulatory body monitors and conducts inspections of MAH.

#### 2.7.4 Tools for reporting ADEs in South Africa

Table 2-5 lists the various methods available in South Africa for anyone seeking to report ADEs to SAHPRA, including paper-based and electronic ones, and information on who may use them (SAHPRA, 2022f:10-11).

**Table 2-5: Tools for ADE reporting in South Africa**

Tool	Who can use the tool
Med Safety Application (App)	Medicine users and healthcare professionals can use this application to report ADEs to SAHPRA (SAHPRA, 2021a). The App can be downloaded from <a href="https://medsafety.sahpra.org.za">https://medsafety.sahpra.org.za</a> .
eReporting	This is a component of the VigiFlow system that medicine users and healthcare professionals can use to report ADEs to SAHPRA (SAHPRA, 2023c) The link to eReporting is available from <a href="https://primaryreporting.who-umc.org/ZA">https://primaryreporting.who-umc.org/ZA</a> .

ADR & Quality Problem Reporting Form	This paper-based form can be completed by both the medicine users and healthcare professionals and emailed to SAHPRA (SAHPRA, 2020a). This form is available from <a href="https://www.sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf">https://www.sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf</a>
AEFI Reporting Form	This paper-based form can be completed by healthcare professionals for ADEs related to immunisations and emailed to the National Expanded Programme on Immunization (EPI) Coordinator (DoH, 2021a). This form is available from <a href="https://www.sahpra.org.za/wp-content/uploads/2021/03/Case-Report-Form_AEFI_All-vaccines-incl-COVID-19_20210128.pdf">https://www.sahpra.org.za/wp-content/uploads/2021/03/Case-Report-Form_AEFI_All-vaccines-incl-COVID-19_20210128.pdf</a>
E2b	This is an electronic reporting tool that pharmaceutical companies can use. Reporting is done via e2b@sahpra.org.za
Council for International Organisation of Medical Science (CIOMS) reporting form	This is a paper-based form that can be completed by pharmaceutical companies and emailed to SAHPRA (CIOMS, 2017) This form is available from <a href="https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf">https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf</a>

## 2.8 Chapter Summary

In this chapter, literature on what is currently known, was provided. The findings are summed up as follows:

- The literature generally displays conflicting views regarding the medicine users' understanding of the phrase "adverse drug event," and there is a general lack of knowledge regarding the existence of national pharmacovigilance centres. However, understanding of ADRs and pharmacovigilance among HCPs was determined to be adequate. Knowledge regarding the reporting process of ADEs was found to be lacking in both HCPs and medicine users.
- In general, there is consensus in the literature among both HCPs and medicine users about the importance of reporting ADEs, which is encouraging since it provides a starting point for ensuring that initiatives to promote ADE reporting are well received. When it comes to the practice of reporting ADEs, it has been shown that the majority of medicine users who reported having encountered ADEs reported them; this is in contrast with the HCPs where the majority, despite being aware of the ADEs, still choose not to report. The HCP is the most preferred person to report to.
- The barriers and facilitators that affect ADE reporting globally were widely explored in the reviewed literature, with lack of awareness being listed as the most common barrier, and

humanitarian concern for others being cited as the most common enabler. One of the obstacles influencing the practice of ADE reporting by HCPs is a lack of awareness.

- According to Regulation 40 of the Medicines and Related Substances Act 101 of 1965, as amended, pharmacovigilance is one of the prerequisites for medicine registration in South Africa. There is a well-established national pharmacovigilance system in place in South Africa, and existing tools support the reporting of ADEs by medicine users.

Although there is a lot of information about pharmacovigilance and consumer reporting, consumer engagement in some countries is still low. By understanding the drivers and barriers to ADE reporting, we may build strategies to increase consumer reporting globally.

## **CHAPTER 3      RESULTS AND DISCUSSION**

The findings of the study's empirical investigation are presented in this chapter. The following were the objectives of the study's empirical section:

- To assess adults' awareness of pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa.
- To describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa.

Two articles have been prepared for publication as comprehensive summaries of the results. See details of the articles in Table 3-1.

**Table 3-1: Manuscript details**

Objectives	Questionnaire section	Manuscript
<p><b>Objective 1</b> To assess adults' awareness of pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa.</p>	<p><b>Related questions:</b></p> <p><b>Section A: Demographics</b></p> <p><b>Section B</b></p> <ul style="list-style-type: none"> <li>• Have you heard about the term adverse drug events?</li> <li>• Do adverse drug events have to be reported?</li> <li>• Where did you hear about the reporting of adverse drug events?</li> <li>• Which age groups can experience adverse drug events?</li> <li>• Who can report adverse drug events?</li> <li>• Have you heard of Med Safety App, a mobile application that can be used to report suspected adverse drug events?</li> <li>• Have you heard of the South African Health Products Regulatory Authority ?</li> </ul> <p><b>Section C</b></p> <ul style="list-style-type: none"> <li>• Have you or anyone you look after ever used medication?</li> <li>• Did you ask your healthcare professional about the potential adverse effects of your medication?</li> <li>• Did your healthcare professional inform you about the potential adverse effects of your medication?</li> <li>• I did not get the medicine from a healthcare professional.</li> <li>• Do you ever read the patient information leaflet that comes with your prescription medication?</li> <li>• Do you believe it is important or necessary to report adverse events that you may experience after taking medication?</li> <li>• Why it is important to report adverse drug events?</li> <li>• Do you feel well informed about the adverse effects that your medication may cause?</li> <li>• Do you wish you could get more information about the adverse effects of your medication?</li> </ul>	<p>Manuscript 1</p> <p>Title Awareness and attitudes regarding adverse drug events and reporting in South Africa</p> <p>Journal <i>Pharmacoepidemiology and Drug Safety.</i></p>

<p><b>Objective 2</b> To describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa.</p>	<p><b>Section A: Demographics</b></p> <p><b>Section C</b></p> <ul style="list-style-type: none"> <li>• Have you ever experienced adverse drug events after taking medicine?</li> <li>• Did this occur after using or taking medicine; vaccination /immunisation, using a medical device?</li> <li>• Was this reported to anyone?</li> </ul> <p><b>Section D</b></p> <ul style="list-style-type: none"> <li>• When was the adverse drug event reported?</li> <li>• To whom did you report the adverse drug event?</li> <li>• To what extent did the below motivate your decision to report?</li> </ul> <p><b>Section E</b></p> <ul style="list-style-type: none"> <li>• To what extent did the below influence your decision not to report?</li> <li>• Are you likely to report any adverse drug events you may have in the future?</li> </ul>	<p>Manuscript 2</p> <p>Title Barriers and enablers of adverse drug event reporting in South Africa: a cross-sectional survey of medicine users</p> <p>Journal <i>BMC Public Health.</i></p>
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### 3.1 Manuscript 1

**Title:** Awareness and attitudes regarding adverse drug events reporting in South Africa

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**Abstract**

**Purpose:** Reporting of adverse drug events (ADEs) by consumers, enhances medication-related risk surveillance, public awareness, and understanding of medicine safety. The aim of this study was to explore adults' awareness of ADEs, attitudes towards reporting and perceptions of their role in reporting ADEs in South Africa.

**Method:** We conducted a cross-sectional, analytical study in which adults residing in South Africa completed an online questionnaire. The data collected was analysed using both descriptive and inferential statistics.

**Results:** We received responses from 350 participants. Most participants (86.2%,  $n = 302$ ;  $N = 350$ ) reported having heard about ADEs and the majority of participants (94.4%,  $n = 301$ ;  $N = 319$ ) indicated that reporting of ADEs was important. The Med Safety App was not widely known (17.3%,  $n = 58$ ;  $N = 336$ ) while the South African Health Products Regulatory Authority (SAHPRA) was relatively well known (77.4%,  $n = 260$ ;  $N = 336$ ). Healthcare providers only educated 55.7% ( $n = 180$ ;  $N = 323$ ) of the participants about ADEs and only 50.5% ( $n = 163$ ;  $N = 323$ ) of the participants asked their healthcare providers about ADEs. Awareness regarding ADEs was

significantly higher ( $p < 0.001$ ) among healthcare professionals (HCPs) compared to non-healthcare professionals (non-HCP)

**Conclusion:** Most participants were aware of ADEs and agreed it was important to report ADEs although reporting tools, such as the Med Safety App, were not well known. We recommend awareness campaigns on reporting processes because this could improve consumer reporting of ADEs in South Africa.

**Keywords:** Adverse drug events; drug side-effects, reporting, consumer, pharmacovigilance.

### **Key Points**

- Most participants were aware of the need to report any ADEs they experience.
- Awareness of ADEs was noticeably higher among HCP compared to non-HCP.
- A small proportion of participants knew about the Med Safety App, which was launched in 2021 in South Africa to improve ADE reporting.
- There is agreement among the participants regarding the importance of ADE reporting in order to raise awareness of and protect others from experiencing the same ADEs.

### **Plain language summary**

Reporting of side effects by consumers makes risks associated with the use of medicine easily identifiable and this contributes to raising public awareness regarding medicine safety. This study assessed adults' awareness about pharmacovigilance, adverse drug events (ADE), attitudes towards reporting and perceptions of their role in reporting ADEs in South Africa. Adults in South Africa were invited to participate in an online survey on SurveyMonkey®. The findings indicate that there is awareness of ADEs, however, there is a lack of knowledge about the MedSafety App, which was launched in 2021 to promote ADE reporting in South Africa. There is agreement among participants that it is important to report ADEs. Awareness campaigns to promote the available methods may result in enhanced reporting.

## **1. INTRODUCTION**

Medicines are of great importance because they are used to treat and prevent a range of diseases. However, the use of medicines is not without challenges. It is important to monitor the

adverse effects that are experienced in order to gather information on which risk-benefit assessments can be made. Therefore, systems should be in place to monitor and report any suspected ADEs.<sup>1</sup>

Spontaneous reporting of ADEs to pharmacovigilance centres is the key method for gathering post-marketing data on medicine safety.<sup>2</sup> These reports can be received from various sources, including medicine users or consumers, HCPs, the pharmaceutical industry and medical literature.<sup>3</sup>

In recent years, there has been an increase in direct consumer reporting of ADEs to national pharmacovigilance centres.<sup>4</sup> Consumer reporting offers additional perspectives on people's experiences with ADEs that are unavailable from the HCP reports. With the rise of the internet and social media, consumers can play a significant role in pharmacovigilance because their opinions could alter the benefit-harm analysis of drugs.<sup>5</sup>

To allow for consumer involvement in pharmacovigilance, they must be aware of what needs to be reported, who to report to, and they must have easy access to the reporting tools.<sup>6</sup> Therefore, awareness campaigns aimed at increasing consumer reporting, which focuses on both consumers and HCPs, must be undertaken.<sup>7</sup>

South Africa became the first African nation to join the World Health Organization's Programme for International Drug Monitoring as a full member in 1992.<sup>8</sup> As a member state of this programme, South Africa must conduct pharmacovigilance activities in the country including the establishment of a system to collect, document, and evaluate ADE reports.<sup>9</sup> The Medicines and Related Substances Act, 1965 (Act No. 101 of 1965)<sup>10</sup>, as amended, requires the South African Health Products Regulatory Authority (SAHPRA) to oversee the use of all health products in South Africa. The vigilance unit of SAHPRA in cooperation with the National Department of Health (NDoH), serves as the central coordinator of pharmacovigilance activities in South Africa.<sup>11</sup> Despite existence of these systems, under-reporting of ADEs remains a challenge in South Africa.<sup>12</sup>

The Med Safety App is a mobile application created to simplify and make more effective, the reporting of suspected ADEs, including adverse events after immunization (AEFIs) . The application was introduced by SAHPRA in 2021 as part of its initiatives to improve reporting of side effects of health products. This application allows both the public and HCPs to learn about medicine safety from SAHPRA, and raises awareness about medicines, their possible side effects, and pharmacovigilance.<sup>13</sup>

The aim of this study was to evaluate adults' knowledge of pharmacovigilance, attitudes toward reporting adverse drug events, and perceptions of their role in reporting adverse drug events in South Africa. The knowledge gained from this study will provide information that may help guide the actions needed to promote ADE reporting and ultimately improve medicine safety in South Africa.

## **2. METHODS**

An analytical, cross-sectional study was conducted. A self-administered, online, structured questionnaire was created using questionnaires from published studies with comparable objectives.<sup>14-18</sup> A statistician evaluated the questionnaire's face validity, and experts from the Medicine Usage in South Africa Scientific Committee evaluated its relationship to the study's objectives. The same questionnaire was given to each participant to fill out. The questionnaire contained 32 questions organised into: Section A: Socio-demographic information; Section B: Awareness of adverse drug events; Section C: Attitudes regarding adverse drug events and adverse drug events reporting; Section D: Practices and experience with reporting adverse drug events; Section E: Barriers to reporting adverse drug events. The questionnaire's section A, B and C are presented in this paper.

To recruit participants, a news article<sup>19</sup> was published on the English News24 and Afrikaans Netwerk24 online platforms that contained a link to SurveyMonkey®<sup>20</sup> to complete the survey. The survey was available for data collection from 18 April 2023 to 18 June 2023. To participate in this study participants had to be at least 18 years old, live in South Africa, and give their consent. Due to the recruitment strategy employed in this study, the response rate could not be determined.

The statistical analysis for both descriptive (numbers and or percentages) and inferential statistics was carried out using R statistical software version 4.3.1.<sup>21</sup> In addition, Pearson's chi-square test or Fischer's test was used, when appropriate, to test for an association between two categorical variables. The Wilcoxon rank sum test was used to compare median ages between groups of participants. All statistical tests were two-tailed, and the type-I error rate was set at 5% ( $\alpha=0.05$ ).

## **3. RESULTS**

A total 374 responses were retrieved from SurveyMonkey® and 350 records were analysed after exclusion of records with missing age, those who only completed the demographic section and participants residing outside South Africa (completion rate of .93.6%).

## Participants' characteristics:

The median age (IQR) of participants was 52 (38 - 62) and the majority of participants (71.4%,  $n = 250$ ;  $N = 350$ ) were female. The majority of participants, 86.0% ( $n = 301$ ;  $N = 350$ ) had tertiary education and only 0.3% ( $n = 1$ ;  $N = 350$ ) reported having no formal education. All provinces of South Africa were represented in the study, with the majority of the participants residing in Gauteng (42.6%,  $n = 149$ ;  $N = 350$ ), Western Cape (22.0%,  $n = 77$ ;  $N = 350$ ), North West (9.4%,  $n = 33$ ;  $N = 350$ ) and KwaZulu-Natal (9.1%,  $n = 32$ ;  $N = 350$ ). Most participants (91.4%,  $n = 320$ ;  $N = 350$ ) lived in urban areas. Participant characteristics are provided in Table 1. The majority of the participants indicated that they visit their private family doctors to seek treatment for general health problems (Figure 1).

**Table 1: Participant characteristics**

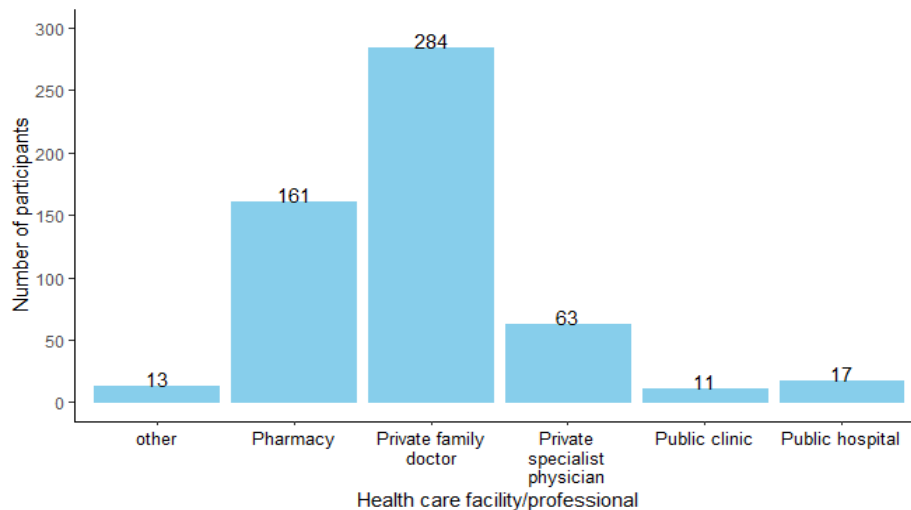
Characteristic	Overall, $N = 350^1$	Non-HCP $N = 248^1$	HCP $N = 102^1$	p-value <sup>2</sup>
<b>Median Age<sup>1</sup></b>	52 (38 - 62)	53 (41 - 64)	46 (34 - 59)	0.002
<b>Age Range (years)</b>				0.014
19-30	40 (11.4%)	26 (10.5%)	14 (13.7%)	
31-40	61 (17.4%)	34 (13.7%)	27 (26.5%)	
41-50	66 (18.9%)	45 (18.1%)	21 (20.6%)	
51-60	86 (24.6%)	67 (27.0%)	19 (18.6%)	
61 and above	97 (27.7%)	76 (30.6%)	21 (20.6%)	
<b>Sex</b>				0.004
Female	250 (71.4%)	166 (66.9%)	84 (82.4%)	
Male	100 (28.6%)	82 (33.1%)	18 (17.6%)	
<b>Province</b>				-
Eastern Cape	13 (3.7%)	7 (2.8%)	6 (5.9%)	
Free State	17 (4.9%)	13 (5.2%)	4 (3.9%)	
Gauteng	149 (42.6%)	110 (44.4%)	39 (38.2%)	
KwaZulu-Natal	32 (9.1%)	21 (8.5%)	11 (10.8%)	
Limpopo	8 (2.3%)	3 (1.2%)	5 (4.9%)	
Mpumalanga	17 (4.9%)	12 (4.8%)	5 (4.9%)	

<b>Characteristic</b>	<b>Overall, N = 350<sup>1</sup></b>	<b>Non-HCP N = 248<sup>1</sup></b>	<b>HCP N = 102<sup>1</sup></b>	<b>p-value<sup>2</sup></b>
North West	33 (9.4%)	19 (7.7%)	14 (13.7%)	
Northern Cape	4 (1.1%)	4 (1.6%)	0 (0.0%)	
Western Cape	77 (22.0%)	59 (23.8%)	18 (17.6%)	
<b>Level of education</b>				<b>&lt;0.001</b>
No formal education	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Primary school	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Secondary school	47 (13.4%)	44 (17.7%)	3 (2.9%)	
Tertiary education	301 (86.0%)	202 (81.5%)	99 (97.1%)	
<b>Area of residence</b>				<b>0.072</b>
Rural	30 (8.6%)	17 (6.9%)	13 (12.7%)	
Urban	320 (91.4%)	231 (93.1%)	89 (87.3%)	

<sup>1</sup> Median (IQR); n (%)

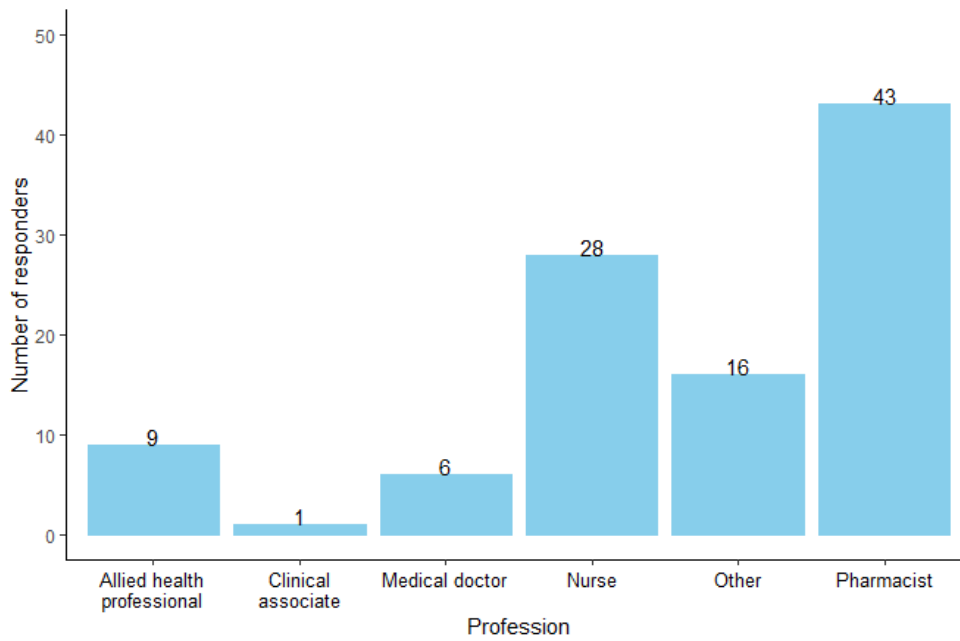
<sup>2</sup> Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.



**Figure 1: HCPs consulted for health-related needs**

Out of 350 participants, 29.1% ( $n = 102$ ;  $N = 350$ ) reported to be HCPs or were currently studying to be HCPs, with pharmacists representing the majority of these participants (42.2%,  $n = 43$ ;  $N = 102$ ). The distribution by field of practice is shown in Figure 2. To account for participants' medical training, the responses from the HCPs and non-HCPs will be reported separately where applicable.



**Figure 2: Professions of healthcare workers**

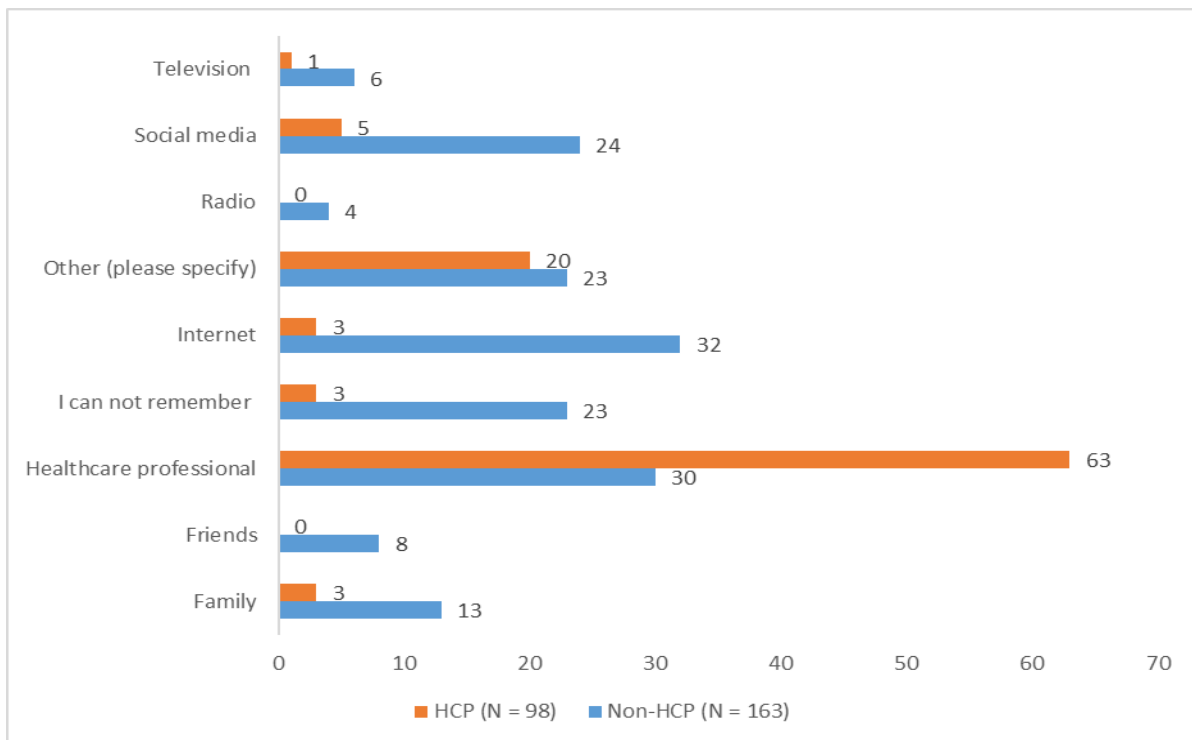
The category referred to as “other” includes fields such as epidemiologist, medical scientist and paramedics.

### **Awareness of ADE**

Of the 350 participants 302 (86.3%) had heard of ADEs, including 98.0% ( $n = 100$ ;  $N = 102$ ) of HCPs and 81.5% ( $n = 202$ ;  $N = 248$ ) of non-HCPs ( $p < 0.001$ ). Among those who had heard of ADEs, 94.8% ( $n = 276$ ;  $N = 291$ ) of participants accurately stated that ADEs can be experienced by any age group and there was no statistically significant difference between HCPs and non-HCPs ( $p = 0.4$ ). Overall, 80.9% ( $n = 157$ ;  $N = 194$ ) of non-HCPs and 92.8% ( $n = 90$ ;  $N = 97$ ) of HCPs were aware that anybody can report ADEs ( $p = 0.008$ ).

Most participants were aware of the need to report ADEs, with 97.0% ( $n = 97$ ;  $N = 100$ ) HCPs and 82.7% ( $n = 167$ ;  $N = 202$ ) of non-HCPs knowing that ADEs had to be reported. This indicates that the HCPs were statistically more aware of ADEs and the need to report ( $p < 0.001$ ). The majority knew that any person could report ADEs as indicated by 92.8% ( $n = 90$ ;  $N = 97$ ) of HCPs

and 80.9% ( $n = 157$ ;  $N = 194$ ) of non-HCPs. Non-HCPs indicated that the internet was the source of information used to learn about reporting ADEs, whereas HCPs indicated that they learned from HCPs. Figure 3 depicts the various sources of information for learning about ADE reporting.



**Figure 3: Participants' sources of information for learning about ADE reporting**

The category referred to as “other” includes work, school, and medicine package inserts.

Overall, 77.4% ( $n = 260$ ;  $N = 336$ ) of the participants had heard of SAHPRA, with 92.9% ( $n = 92$ ;  $N = 99$ ) of the HCPs as opposed to 70.9% ( $n = 168$ ;  $N = 237$ ) of non-HCPs ( $p < 0.001$ ). Awareness of the Med Safety App was lower among non-HCPs (8.4%,  $n = 20$ ;  $N = 237$ ) compared to HCPs (38.4%,  $n = 38$ ;  $N = 99$ ) ( $p < 0.001$ ). Table 2 shows the obtained data on awareness criteria that were assessed during this study.

**Table 2: Awareness of ADEs**

Characteristic	<i>N</i>	Non-HCP <sup>1</sup>	HCP <sup>1</sup>	p-value
Has heard about the Med Safety app	336	<i>N</i> =237 20 (8.4%)	<i>N</i> =99 38 (38.4%)	<0.001 <sup>2</sup>

Characteristic	N	Non-HCP <sup>1</sup>	HCP <sup>1</sup>	p-value
Has heard about SAHPRA	336	N=237 168 (70.9%)	N=99 92 (92.9%)	<0.001 <sup>2</sup>
Has heard about the term adverse drug events	350	N=248 202 (81.5%)	N=102 100 (98.0%)	<0.001 <sup>2</sup>
Know that adverse drug events should be reported	302	N=202 167 (82.6%)	N=100 97(97.0%)	<0.001 <sup>2</sup>
Know that all age groups can experience adverse drug events	291	N=194 182 (93.8%)	N=97 94 (96.9%)	0.4 <sup>3</sup>
Aware that any person can report ADEs	291	N=194 157 (80.9%)	N=97 90 (92.8%)	0.008 <sup>2</sup>

<sup>1</sup> n (%)

<sup>2</sup> Pearson's Chi-squared test

<sup>3</sup> Fisher's exact test

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.

### Attitudes towards ADE and ADE reporting

With slight variation ( $p = 0.7$ ) between HCPs and non-HCPs, 97.9% ( $n = 329$ ;  $N = 336$ ) reported having used medicine in the past and the majority (90.1%,  $n = 290$ ;  $N = 322$ ) reported that they read the medication leaflet that came with their medicine. For some participants, not reading this was due to the medication leaflet not being included with their medication.

Regarding the importance of reporting ADEs, 98% ( $n = 93$ ;  $N = 95$ ) of HCPs and 93% ( $n = 208$ ;  $N = 224$ ) of non-HCPs agreed that reporting was important ( $p=0.075$ ). The three key reasons why the participants felt (agree and strongly agree) it was important to report ADEs were indicated as making the HCP aware of what the medicine has caused (95.9%  $n = 306$ ;  $N = 319$ ); avoiding the repeat of the reaction in other people, (94.6%,  $n = 302$ ;  $N = 319$ ); and ensuring that the report reaches the medicine's manufacturer (92.2%,  $n = 294$ ;  $N = 319$ ). Both the HCP and the non-HCP concur with these reasons. The desire to be compensated for the experienced ADEs as a

motivating factor for reporting was the least mentioned reason for the importance of reporting (25.7%,  $n = 82$ ;  $N = 319$ ). Table 3 presents the participant's responses.

**Table 3: Reason why reporting of ADEs is important**

<b>Participant response</b>	<b>Non-HCP N = 224<sup>1</sup></b>	<b>HCP N = 95<sup>1</sup></b>
<b>To protect only oneself from harm</b>		
Strongly Disagree	39 (17.4%)	17 (17.9%)
Disagree	33 (14.7%)	13 (13.7%)
Uncertain	9 (4.0%)	0 (0%)
Agree	53 (23.7%)	18 (18.9%)
Strongly Agree	90 (40.2%)	47 (49.5%)
<b>To make the healthcare professional aware of what the medicine has caused</b>		
Strongly Disagree	6 (2.7%)	3 (3.2%)
Disagree	0 (0.0%)	0 (0.0%)
Uncertain	4 (1.8%)	0 (0.0%)
Agree	60 (26.8%)	17 (17.9%)
Strongly Agree	154 (68.8%)	75 (78.9%)
<b>To make sure the medicine is not fake</b>		
Strongly Disagree	8 (3.6%)	6 (6.3%)
Disagree	14 (6.3%)	9 (9.5%)
Uncertain	30 (13.4%)	15 (15.8%)
Agree	60 (26.8%)	19 (20.0%)
Strongly Agree	112 (50.0%)	46 (48.4%)
<b>To ensure that the healthcare professional is reprimanded.</b>		
Strongly Disagree	24 (10.7%)	34 (35.8%)
Disagree	47 (21.0%)	26 (27.4%)
Uncertain	49 (21.9%)	13 (13.7%)
Agree	53 (23.7%)	9 (9.5%)
Strongly Agree	51 (22.8%)	13 (13.7%)

<b>Participant response</b>	<b>Non-HCP N = 224<sup>1</sup></b>	<b>HCP N = 95<sup>1</sup></b>
<b>To avoid a repeat of the reaction in other people</b>		
Strongly Disagree	6 (2.7%)	1 (1.1%)
Disagree	1 (0.4%)	1 (1.1%)
Uncertain	6 (2.7%)	2 (2.1%)
Agree	64 (28.6%)	18 (18.9%)
Strongly Agree	147 (65.6%)	73 (76.8%)
<b>To ensure that the report reaches the medicine's manufacturer</b>		
Strongly Disagree	6 (2.7%)	0 (0.0%)
Disagree	2 (0.9%)	0 (0.0%)
Uncertain	11 (4.9%)	6 (6.3%)
Agree	52 (23.2%)	14 (14.7%)
Strongly Agree	153 (68.3%)	75 (78.9%)
<b>To make sure the medicine's manufacturer stops making the medicine</b>		
Strongly Disagree	15 (6.7%)	10 (10.5%)
Disagree	50 (22.3%)	28 (29.5%)
Uncertain	60 (26.8%)	27 (28.4%)
Agree	36 (16.1%)	12 (12.6%)
Strongly Agree	63 (28.1%)	18 (18.9%)
<b>To ensure that you get compensated for the experienced adverse drug event</b>		
Strongly Disagree	35 (15.6%)	29 (30.5%)
Disagree	56 (25.0%)	28 (29.5%)
Uncertain	67 (29.9%)	22 (23.2%)
Agree	33 (14.7%)	11 (11.6%)
Strongly Agree	33 (14.7%)	5 (5.3%)

<sup>1</sup> n (%)

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.

When asked if they had asked their healthcare provider regarding ADEs, 52.4% ( $n=118$ ;  $N=225$ ) of non-HCPs and 45.9% ( $n=45$ ;  $N=98$ ) of HCPs responded that they did ( $p=0.3$ ). Altogether

51.1% ( $n = 115$ ;  $N = 225$ ) of non-HCPs were provided information about the potential ADEs by their HCPs, as opposed to 66.3% ( $n = 65$ ;  $N = 98$ ) of HCPs ( $p = 0.011$ ). Not receiving medicines from HCPs was one aspect that contributed to not obtaining information from the HCP, with nearly 18.7% ( $n = 42$ ;  $N = 225$ ) of non-HCPs and 10.2% ( $n = 10$ ;  $N = 98$ ) of HCPs obtaining their medicine from other sources ( $p = 0.057$ ). Table 4 shows the obtained data on medicine user attitudes.

**Table 4: Attitudes on ADE and ADE reporting**

Characteristic	N	Non-HCP <sup>1</sup>	HCP <sup>1</sup>	p-value
History of medication use	336	$N=237$ 231 (97.5%)	$N=99$ 98 (99.0%)	0.7 <sup>3</sup>
Asked the health professional about ADEs	323	$N=225$ 118 (52.4%)	$N=98$ 45 (45.9%)	0.3 <sup>2</sup>
Read the medication leaflet	322	$N=225$ 200 (88.9%)	$N=97$ 90 (92.8%)	0.3 <sup>2</sup>
Healthcare professionals provided information on ADEs	323	$N=225$ 115 (51.1%)	$N=98$ 65 (66.3%)	0.011 <sup>2</sup>
Medicine not obtained from health professional	323	$N=225$ 42 (18.7%)	$N=98$ 10.2 (10%)	0.057 <sup>2</sup>
Believe it is important or necessary to report ADEs	319	$N=224$ 208 (92.9%)	$N=95$ 93 (97.9%)	0.075 <sup>2</sup>

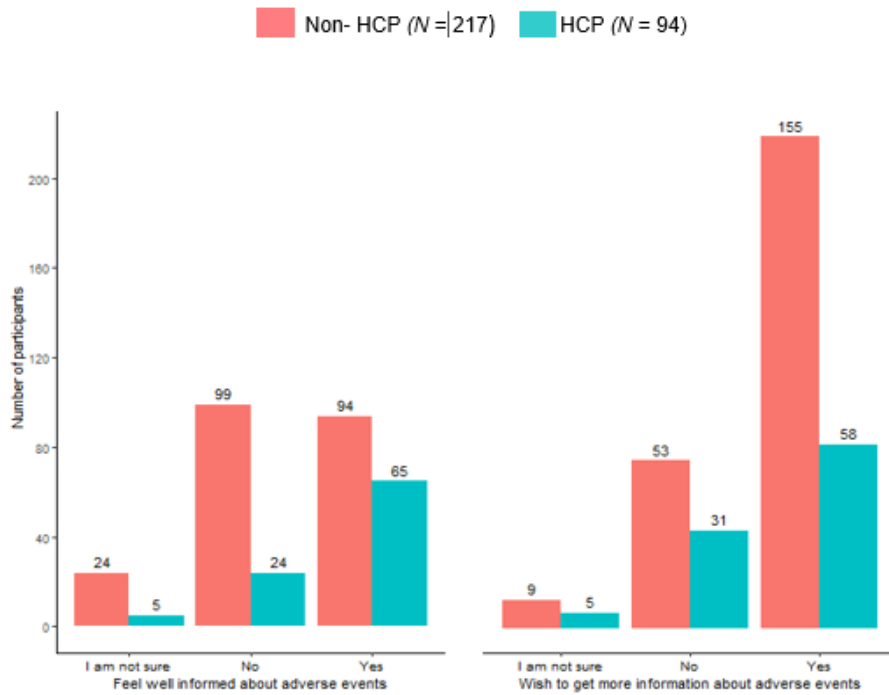
<sup>1</sup> n (%)

<sup>2</sup> Pearson's Chi-squared test

<sup>3</sup> Fisher's exact test

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.

Overall, 45.6% ( $n = 99$ ;  $N = 217$ ) of non-HCPs did not feel well informed about the adverse effects that their medication may cause, compared with 25.5% ( $n = 24$ ;  $N = 94$ ) of the HCPs. A larger percentage (71.4%,  $n = 155$ ;  $N = 217$ ) of non-HCPs expressed a wish to learn more about the side effects of their medicine compared with 61,7% ( $n = 58$ ;  $N = 94$ ) of the HCPs. The responses that were received are presented in Figure 4.



**Figure 4: Participants' current knowledge on, and desire to learn about ADEs**

#### 4. DISCUSSION

Study participants were aware of ADEs with 86.3% having heard about the term ADEs. Most participants (94.8%) knew that ADEs can be experienced by any age group; 87.4% of participants knew that ADEs had to be reported and 84.9% were aware that anybody can report ADEs. This awareness among participants can be explained by the fact that 85.8% of participants had attained tertiary education and 91.5% resided in urban areas. It has been shown that participants with higher education and those who live in urban areas have higher levels of awareness of ADEs.<sup>6</sup> With 90.1% of participants having read the medication leaflet, this heightened awareness is expected. Similar results were obtained from a study done in South Africa which reported that 70.9% of participants were aware of ADEs.<sup>12</sup> According to comparable studies, between 25.7% and 51.9% of participants could correctly define an ADE,<sup>15, 17, 18</sup> with up to 32.2% of participants not knowing about ADEs, according to one study.<sup>22</sup> Awareness regarding ADEs was significantly higher ( $p < 0.001$ ) in the HCPs and this is aligned with previous studies, which also found awareness regarding ADEs and pharmacovigilance to be high amongst HCPs.<sup>23-25</sup>

Only 8.4% of the non-HCPs knew about the Med Safety App. The Med Safety App was launched in South Africa in 2021 and enables users to report suspected ADEs.<sup>26</sup> Despite marketing efforts

made to increase awareness of the Med Safety App at its launch<sup>27, 28</sup> it is important to sustain these efforts to improve awareness and enhance reporting of ADEs in South Africa. Awareness of Med Safety App was significantly higher among the HCPs ( $p < 0.001$ ), however, only 38.4% knew about the existence of this tool. This lack of awareness regarding the reporting process or tools has also been noted as a barrier to reporting of ADEs by HCPs in other studies.<sup>29-31</sup> This indicates that in conjunction with efforts aimed at consumers to improve reporting of ADEs, efforts must be extended to HCPs.<sup>16</sup> Similar to our findings, studies conducted in Ghana and Nigeria that assessed consumers' awareness of ADE reporting tools also observed insufficient awareness.<sup>6,14</sup> This highlights the importance of raising consumers' awareness of reporting tools after they are developed.

As expected, knowledge of SAHPRA by participants was lower among non-HCPs compared to HCPs (70.9% vs 92.9%;  $p < 0.001$ ) because HCPs can interact with SAHPRA on other topics other than ADE reporting. In South Africa all patient information leaflets must contain a statement that informs readers that they can report any side effects to SAHPRA if they occur<sup>32</sup>, with 90.1% of the participants having read the medication leaflet, so this heightened awareness is to be anticipated.

The largest source of information on reporting of ADEs for the HCPs was other HCPs, while for non-HCPs the largest source was the internet. This is troubling because 81.8% of non-HCPs who reported a history of medicine use acquired the medicines from a HCP, indicating that consumers may not be actively informed about ADEs during interactions with HCPs. This finding is similar to another study in which only 29.5% of HCPs encouraged patients to report ADEs.<sup>17</sup>

The majority, 98% of HCPs and 93% of non-HCPs agreed it was important to report ADEs. This intrinsic belief, which is expressed in this study, is encouraging because it increases the likelihood that campaigns to promote the reporting of ADEs may be well received. Similar conclusions regarding the significance of reporting ADEs were found in comparable research involving consumers.<sup>12, 14, 15, 17</sup> However it must be noted that high awareness and positive attitudes regarding the reporting of ADEs does not always influence the practice of reporting.<sup>12, 33</sup>

The most common reasons given by both HCPs and non-HCPs participants for thinking it is essential to report ADEs were to ensure that the HCP is made aware of what the medicine has caused, to avoid the same reaction in other people, and to ensure that the report reaches the medicine's manufacturer. This communalist mind-set was also seen in similar studies.<sup>12, 15, 34-38</sup>

Reporting to only protect oneself from harm was significant to 63.8% of non-HCPs and 68.4% ( $n = 65$ ;  $N = 95$ ) of HCPs, even though it was ranked lower than the aforementioned reasons.

Fear of litigation is frequently cited as a deterrent to ADE reporting by HCPs<sup>6, 15, 29, 30, 33</sup> and this fear may not be unfounded as for 46.4% of non-HCPs and 23.2% of HCPs ADE reporting was important to ensure that the healthcare provider is reprimanded. For 76.8% of non-HCPs and 68.4% of HCPs, ADE reporting was important to assure themselves of the medicine's authenticity. This concern is justified because fake medications pose a serious risk to public safety in developing nations and lead to the use of ineffective medications and subsequent treatment failures.<sup>39</sup>

Our results show that 45.6% of non-HCPs and 25.5% of HCPs did not feel well informed about the adverse effects that their medication may cause. According to a scoping study conducted across six countries, it was found that in addition to drug use and storage information, patients in particular requested information on ADEs.<sup>40</sup> Having a setting where patients feel knowledgeable and assured, is an important factor that may lead to increased public involvement in pharmacovigilance.<sup>41</sup> Therefore, it is essential to improve interactions between patients and HCPs so that information about ADEs can be shared. Because it is assumed that HCPs have access to more resources to obtain any additional information they may need regarding their medication, it is concerning that 25.5% felt under-informed about the potential side effects of their medication. It is encouraging that the majority of participants expressed a desire to learn more about the side effects of their medication, demonstrating a willingness to learn and adapt practices in relation to ADEs.

Almost all the participants, 97.9% reported to have used medicines. Receiving guidance from the HCP regarding potential ADEs and the need to report them is one of the cited reasons that ADEs are reported.<sup>34, 42</sup> Only 51.5% of the non-HCPs stated that the healthcare provider had provided them information on ADEs. Strategies to improve communication regarding ADEs during health-seeking interactions may favorably influence ADE reporting given that the internet and social media are largely responsible for the non-HCPs' knowledge that ADEs are reportable. Patient-initiated communication should also be emphasised in these communication strategies as only 52.4% of the participants in this study reported to have asked their HCP about ADEs; this is lower than the results obtained in another study which reported 64%.<sup>17</sup> Regarding the history of medication use, reading the medication leaflet, and belief that reporting ADEs is important or necessary, there was no discernible difference between the HCP and non-HCPs. Unexpectedly, 66.3% of the HCPs indicated that they obtained information on ADEs from their healthcare

providers compared to 51.5% of the non-HCP. This finding, suggests that healthcare providers need to be encouraged to provide information on ADEs more often to their patients.

A strong pharmacovigilance program must be supported by a drug safety awareness culture where all stakeholders including healthcare providers and users of medicines are confident in their understanding of the benefits and risks associated with the products they recommend, prescribe, or use.<sup>43</sup>

## **5. CONCLUSION**

The results of this study indicate that there is awareness regarding ADEs and ADE reporting among adult South Africans. Healthcare professionals were more aware than non-HCPs regarding this aspect. There is a positive attitude regarding the reporting of ADEs, with participants agreeing on the importance of reporting ADEs. The optimistic outlook seen in this study should be leveraged to support initiatives that encourage the reporting of ADEs in South Africa. Both HCPs and non-HCPs must be the target of these activities.

## **Author contributions**

**Nokukhanya Ncube:** Study conception and design, data analysis and interpretation, and manuscript writing.

**Nkengafac V. Motaze:** Study conception and design, data analysis and interpretation, and manuscript review and approval.

**Martha S. Lubbe:** Study conception and design, data analysis and interpretation, and manuscript review and approval.

**Hanlie Steyn:** Study conception and design, data analysis and interpretation, and manuscript review and approval.

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## **Conflict of interest disclosure**

The authors declare that they have no conflicts of interest.

## **Data Sharing and Data Availability**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## **Ethics statement**

This study was approved by the NWU-Health Research Ethics Committee of the Faculty of Health Sciences of the North-West University (NWU-00223-22-S1).

## **Participant's consent statement**

All participants in this study consented to participate voluntarily.

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## 3.2 Manuscript 2

**Title:** Barriers and enablers of adverse drug event reporting in South Africa: a cross-sectional survey of medicine users

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**Abstract**

**Background:** Spontaneous reporting is the most frequently used method to collect data on adverse drug events (ADEs). To promote ADE reporting and enhance medicine safety, it is important to understand enablers and barriers to ADE reporting. This study described adults' practices and previous experiences with reporting ADEs, including barriers and enablers to reporting ADEs in South Africa.

**Methods:** This was a cross-sectional, analytical study in which adults residing in South Africa were requested to complete an online questionnaire.

**Results:** The majority of participants (70.5%,  $n = 203$ ;  $N = 288$ ) indicated that they experienced ADEs in the past and 77.0% ( $n = 181$ ;  $N = 235$ ) of these events occurred after the use of medication. Only 59.1% ( $n = 120$ ;  $N = 203$ ) of participants who experienced ADEs, reported them. There was no difference in reporting frequency between healthcare professionals (HCP) and non-HCPs ( $p > 0.9$ ). Furthermore, 78.3% ( $n = 94$ ;  $N = 120$ ) of participants reported ADEs to their doctor.

The main enabler for reporting ADEs indicated by both HCP and non-HCPs was that reporting could help to keep others safe. The most cited barrier to ADE reporting for both HCP and non-HCPs was the assumption that the side effects would go away once the medication was stopped.

**Conclusions:**

A large proportion of participants who experienced ADEs reported them to their doctors, and reporting of ADEs was similar between HCPs and non-HCPs. The barriers and enablers to reporting ADEs were similar for HCPs and non-HCPs. These results could help in planning awareness-raising campaigns aimed at improving ADE reporting in South Africa.

**Keywords:** adverse drug events; barriers, enablers, pharmacovigilance, consumers

**Background**

Adverse drug events (ADEs) are the unexpected and harmful effects of taking medications and they are the main reason for unanticipated hospitalisation and fatalities [1]. They can place a significant financial burden on the healthcare system and are reported to be a key driver of unscheduled hospital admissions and emergency room visits [2]. Globally, an average of 13% of

outpatients and approximately 5% of patients receiving care in hospitals are reported to have experienced ADEs, and 11–90% of the ADEs are considered avoidable [3].

It is estimated that patients in low-income countries face medication-related injury at a rate that is at least two times higher than those in high-income countries [4]. However, the rate of reporting is low. This could be explained by underreporting, which has been identified as one of the primary challenges to pharmacovigilance in Africa [5]. A review of studies on ADEs conducted in Ethiopia, Morocco, Nigeria, South Africa, Tunisia, and Uganda found that, on average, 8.4% of patients stated that they experienced an ADE during hospitalisation. In contrast, about 2.8% of patients were admitted to health facilities due to ADEs [6].

A spontaneous report is a report to a medicine manufacturer, regulatory agency, or other association that can be made by healthcare providers, patients or consumers detailing a possible ADE which occurred in a patient who has used a specific medicine and this information is not the result of a study [7]. Spontaneous reports are a critical component of pharmacovigilance as they can provide important information about the country from which they were received. This can be utilised as a guide when country-specific programmes are created to increase the safety of medications [8].

Patient reporting has been shown to play a significant role in the pharmacovigilance system, as reports of adverse events increased by about 30% in a year with the involvement of both patients and those who look after them [9]. Adverse drug events that patients report, have been found to contain clinical data that is comparable to reports from HCP. On the other hand, patient reports have the added advantage of providing thorough accounts of the ADE experience and its effects on their daily lives [10]. When combined with HCP reporting, patient reporting adds richness to the reports that are received, making them valuable for pharmacovigilance [11].

The Medicines and Related Substances Act, 1965, as amended (Act No. 101 of 1965) [12], mandates the South African Health Products Regulatory Authority (SAHPRA) to ensure that

health products and their use are regulated in South Africa. The vigilance unit of SAHPRA oversees the vigilance activities, which include the gathering and assessment of reported ADEs [7]. The minimum requirements for reporting an ADE are the presence of an involved patient, the requirement that a product be involved, the suspicion of an ADE, and the reporter's contact information [13]. Although South Africa has an established pharmaceutical surveillance system and currently contributes ADE data to the World Health Organization's (WHO) International Drug Monitoring Program [14], underreporting of ADEs in South Africa is still a problem [15].

Lack of reporting of ADEs makes it difficult to promptly recognise medicine-related risks to patient safety. Therefore, it is critical to understand the factors that act as barriers and enablers to ADE reporting to promote learning and enhancement of patient safety [16]. In a systematic review of variables affecting ADEs reporting, it was found that ADE reporting was hindered by various factors, including lack of awareness, ambiguity regarding who must report, a challenging reporting process, a lack of feedback, or a bad reporting experience [17]. Public participation results when consumers have a platform to share their experiences and receive acknowledgement of their reports [18].

This study aimed to describe adults' practices and previous experience with reporting ADEs, including the barriers and enablers to reporting ADEs in South Africa. The knowledge gained from this study will provide insights into the barriers that medicine users face in reporting ADEs and guide the actions that enhance enablers of ADE reporting by consumers in South Africa.

## **Methods**

We conducted an analytical, cross-sectional study using a self-administered, online, structured questionnaire as the data collection tool, which was generated using questionnaires from published studies with similar aims [19-23]. The survey's 32 questions were arranged in the following sections: Section A: Socio-demographic information; Section B: Awareness of adverse drug events; Section C: Attitudes regarding adverse drug events and adverse drug events

reporting; Section D: Practices and experience with reporting adverse drug events; Section E: Barriers to reporting adverse drug events. The questionnaire's section A, C, D and E are presented in this paper. The face validity of the questionnaire was assessed by a statistician, and its relevance to the objectives of the study was assessed by specialists from the Medicine Usage in South Africa Scientific Committee. Every participant was given the identical questionnaire to complete.

Participants were recruited via a news article published on 18 April 2023 on the News24 online platform in English and translated to Afrikaans and published on Netwerk24 [24]. The article, which was accessible to all individuals with access to these publishing platforms, contained a link to direct the readers to SurveyMonkey® [25] to complete the survey. The survey was launched on 18 April 2023 and data was collected until 18 June 2023. The response rate could not be determined due to the recruitment strategy used in this study. Participants in this study had to be at least 18 years old, reside in South Africa, and consent to participate.

The R statistical software version 4.3.1 [26] was used to perform the statistical analysis for both descriptive (numbers and or percentages) and inferential statistics. Additionally, when appropriate, the Fischer's test or Pearson's chi-square test were used to determine whether two categorical variables were associated. The Wilcoxon rank sum test was employed to compare the median ages of the participant groups. All statistical tests were two-tailed, and the type-I error rate was set at 5% ( $\alpha=0.05$ ).

## **Results**

A total of 374 survey responses were retrieved and 350 (completion rate of .93.6%) were analysed after excluding participants who did not reside in South Africa, records with missing ages and those who only completed the demographic section.

### **Participants' characteristics:**

The majority of participants (71.4%,  $n = 250$ ;  $N = 350$ ) were female with a median (IQR) age of 52 (38 – 62). The participants reported having a high level of education, with only 0.3% ( $n = 1$ ;  $N = 350$ ) reporting no formal education and 86.0% ( $n = 301$ ;  $N = 350$ ) reporting tertiary education.

The majority of participants (91.4%  $n = 320$ ;  $N = 350$ ) lived in urban areas and all of South Africa's provinces were represented in the study; the majority of participants resided in Gauteng (42.6%,  $n = 149$ ;  $N = 350$ ), the Western Cape (22.0%,  $n = 77$ ;  $N = 350$ ), the North West (9.4%,  $n = 33$ ;  $N = 350$ ), and KwaZulu-Natal (9.1%,  $n = 32$ ;  $N = 350$ ). The characteristics of the participants are fully described in Table 1.

Of the 350 participants, 29.1% ( $n = 102$ ;  $N = 350$ ) declared they were HCPs (HCP) or pursuing a career in healthcare, and the majority of these participants (42.2%,  $n = 43$ ;  $N = 102$ ) were pharmacists. To provide insights that take into account participants' presumptive medical training, the subsequent responses from the HCPs and non-HCPs groups will be provided separately where appropriate.

### **Experience with ADEs and ADE reporting**

A larger number of the participants (70.5%,  $n = 203$ ;  $N = 288$ ) declared to have experienced an ADE in the past, with 74.3% ( $n = 150$ ;  $N = 202$ ) of non-HCPs compared with 61.6% ( $n = 53$ ;  $N = 86$ ) of the HCPs reporting a history of ADE. The majority of the reported ADEs occurred after the use of medication (77.0%,  $n = 181$ ;  $N = 235$ ). Of the participants who experienced ADEs, 59.1% ( $n = 120$ ;  $N = 203$ ) with 59.3% ( $n = 89$ ;  $N = 150$ ) of non-HCPs and 58.5% ( $n = 31$ ;  $N = 53$ ) of the HCPs indicated that they reported these events ( $p > 0.9$ ). The dominant portion of participants 78.3% ( $n = 94$ ;  $N = 120$ ) reported these events to doctors. The majority (71.7%;  $n = 84$ ;  $N = 117$ ) of ADEs were reported within the past five years. Overall, 39.3% ( $n = 59$ ;  $N = 150$ ) of non-HCPs and 37.7% ( $n = 20$ ;  $N = 53$ ) of the HCPs who also reported a history of ADE experience chose not to report the ADEs.

### **Enablers of reporting ADEs**

The participants who reported ADEs were asked for more information regarding the motivating factors behind their decision. Three of the 89 non-HCPs who reported ADEs but did not elaborate on their reasons for doing so, were not included in the analysis. The three main factors across all the participants that influenced (agree and strongly agree) their decision to report the ADE include: reporting could help to keep others safe (92.3%,  $n = 108$ ;  $N = 117$ ); being concerned about the adverse event they were experiencing (88.0%,  $n = 103$ ;  $N = 117$ ); and wanting to share their experience (82.9%,  $n = 97$ ;  $N = 117$ ). Only 4.3 % ( $n = 5$ ;  $N = 117$ ) of participants were motivated by the need to obtain a refund of the money they had spent on the medicine. All the factors and the participants' responses are listed in Table 2.

### **Barriers to reporting ADEs**

Participants who opted not to report the ADEs were questioned further about the barriers preventing them from doing so. One of the 59 non-HCPs who did not report the ADEs and did not give any reasons for doing so, was not included in the analysis. Three main barriers (agree and strongly agree) to reporting were cited by non-HCPs. Firstly, assuming that once medication was stopped, the side effects would go away (82.8.4%,  $n=48$ ;  $N = 58$ ). Secondly, not knowing where to report (77.6%,  $n=45$ ;  $N = 58$ ). Lastly, reading that the event they experienced was a side effect (72.4%,  $n=42$ ;  $N = 58$ ). Similarly, three main barriers were cited by the HCPs. Firstly, assuming that once medication was stopped, the side effects would go away, (75.0%,  $n=15$ ;  $N = 20$ ). Secondly, reading in the medicine leaflet that the event they had was a side effect (75.0%,  $n=15$ ;  $N = 20$ ). Lastly, the belief that all medications have side effects implies it is not necessary to report (65.0%,  $n=13$ ;  $N = 20$ ). The complete list of barriers and participants' responses are listed in Table 3.

When participants who chose not to report their ADEs were asked if they were likely to report any future ADEs they might experience, 72.4% ( $n=42$ ;  $N=58$ ) of non-HCPs and 70.0% ( $n=14$ ;  $N=20$ ) of HCPs indicated they would report in the future while 24.1% ( $n=14$ ;  $N=58$ ) of non-HCPs and 25.0% ( $n=5$ ;  $N=20$ ) of HCPs continued to stand by their decision not to report.

## **Discussion**

This study described adults' reporting habits and experiences, as well as the barriers and enablers to reporting ADEs in South Africa.

The majority of non-HCPs (74.3%,  $n=150$ ;  $N=202$ ) reported to have experienced ADEs in the past. While this result is similar to that of another South African study in which 72% of participants had experienced ADEs [27], it is considerably higher than findings of other studies in which only half of participants reported that they experienced ADEs [5, 19, 21, 28, 29].

Occurrence of ADEs was significantly lower ( $p=0.032$ ) among HCPs (61.6%,  $n=53$ ;  $N=86$ ). This difference may be partly due to the fact that HCPs may have anticipated the events and thus not considered them to be adverse events [30]. The belief expressed by the HCPs (65.0%,  $n=13$ ;  $N=20$ ) that all medications have side effects so it is not necessary to report, might act as a barrier to the recognition of ADEs by this group.

Compared to the reporting rate of a comparable study performed in South Africa in which only 47% of the participants reported ADEs [27], in this study a greater proportion of participants who experienced ADEs reported them with 59.3% ( $n=89$ ;  $N=150$ ) of non-HCPs and 58.5% ( $n=31$ ;  $N=53$ ) of the HCPs indicated that they reported. Regarding this aspect, there was no discernible difference between the frequency of reporting between the non-HCP and the HCPs ( $p>0.9$ ). This high rate of reporting was also seen in similar studies [5, 15, 19, 21, 28]. As seen in other studies [5, 15, 19, 21, 28, 31] participants of this study also preferred to report their ADEs to their doctors

(80.3%,  $n = 94$ ;  $N = 117$ ) and this demonstrates that doctors are in a good position to influence reporting of ADEs.

The three main reasons given by study participants as to why they decided to report were: reporting can help keep others safe, being concerned about what was happening, and wanting to share their experience. Similar studies where participants reported ADEs mostly with the intention of protecting others, highlighted the communal motives expressed by participants [15, 17, 20, 31-34].

Overall, 39.3% ( $n = 59$ ;  $N = 150$ ) of non-HCPs and 37.7% ( $n = 20$ ;  $N = 53$ ) of the HCPs chose to not report ADEs that they experienced. When asked for reasons why the ADEs were not reported, the most cited for the non-HCP group was assuming that once the medication was stopped, the side effects would go away; reading that the event they had was a side effect and not knowing where to report. The HCPs shared two barriers with non-HCPs. However; the third most cited barrier for HCPs was the belief that all medications have side effects so it is not necessary to report. The barriers as identified in this study are consistent with previous research, which found that barriers to reporting ADEs included a lack of process awareness, knowledge that ADEs were listed as side effects, and expectations that the condition would stop when medication was stopped [17, 20, 22, 23, 28, 29, 31, 32, 35-39]. The barriers mentioned in this study suggest that participants may not be fully aware of the reporting criteria.

Lack of awareness regarding what constitutes an ADE has been cited as one of the barriers to reporting ADEs [22, 23, 29]. Interestingly, study participants mentioned that knowing about and expecting ADEs, acted as a barrier to reporting. Patients need to know that even though ADEs may be expected or listed in the package insert, they should still be reported. Awareness campaigns aimed at improving ADE reporting must also emphasize what information should be provided.

Concerning the willingness of participants who had not previously reported ADEs to do so in the future, it is encouraging that 72.4% ( $n=42$ ;  $N=58$ ) of non-HCPs and 70.0% ( $n=14$ ;  $N=20$ ) of HCPs indicated they would report ADEs. Nonetheless, 24.1% ( $n=14$ ;  $N=58$ ) of non-HCPs and 25.0% ( $n=5$ ;  $N=20$ ) of HCPs continued to support their decision not to report.

## **Conclusions**

High reporting rates for ADEs were observed among participants and doctors were the preferred recipients of these reports. We found that HCP were similar to non-HCPs regarding reporting of ADEs and reasons for doing so. We identified several barriers to reporting, and one of them is awareness of the anticipated ADEs. This study presents information on the barriers and facilitators to reporting ADEs, which can be used to enhance awareness-raising campaigns aimed at improving ADE reporting in South Africa.

## **List of abbreviations**

ADE: Adverse Drug Event

HCP: Healthcare professional

SAHPRA: South African Health Product Regulatory Authority

WHO: World Health Organization

## **Declarations**

### **Ethics approval and consent to participate**

This study was approved by the NWU-Health Research Ethics Committee of the Faculty of Health Sciences of the North-West University (NWU-00223-22-S1)

All participants in this study consented to participate voluntarily.

### **Consent for publication**

Not applicable

### **Availability of data and materials**

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

### **Competing interests**

The authors declare that they have no competing interests.

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### **Author contributions**

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**Table 1: Participant characteristics**

<b>Characteristic</b>	<b>Overall, N =350<sup>1</sup></b>	<b>Non-HCP, N = 248<sup>1</sup></b>	<b>HCP N = 102<sup>1</sup></b>	<b>p-value<sup>2</sup></b>
<b>Sex</b>				0.004
Female	250 (71.4%)	166 (66.9%)	84 (82.4%)	
Male	100 (28.6%)	82 (33.1%)	18 (17.6%)	
<b>Age (year) (median, IQR)</b>	52 (38- 62)	53 (41- 64)	46 (34- 59)	0.002
<b>Age Range (year)</b>				0.014
19-30	40 (11.4%)	26 (10.5%)	14 (13.7%)	
31-40	61 (17.4%)	34 (13.7%)	27 (26.5%)	
41-50	66 (18.9%)	45 (18.1%)	21 (20.6%)	
51-60	86 (24.6%)	67 (27.0%)	19 (18.6%)	
61 and above	98 (27.7%)	77 (30.6%)	21 (20.6%)	
<b>Area of residence</b>				0.072
Rural	30 (8.6%)	17 (6.9%)	13 (12.7%)	
Urban	320 (91.4%)	231 (93.1%)	89 (87.3%)	
<b>Province</b>				-
Eastern Cape	13 (3.7%)	7 (2.8%)	6 (5.9%)	
Free State	17 (4.9%)	13 (5.2%)	4 (3.9%)	
Gauteng	149 (42.6%)	110 (44.4%)	39 (38.2%)	
KwaZulu-Natal	32 (9.1%)	21 (8.5%)	11 (10.8%)	
Limpopo	8 (2.3%)	3 (1.2%)	5 (4.9%)	
Mpumalanga	17 (4.9%)	12 (4.8%)	5 (4.9%)	
North West	33 (9.4%)	19 (7.7%)	14 (13.7%)	
Northern Cape	4 (1.1%)	4 (1.6%)	0 (0.0%)	
Western Cape	77 (22.0%)	59 (23.8%)	18 (17.6%)	

<b>Characteristic</b>	<b>Overall, N =350<sup>1</sup></b>	<b>Non-HCP, N = 248<sup>1</sup></b>	<b>HCP N = 102<sup>1</sup></b>	<b>p-value<sup>2</sup></b>
<b>Level of education</b>				<0.001
No formal education	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Primary school	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Secondary school	47 (13.4%)	44 (17.7%)	3 (2.9%)	
Tertiary education	301 (86.0%)	202 (81.5%)	99 (97.1%)	

<sup>1</sup> Median (IQR); n (%)

<sup>2</sup> Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.

**Table 2: Factors that influenced ADE reporting**

<b>Characteristic</b>	<b>Non-HCP N= 86<sup>1</sup></b>	<b>HCP N = 31<sup>1</sup></b>
Was told by a healthcare professional to report		
Strongly Disagree	19 (22.1%)	5 (16.1%)
Disagree	30 (34.9%)	8 (25.8%)
Uncertain	17 (19.8%)	2 (6.5%)
Agree	14 (16.3%)	11 (35.5%)
Strongly Agree	6 (7.0%)	5 (16.1%)
Wanted a refund		
Strongly Disagree	38 (44.2%)	21 (67.7%)
Disagree	35 (40.7%)	7 (22.6%)
Uncertain	9 (10.5%)	2 (6.5%)
Agree	1 (1.2%)	0 (0.0%)
Strongly Agree	3 (3.5%)	1 (3.2%)
Worried about what was happening		
Strongly Disagree	1 (1.2%)	0 (0.0%)
Disagree	4 (4.7%)	3 (9.7%)
Uncertain	4 (4.7%)	2 (6.5%)
Agree	32 (37.2%)	8 (25.8%)
Strongly Agree	45 (52.3%)	18 (58.1%)
Wanted additional information		
Strongly Disagree	4 (4.7%)	4 (12.9%)
Disagree	7 (8.1%)	4 (12.9%)
Uncertain	8 (9.3%)	2 (6.5%)
Agree	36 (41.9%)	9 (29.0%)
Strongly Agree	31 (36.0%)	12 (38.7%)
Reporting is easy		
Strongly Disagree	15 (17.4%)	3 (9.7%)
Disagree	22 (25.6%)	5 (16.1%)
Uncertain	21 (24.4%)	5 (16.1%)
Agree	17 (19.8%)	11 (35.5%)
Strongly Agree	11 (12.8%)	7 (22.6%)
Wanted to share my experience		
Strongly Disagree	0 (0.0%)	0 (0.0%)
Disagree	8 (9.3%)	4 (12.9%)
Uncertain	8 (9.3%)	0 (0.0%)
Agree	39 (45.3%)	14 (45.2%)
Strongly Agree	31 (36.0%)	13 (41.9%)

<b>Characteristic</b>	<b>Non-HCP N= 86<sup>1</sup></b>	<b>HCP N = 31<sup>1</sup></b>
Was upset about the situation		
Strongly Disagree	4 (4.7%)	3 (9.7%)
Disagree	14 (16.3%)	7 (22.6%)
Uncertain	6 (7.0%)	4 (12.9%)
Agree	33 (38.4%)	5 (16.1%)
Strongly Agree	29 (33.7%)	12 (38.7%)
Reporting can help to keep others safe		
Strongly Disagree	0 (0.0%)	1 (3.2%)
Disagree	2 (2.3%)	1 (3.2%)
Uncertain	4 (4.7%)	1 (3.2%)
Agree	26 (30.2%)	5 (16.1%)
Strongly Agree	54 (62.8%)	23 (74.2%)
It is my responsibility to report		
Strongly Disagree	0 (0.0%)	0 (0.0%)
Disagree	1 (1.2%)	1 (3.2%)
Uncertain	17 (19.8%)	1 (3.2%)
Agree	32 (37.2%)	10 (32%)
Strongly Agree	36 (41.9%)	19 (61.3%)

<sup>1</sup> n (%)

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.

**Table 3: Barriers to ADE reporting**

<b>Characteristic</b>	<b>Non-HCP N = 58<sup>1</sup></b>	<b>HCP N = 20<sup>1</sup></b>
Did not know it had to be reported		
Strongly Disagree	4 (6.9%)	3 (15.0%)
Disagree	8 (13.8%)	9 (45.0%)
Uncertain	8 (13.8%)	3 (15.0%)
Agree	22 (37.9%)	3 (15.0%)
Strongly Agree	16 (27.6%)	2 (10.0%)
Did not know where to report it		
Strongly Disagree	5 (8.6%)	3 (15.0%)
Disagree	3 (5.2%)	6 (30.0%)
Uncertain	5 (8.6%)	1 (5.0%)
Agree	23 (39.7%)	6 (30.0%)
Strongly Agree	22 (37.9%)	4 (20.0%)
Reporting is too difficult.		
Strongly Disagree	2 (3.4%)	0 (0.0%)
Disagree	4 (6.9%)	4 (20.0%)
Uncertain	23 (39.7%)	4 (20.0%)
Agree	12 (20.7%)	9 (45.0%)
Strongly Agree	17 (29.3%)	3 (15.0%)
Belief that all medications have side effects so it is not necessary to report		
Strongly Disagree	8 (13.8%)	2 (10.0%)
Disagree	10 (17.2%)	4 (20.0%)
Uncertain	7 (12.1%)	1 (5.0%)
Agree	21 (36.2%)	10 (50.0%)
Strongly Agree	12 (20.7%)	3 (15.0%)
Assumed that once the medication was stopped, the side effects would go away		
Strongly Disagree	1 (1.7%)	3 (15.0%)
Disagree	4 (6.9%)	2 (10.0%)
Uncertain	5 (8.6%)	0 (0.0%)
Agree	35 (60.3%)	9 (45.0%)
Strongly Agree	13 (22.4%)	6 (30.0%)
No need to report because I stopped taking the medicine and the effect stopped		
Strongly Disagree	6 (10.3%)	4 (20.0%)
Disagree	12 (20.7%)	7 (35.0%)
Uncertain	8 (13.8%)	0 (0.0%)
Agree	22 (37.9%)	6 (30.0%)
Strongly Agree	10 (17.2%)	3 (15.0%)

<b>Characteristic</b>	<b>Non-HCP N = 58<sup>1</sup></b>	<b>HCP N = 20<sup>1</sup></b>
<b>Read that the event I had was a side effect</b>		
Strongly Disagree	2 (3.4%)	2 (10.0%)
Disagree	6 (10.3%)	2 (10.0%)
Uncertain	8 (13.8%)	1 (5.0%)
Agree	28 (48.3%)	10 (50.0%)
Strongly Agree	14 (24.1%)	5 (25.0%)
<b>Did not realise the event was related to medicine</b>		
Strongly Disagree	15 (25.9%)	6 (30.0%)
Disagree	17 (29.3%)	12 (60.0%)
Uncertain	9 (15.5%)	0 (0.0%)
Agree	9 (15.5%)	2 (10.0%)
Strongly Agree	8 (13.8%)	0 (0.0%)

<sup>1</sup> n (%)

Note: HCP denotes participants who reported that they were healthcare professionals or who were enrolled in programs to become HCPs. Non- HCP refers to participants who are not healthcare professionals.

### **3.3 Chapter summary**

The findings of the empirical inquiry were provided in this chapter. Two manuscripts addressed the defined objectives of this study. The study's conclusions, as well as its strengths and limitations and any recommendations that can be made in light of the findings, are covered in the following chapter.

## **CHAPTER 4 CONCLUSIONS, STRENGTHS, LIMITATIONS AND RECOMMENDATIONS**

### **4.1 Introduction**

This chapter discusses the study's findings relative to the stated objectives described in Chapter 1 as well as the conclusions reached. This chapter will also analyse the study's strengths and limitations and will close with potential research recommendations.

### **4.2 Study outline**

Four chapters, including an overview of the overall study, a review of relevant literature, results, and a conclusion, make up this dissertation. In Chapter 1, a description was provided of the background of the study, aims, objectives, research questions, the methodology used to conduct the study as well as the ethical considerations that were set for the study.

Chapter 2 presented the literature review which discussed the key pharmacovigilance definitions and organisations. Pharmacovigilance and experiences with ADE reporting were discussed, followed by the attitudes and practices of consumers regarding ADE reporting. The enablers and barriers that consumers face when reporting ADEs were outlined. Lastly, the regulatory requirements for ADE reporting in South Africa were discussed.

Chapter 3 presented the results of the empirical investigation of the study in manuscript format over two manuscripts, entitled:

- Manuscript 1: Awareness and attitudes regarding adverse drug events and reporting in South Africa.
- Manuscript 2: Barriers and enablers of adverse drug event reporting in South Africa: a cross-sectional survey of medicine users.

### **4.3 Study conclusion**

The aim of this study was to explore adults' awareness about pharmacovigilance and ADEs, attitudes regarding their perceived role in reporting ADEs, and the practice of and experience with ADE reporting in South Africa. To meet this aim, a literature review and empirical investigation with set objectives were performed and the conclusions are discussed.

### 4.3.1 Literature review conclusions

The literature review objectives of this study, as outlined in Chapter 1, were to:

- describe what is currently known about pharmacovigilance and experiences with ADE reporting by users of medicines globally,
- review the attitudes and practices of medicine users regarding ADE reporting globally,
- describe the barriers and enablers that affect ADE reporting globally, and
- examine the current regulatory requirements for ADE reporting in South Africa and how they support ADE reporting.

Presented in the sections below are the findings that may be inferred from the literature review.

#### 4.3.1.1 Objective 1: What is currently known about pharmacovigilance and experiences with ADE reporting by users of medicines globally?

The World Health Organization (WHO, 2023c) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/ vaccine-related problem". This definition of pharmacovigilance appears typically in the pharmacovigilance literature, showing that the term is used similarly around the world and that everyone shares the same understanding of pharmacovigilance (Fornasier *et al.*, 2018:744; Garashi *et al.*, 2022:717; Kiguba *et al.*, 2022:1; Potts *et al.*, 2020:521; Santoro *et al.*, 2017:856).

Pharmacovigilance is aimed at improving patient care and patient safety related to the use of medicines and promote public health initiatives by offering trustworthy, impartial information to evaluate the risk-benefit profile of medication (WHO, 2023d) and typically the National Medicines Regulatory Authority (NMRA) in each country organises and coordinates the national pharmacovigilance system strategies (WHO, 2018).

Pharmacovigilance was initially established in South Africa in 1987 and since its creation in 2018, SAHPRA has been tasked with monitoring the safety of health products and helping to understand the potential adverse effects of medications better when used outside of the tightly controlled conditions of clinical trials.

Across the world spontaneous reporting is the main method for gathering post-marketing data on the safety of medications and identifying safety signals in pharmacovigilance (Hazell *et al.*, 2013:200) as it can cover a huge population of prospective reporters and can involve a wide range of (Schurer *et al.*, 2017:81). Permitting direct consumer reporting of ADEs to national pharmacovigilance centers has seen a worldwide increase in recent years, and organisations like the WHO recognise the benefits of this practice (Inacio *et al.*, 2017:228). To allow for consumer involvement in pharmacovigilance, consumers must know what to report, where to report, and be able to access reporting systems (Jacobs *et al.*, 2018:2).

As consumers include in their reports, personal information about how ADEs affect their everyday lives (Inacio *et al.*, 2017:244-245), consumers' ability to report drug side effects, enhances medication-related risk surveillance, enables the identification of safety signals that are supplementary to those presented by medical professionals, and, ultimately, participation by consumers will eventually contribute in raising public awareness, competency, and understanding of safety (Margraff & Bertram, 2014:418).

Therefore, consumer participation in pharmacovigilance is crucial and must be actively promoted. Interventions directed at both consumers and HCPs may include internet tools and awareness campaigns (Matlala *et al.*, 2023:8-9).

#### **4.3.1.2 Objective 2: Attitudes and practices of medicine users regarding ADE reporting**

The identification of elements that can be targeted in future efforts directed at enhancing ADE reporting, must address available knowledge on attitudes and practices of medicine users regarding ADEs (Sabblah *et al.*, 2017:913). In the literature, the following information about the awareness, attitudes and practices of medicine users was provided.

There was a wide range in the literature's studies regarding participants' awareness of ADEs, from as little as 25.7% in some to as much as 86.0% in others, this included participants who knew the term or could define ADEs correctly (Jacobs *et al.*, 2018:5; Kim *et al.*, 2020:4; Patel *et al.*, 2019:1779; Sales *et al.*, 2017:869; Wang *et al.*, 2022:4). In a similar study conducted in South Africa, participants' awareness was found to be at 70.9% (Pillay *et al.*, 2021:6). Participants in various studies showed wide variations in their knowledge of the ADE reporting process, ranging from 3.9 to 86.6% (Adisa *et al.*, 2019:1067; Jacobs *et al.*, 2018:5; Kim *et al.*, 2020:4; Pillay *et al.*, 2021:4; Sales *et al.*, 2017:871; Wang *et al.*, 2022:6). The percentage of people who knew they needed to report ADEs ranged from 72.9 to 94%.

More than 90% of participants in the studies overall, indicated that reporting ADEs was important (Adisa *et al.*, 2019:1067; Kim *et al.*, 2020:4; Pillay *et al.*, 2021:5; Sales *et al.*, 2017:870). Despite the fact that participants know about the importance of reporting, this does not always translate into reporting of ADEs, as was seen in the study by Kim *et al.* (2020:4) where 93.9% of the participants agreed on the importance of reporting, however only 3.4% of the participants reported the experienced ADEs. In general, a high percentage of people who indicated to have encountered ADEs, reported them (Adisa *et al.*, 2019:1067; Elkalmi *et al.*, 2013:226; Jacobs *et al.*, 2018:5; Patel *et al.*, 2019:1779; Sabblah *et al.*, 2017:917); however in other studies, reporting rates were found to be very low (Hariraj & Aziz, 2018:758; Kim *et al.*, 2020:4)

The severity of the ADE has an impact on consumer reporting. Consumers tend to report more ADEs that are serious or severe compared to those that are mild, therefore the severity of the ADE is reportedly one of the factors that encourages consumers to report ADEs (Al Dweik *et al.*, 2017:881; Kitisopee *et al.*, 2022:8; Krska *et al.*, 2011:1101; Pillay *et al.*, 2021:5; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147).

It was discovered that HCPs are the preferred group to whom ADEs are reported (Adisa *et al.*, 2019:1067; Elkalmi *et al.*, 2013:226; Hariraj & Aziz, 2018:758; Jacobs *et al.*, 2018:7; Patel *et al.*, 2019:1779; Sabblah *et al.*, 2017:916). Due to the intimate contact that HCPs have with consumers, consumer reporting of ADEs cannot be completely separated from HCPs, hence strategies to encourage HCPs and consumer collaboration in reporting ADEs are necessary (Inacio *et al.*, 2018:750).

#### **4.3.1.3 Objective 3: Barriers and enablers that affect ADE reporting globally**

The decision to report an ADE or not is influenced by several factors that have been identified in the literature; a summary of the barriers and enablers that consumers encounter when reporting an ADE, is provided below.

##### **4.3.1.3.1 Barriers to ADE reporting**

It is critical to identify influential factors that function as obstacles to reporting in order to develop strategies for enhancing the voluntary reporting of ADEs by patients (Al Dweik *et al.*, 2017:876). These are the four most common reasons cited by participants who experienced ADEs but did not report.

- Lack of awareness

Participants of the studies that were conducted, were either unaware of what ADEs were, what to report, unaware of reporting systems that are accessible and unaware of their role in reporting, as well as unsure about who needed to report and to whom these reports should be transmitted, including lack of awareness regarding the national pharmacovigilance centres (Adisa *et al.*, 2019:1064; Al Dweik *et al.*, 2017:877; Arnott *et al.*, 2013:1115; Elkalmi *et al.*, 2013:227; Hariraj & Aziz, 2018:758; Jha *et al.*, 2014:34; Kim *et al.*, 2020:5; Kitisopee *et al.*, 2022:9; Krska *et al.*, 2011:1101; Patel *et al.*, 2019:1776; Robertson & Newby, 2013:685; Sales *et al.*, 2017:871; Salvo *et al.*, 2013:176; Valinciute-Jankauskiene & Loreta, 2021:6; Wang *et al.*, 2022:6).

- Difficult reporting process

Reported under this section were concerns regarding the paperwork that needed to be completed as the reporting forms are not easy to fill out, completion thereof is a time-consuming process, and a lack of resources or time during the consultation to facilitate consumer reporting to their HCP (Al Dweik *et al.*, 2017:878; Hariraj & Aziz, 2018:758; Kim *et al.*, 2020:8; Kitisopee *et al.*, 2022:9; Matos *et al.*, 2016:1106; Valinciute-Jankauskiene & Loreta, 2021:6)

- The expectation that the experienced ADEs would resolve.

When participants were aware of what to expect regarding the ADE profile of the medicines, they tended to not report ADEs; this included participants who believed that the ADEs would resolve in time without any intervention, as well as those who had been told by their HCP to expect the occurrence of the ADE, those who had previously experienced the same ADE, and the participants who believed that their experienced ADE was not serious (Al Dweik *et al.*, 2017:878; Hariraj & Aziz, 2018:758; Krska *et al.*, 2011:1101; Robertson & Newby, 2013:685; Wang *et al.*, 2022:6)

- Apprehension of harmful consequences from HCP

In certain cases, it was reported that medicine users are actively discouraged by their healthcare providers from learning more about their medicine as well as reading the package inserts and for these participants when ADEs were experienced, fear of appearing to challenge or offend the healthcare providers acted as a barrier to their reporting (Al Dweik *et al.*, 2017:877; Arnott *et al.*, 2013:1115; Robertson & Newby, 2013:685; Valinciute-Jankauskiene & Loreta, 2021:6). Similar worries were voiced by participants in South Africa (Pillay *et al.*, 2021:5).

Training initiatives can assist in overcoming barriers and can assist in enhancing the reporting of ADEs. The main aspects regarding the improvement of direct reporting by consumers are to inform and teach consumers as well as to develop more effective ways to involve them in the entire pharmacovigilance process(Kruger & Gasperini, 2020:4)

#### 4.3.1.3.2 Enablers of ADE reporting

Participants who said they had previously reported ADEs had some factors in common that they felt encouraged or made it easier for them to report and the below are the most frequent reasons why these participants reported.

- Noble motives

For these participants, reporting of ADEs was motivated by the need to contribute to research and information about medicine by sharing their experiences, those who felt it was their responsibility to report or to promote awareness regarding the ADEs, and those who wished to prevent others from experiencing the same ADEs (Al Dweik *et al.*, 2017:877; Hariraj & Aziz, 2018:758; Kim *et al.*, 2020:5; Kitisopee *et al.*, 2022:6; Pillay *et al.*, 2021:5; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147).

- Severity of ADEs

The severity of the experienced ADEs appears to be another enabler for reporting, with the participants who perceived their experienced ADEs to be serious or severe being more likely to report as opposed to those who experienced minor ADEs ((Al Dweik *et al.*, 2017:881; Krska *et al.*, 2011:1101; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147). This idea was supported in the South African study (Pillay *et al.*, 2021:5).

#### **4.3.1.4 Objective 4: Regulatory requirements for ADE reporting in South Africa and how they support ADE reporting**

Regulation 40 of South Africa's *Medicines and Related Substances Act* 101 of 1965, as amended (refer to section 2.7) , creates the tone that supports reporting of ADEs by anybody and holds medicine manufacturers accountable when it comes to executing their role in ensuring medicine safety in South Africa.

Further to the regulations above, SAHPRA provides oversight of the pharmaceutical industry to enable ADE reporting in South Africa as provided for in Pharmacovigilance Systems Guideline.

This Guideline sets minimum requirements that each pharmaceutical company must have in place to ensure safe and effective use of medicine; collection, review and submission of ADEs to SAHPRA (SAHPRA, 2022e)

#### **4.3.2 Conclusions following empirical investigation**

The following objectives were developed to address the aims of the empirical investigation:

- To assess adults' awareness about pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa
- To describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa

The conclusions that can be drawn from the empirical investigation are presented in the parts that follow.

##### **4.3.2.1 Objective 1: Assess adults' awareness about pharmacovigilance, adverse drug events and attitudes regarding their perceived role in reporting adverse drug events in South Africa**

The results of this study indicate that an overwhelming majority of the participants had heard of ADEs and knew that ADEs can affect people of any age, ADEs should be reported and that anyone could report them. The fact that most participants had completed tertiary education and lived in urban areas may contribute to the awareness seen in this study. The level of awareness observed in our study was comparable to that of a study conducted in South Africa (Pillay *et al.*, 2021:6); however, in other research on this subject, fewer participants were aware of ADEs (Kim *et al.*, 2020:4; Patel *et al.*, 2019:1779; Sales *et al.*, 2017:869; Wang *et al.*, 2022:4). Healthcare professionals showed a greater awareness of ADEs compared to non-HCP and other studies have demonstrated that this is to be expected (Gordhan & Bangalee, 2022:81; Hussain *et al.*, 2021:4; Khan *et al.*, 2023:17).

Although more HCPs than non-HCPs were aware of the Med Safety App, it was not widely known among the participants. Other studies have also noted this lack of awareness regarding reporting tools (Adisa *et al.*, 2019:1071; Jacobs *et al.*, 2018:8) and it has also been identified as one of the barriers to reporting ADEs (Bogolubova *et al.*, 2018:5; Le *et al.*, 2020:126; Varallo *et al.*, 2014:741).

Non-HCPs cited the internet as the primary source of information about reporting ADEs, whereas health professionals were the main source of awareness for HCPs. This shows that patients might not be actively informed about ADEs when interacting with medical professionals to receive care as the vast majority obtained their medicines from healthcare providers.

The majority of participants concurred that it was critical to report ADEs. They attributed this importance to the need to notify HCPs about the medication's side effects, prevent other people from experiencing the same reaction, and make sure the report reached the medication's manufacturer. Studies of a similar nature also revealed this positive socialist attitude among its participants.

More HCP (66.3%) received ADE information from their HCPs compared to non-HCP (51.5%) and according to our findings, 25.5% of HCPs and 45.6% of non-HCPs felt poorly informed about the potential side effects of their medication. Therefore, improving communication about ADEs during interactions with healthcare providers may have a positive impact on ADE reporting. Most participants expressed a willingness to learn more about the side effects of their medication, which is encouraging because it shows that they are willing to adjust their practices in relation to ADEs.

#### **4.3.2.2 Objective 2: Describe adults' practices and previous experience with reporting of ADEs, including the barriers and enablers to reporting ADEs in South Africa**

The majority of the participants experienced ADEs and significantly more of the non-HCP (74.3%) reported this history of ADEs compared to HCP (61.6%). This finding is aligned with a similar South African study (Zondi & Naidoo, 2022:7). Compared to other studies, which on average found that only half of their participants reported having experienced ADEs in the past, this finding is significantly higher (Adisa *et al.*, 2019:1067; Elkalmi *et al.*, 2013:226; Jacobs *et al.*, 2018:5; Patel *et al.*, 2019:1779; Sabblah *et al.*, 2017:917).

In this study, a higher proportion of those who experienced ADEs reported them, and there was no discernible difference between the frequency of reporting between the non-HCP (59.3%) and the HCPs (58.5%). The reports were submitted to the doctor by most of the participants. The reporting rate seen in this study is comparable to similar studies, which also found that doctors were the preferred recipients of these reports (Adisa *et al.*, 2019:1067; Elkalmi *et al.*, 2013:226; Jacobs *et al.*, 2018:7; Pillay *et al.*, 2021:4; Sabblah *et al.*, 2017:916). The three main reasons given by study participants for reporting were that it can help keep others safe, they were concerned about what was going on, and they wanted to share their experience. These reasons

were shared by both the HCP and non-HCP. The communal motivations expressed by participants in our study were highlighted by similar studies that also discovered that individuals reported ADEs primarily to protect others.. (Al Dweik *et al.*, 2017:877; Hariraj & Aziz, 2018:578; Kim *et al.*, 2020:5; Kitisopee *et al.*, 2022:6; Pillay *et al.*, 2021:5; Valinciute-Jankauskiene & Loreta, 2021:6; van Hunsel *et al.*, 2012:1147).

The most cited barrier to ADE reporting for both HCPs and non-HCPs was the belief that once the medication was stopped, the side effects would go away; reading in the medicine leaflet that the event they experienced was a side effect. The third most common reason given by non-HCPs was not knowing where to report, and the third most common reason given by HCPs was the belief that all medications have side effects and thus it is not necessary to report. These barriers are also noted in other studies (Al Dweik *et al.*, 2017:878; Arnott *et al.*, 2013:1115; Elkalmi *et al.*, 2013:227; Hariraj & Aziz, 2018:758; Jha *et al.*, 2014:34; Kim *et al.*, 2020:5; Kitisopee *et al.*, 2022:9; Krska *et al.*, 2011:1101; Patel *et al.*, 2019:1776; Robertson & Newby, 2013:685; Sales *et al.*, 2017:871; Salvo *et al.*, 2013:176; Wang *et al.*, 2022:6). The majority of participants who did report previous ADEs, indicated that they would report in the future, which was encouraging.

#### **4.4 Study limitations**

The limitation of the recruitment and data-collection method is that only participants who had access to the News24 platform or viewed the Netwerk24/News24 platform during the period of the advertisement gained access to the invitation to participate in the study. The data collection instrument was only available in English participants had to be able to respond to the questionnaire in English in order to participate in the study.

Even though participants came from all of South Africa's provinces, the study's results cannot be generalised to the general population due to the study's small sample size. The majority of participants resided in urban areas, so the findings of this study do not represent the opinions of South Africans who live in rural areas.

Although 85.8% of study participants reported having completed tertiary education, South Africa's post-secondary school completion rate is currently 18.8% (StatsSA, 2023). This indicates that the study's participant population is not representative of the general population, and the study's findings may not accurately reflect the perspectives of those with lower educational attainment.

Recall bias could affect the study results as the survey relied on the participant's ability to remember past experiences.

Nevertheless, despite the aforementioned limitation, the study was able to provide the information required to fulfil the study's objectives and offer insights into the current ADE reporting situation in South Africa. The HCP's perspectives as medicine users offered information that can be applied further to initiatives aimed at enhancing patient ADE reporting in South Africa.

#### **4.5 Recommendations**

The findings of this study allow the following recommendations to be made:

- To better understand the experience of medicine users who report ADEs in South Africa, additional studies with larger sample sizes are needed.
- Increasing awareness of the Med Safety App to the public as well as HCPs in South Africa could improve the reporting of ADEs.
- To promote the reporting of ADEs in South Africa, training on the criteria for reporting and the reporting process must be made available to both the public and HCPs.
- In order to ensure that patients using medications have the knowledge necessary for safe medication use, efforts must be made to increase patient knowledge of ADEs.

#### **4.6 Chapter summary**

This chapter presented the study's outcomes from both the literature review and the empirical investigation. It also discussed the study's limitations and made recommendations for further research.

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# ANNEXURE A: ETHICS APPROVAL



Private Bag X1290, Potchefstroom  
South Africa 2520

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North-West University Health Research Ethics  
Committee (NWU-HREC)

Tel: 018 299-1206  
Email: [Ethics-HRECAppl@nwu.ac.za](mailto:Ethics-HRECAppl@nwu.ac.za) (for human  
studies)

28 March 2023

## ETHICS APPROVAL LETTER OF STUDY

Based on approval by the North-West University Health Research Ethics Committee (NWU-HREC) on 28/03/2023, the NWU-HREC hereby approves your study as indicated below. This implies that the NWU-HREC grants its permission that, provided the general conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Awareness of pharmacovigilance and experience with reporting of adverse drug events by adults in South Africa																															
Principal Investigator/Study Supervisor/Researcher: Prof NV Motaze																															
Student: : N Ncube - 44459564																															
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N	W	U	-	0	0	2	2	3	-	2	2	-	A	1																	
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<u>Status:</u> S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation																															
Application Type: Single study	Risk: <table border="1"><tr><td>Minimal</td></tr></table>	Minimal																													
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Commencement date: 28/03/2023																															
Expiry date: 31/03/2023																															
Approval of the study is provided for a year, after which continuation of the study is dependent on receipt and review of an annual monitoring report and the concomitant issuing of a letter of continuation. A monitoring report is due at the end of March annually until completion of the study.																															

<p>General conditions:</p> <p>While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, the following general terms and conditions will apply:</p> <ul style="list-style-type: none"><li>• The principal investigator/study supervisor/researcher must report in the prescribed format to the NWU-HREC:<ul style="list-style-type: none"><li>- Annually on the monitoring of the study, whereby a letter of continuation will be provided annually, and upon completion of the study; and</li><li>- without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.</li></ul></li><li>• The approval applies strictly to the proposal as stipulated in the application form. Should any amendments to the proposal be deemed necessary during the course of the study, the principal investigator/study supervisor/researcher must apply for approval of these amendments at the NWU-HREC, prior to implementation. Should there be any deviations from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.</li><li>• Annually a number of studies may be randomly selected for active monitoring.</li><li>• The date of approval indicates the first date that the study may be started.</li><li>• In the interest of ethical responsibility, the NWU-HREC reserves the right to:<ul style="list-style-type: none"><li>- request access to any information or data at any time during the course or after completion of the study;</li></ul></li></ul>
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- to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process;
- withdraw or postpone approval if:
  - any unethical principles or practices of the study are revealed or suspected;
  - it becomes apparent that any relevant information was withheld from the NWU-HREC or that information has been false or misrepresented;
  - submission of the annual monitoring report, the required amendments, or reporting of adverse events or incidents was not done in a timely manner and accurately; and/or
  - new institutional rules, national legislation or international conventions deem it necessary.
- NWU-HREC can be contacted for further information via [Ethics-HRECApply@nwu.ac.za](mailto:Ethics-HRECApply@nwu.ac.za) or 018 299 1206

The NWU-HREC would like to remain at your service and wishes you well with your study. Please do not hesitate to contact the NWU-HREC for any further enquiries or requests for assistance.

Yours sincerely,



Digitally signed by  
Prof Petra Bester  
Date: 2023.03.28  
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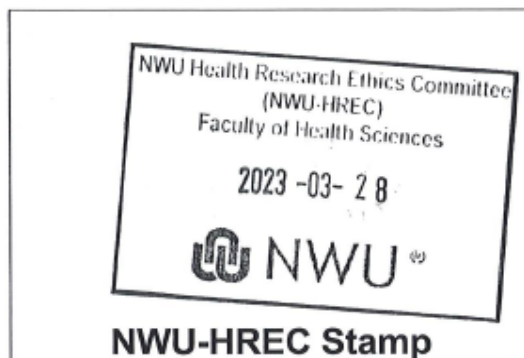
Chairperson NWU-HREC

Current details: (23239522) G:\My Drive\9. Research and Postgraduate Education\9.1.5.4 Templates\9.1.5.4.2\_NWU-HREC\_EAL.docm  
20 August 2019  
File Reference: 9.1.5.4.2

## ANNEXURE B: INFORMED CONSENT



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### INFORMED CONSENT DOCUMENTATION FOR ADULT PARTICIPATION IN AN ONLINE QUESTIONNAIRE

**TITLE OF THE RESEARCH STUDY:**  
**AWARENESS OF PHARMACOVIGILANCE AND EXPERIENCE WITH REPORTING OF ADVERSE DRUG EVENTS BY ADULTS IN SOUTH AFRICA**

**ETHICS REFERENCE NUMBERS: NWU-00223-22-A1**

**PRINCIPAL INVESTIGATOR: PROF. NKENGAFAC VILLYEN MOTAZE**

**POSTGRADUATE STUDENT: NOKUKHANYA NCUBE**

**ADDRESS: 11 HOFFMAN STREET, POTCHEFSTROOM CAMPUS, NORTH-WEST UNIVERSITY POTCHEFSTROOM**

**CONTACT NUMBER: 073 472 0013; 018 285 2227**

You are being invited to take part in a **research study** that forms part of the degree Master of Pharmacy in Pharmacy Practice with Pharmacovigilance and Pharmacoepidemiology at the North-West University. Please take some time to read the information presented here, which will explain the details of this study. At the end of the letter the contact information of the research team is provided should you wish to ask any questions about any part of this study that you do not fully understand. It is very

important that you are fully satisfied that you clearly understand what this research is about and how you might be involved. Also, your participation is **entirely voluntary** and you are free to say “no” to participate. If you say “no”, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part now.

This study has been approved by the **NWU-Health Research Ethics Committee of the Faculty of Health Sciences of the North-West University (NWU-00223-22-A1)** and will be conducted according to the ethical guidelines and principles of *Ethics in health research: principles, processes and structures* (DoH, 2015) and other international ethical guidelines applicable to this study. It might be necessary for the Research Ethics Committee members or other relevant people to inspect the research records.

#### **What is this research study all about?**

- We plan to explore adults' knowledge about pharmacovigilance, adverse drug events, and their understanding of their role in reporting adverse drug reactions in South Africa.
- This study will be conducted via a self-administered, online, structured questionnaire distributed via SurveyMonkey®.

#### **Why have you been invited to participate?**

- You have been invited to be part of this research because you are an adult currently residing in South Africa.
- You will, unfortunately, not be able to take part in this research if you participated in the evaluation of the online structured questionnaire.

#### **What will be expected of you?**

- You will be expected to complete, as a once-off event, an online questionnaire with 32 questions that should take no more than 10-15 minutes to complete.

#### **Will you gain anything from taking part in this research?**

- There will be no direct gains for your participation in the study.
- The gains of the study are for researchers, as data gathered during this research project may provide additional insights that can improve medication safety in South Africa.

#### **Are there risks involved in you taking part in this research and what will be done to prevent them?**

- The risks to you in this study are
  - the discomfort and loss of time associated with answering the research questions, which will be limited by ensuring that the questionnaire is short and well-structured in order to be easy to complete; and
  - identification of study participants, which will be limited by the fact that no identification information will be collected during the study and the research team will not know the identities of the participants.
- There are more gains in joining this study than there are risks.

**How will we protect your confidentiality and who will see your findings?**

- Anonymity of your findings will be protected by the appointment of the study mediator, who will receive completed questionnaires from participants, and by data being exported into an anonymised Excel spreadsheet before the data are shared with the research team.
- Your privacy will be respected, because the questionnaire can be completed online in a location of your choice. Your results will be kept confidential by ensuring that the study mediator has a signed confidentiality agreement in place. Only the research team will be able to look at your findings. These findings will be kept safe in an access-controlled electronic storage that will be password protected. Data will be stored for five years.

**What will happen with the findings or samples?**

- The findings of this study will only be used for this study and may also be used for further studies. If used for further studies, it will always be approved first by the NWU-Health Research Ethics Committee.

**How will you know what the results of this research are?**

- The research findings may be shared with pharmaceutical associations and other role players, and may be published in pharmaceutical journals.

**Will you be paid to take part in this study and are there any costs for you?**

This study is not funded and you will not be paid to take part in the study. The cost of data usage may be incurred by you during participation in this study.

**Is there anything else that you should know or do?**

- You can contact the researchers if you have any further questions or problems.
  - Nokukhanya Ncube      email: [khanyon0@gmail.com](mailto:khanyon0@gmail.com)      tel: 073 472 0013
  - Prof Villyen Motaze      email: [44802889@nwu.ac.za](mailto:44802889@nwu.ac.za)      tel: 018 285 2227
- You can also contact the NWU-Health Research Ethics Committee via Mrs Carolien van Zyl at 018 299 1206 or [carolien.vanzyl@nwu.ac.za](mailto:carolien.vanzyl@nwu.ac.za) if you have any concerns that were not answered about the research or if you have complaints about the research.

Thank you for your time. Your involvement is much valued, as it will directly contribute to the results of this study.

Please click on one of the boxes below to either accept to participate in the study and proceed to the questionnaire or to decline the invitation to participate in the study and exit.

I agree

I do not wish to participate

## ANNEXURE C: RECRUITMENT MATERIAL

### News24 Article¶

#### C-1: English version¶

##### Give your opinion about medication safety?¶

¶

Individuals who use medicines have first-hand knowledge of their experiences with adverse drug events; however, they do not always know what to do when they notice these problems.¶

Adverse drug events are sometimes referred to as side-effects or adverse drug reactions. These side-effects can be experienced with any substance used to prevent, make a diagnosis, cure, or help ease symptoms associated with a disease. Prescription medicines, medicines purchased without a prescription (also known as self-medication or over-the-counter medicines), vaccines, or medical devices can cause side-effects. A medical device is any device used, either alone or in combination, for a medical purpose and examples of these include bandages, pregnancy tests, hearing aids and ventilators.¶

The research entity, Medicine Usage in South Africa (MUSA), at the North-West University is conducting a study to explore adults' awareness of, and their prior experiences with reporting adverse drug events. The findings of this study could improve medicine safety in South Africa.¶

Anyone currently residing in South Africa and are above the age of 18 years can participate in this study.¶

You are invited to respond to an online questionnaire that should not take longer than 10-15 minutes to complete. You may distribute this link to anyone that you think might participate voluntarily. Please click on the following [link](#) for more details regarding the study and to participate.¶

The research entity, MUSA, aims to improve the appropriate use of medicine in South Africa through high-quality research and post-graduate training. To read more about MUSA follow the link: <https://health-sciences.nwu.ac.za/musa>¶

## C-2: Afrikaans version

NETWERK24 DIE BUREAU DIE BURGER Beeld Volksblad Rapport HUIS SARDIE Kuiser bus Baba Wêreld Njy-Sinop Streeknuus
My Profiel

**NETWERK24**Dinsdag, 14 Maart  
Kies 'n streek

TUISBLAD
NUUS
SAKE
SPORT
STEMME
KUNSTE
LEEF
SPEEL
KYK + LUISTER
JEUG
E-PUBLIKASIES

Wys jou slag met **SUDOKU** - en deel jou uitstae.

SPEEL HIER

### Gee jou mening oor medikasie-veiligheid

15 Mrt. 2023

Geborgde inhoud

NETWERK24

Kommentaar

Boekmerk

Wanneer jy medikasie koop, of dit nou met 'n voorskrif is of nie, kan dit newe-effekte inhou. Foto: ISTOCK

REGSTREEKS

- Bangladesh 38/0
- England 0

Sien meer

HOOF TREKKE
GEWILDSTE

- 1.** Marge so laag soos 5% staan tussen jou en ineenstorting van kragtnetwerk
- 2.** Saak teen ramptoestand uitgestel nadat staatsdatum 'minag'
- 3.** Reeksmoordenaar skuldig aan 6 moorde
- 4.** Verkiesing van Tshwane se speaker kan in hof draai
- 5.** GRAFIKA | Kry die jongste oor die kragkrisis – regstreeks

VOORMALIGE AANDEELHOERS VAN WELKOM YIZANI

KOM KRY JOU GELD

KLIK HIER

E-publikasies

Lees jou koerante en tydskrifte gerieflik in digitale formaat.

Begin lees

Het medikasie al 'n ongewenste uitwerking op jou gehad, en het jy dit aangemeld? Dit wat jy weet en al ervaar het, kan help om die veiligheid van geneesmiddels in Suid-Afrika te bevorder.

Mense wat medikasie gebruik, het eerstehandse kennis van hul ongewenste ervarings daarmee, maar weet nie altyd wat om te doen wanneer medikasie 'n ongewenste uitwerking op hulle het nie.

“

**Die navorsingsentiteit Medicine Usage In South Africa (MUSA), aan die Noordwes-Universiteit, is besig met 'n studie oor volwassenes se bewustheid van newe-effekte, asook vorige ervarings met die aanmeld daarvan.**

”

Daar word soms na hierdie ongewenste uitwerking van medikasie as newe-effekte of 'n nadelige reaksie op medikasie verwys. Hierdie newe-effekte kan ervaar word met enige middel wat gebruik word vir die voorkoming, diagnose of genesing van 'n siekte, of om die simptome daarvan te verlig. Voorskrif-medisyne, medisyne wat sonder 'n voorskrif gekoop kan word (ook bekend as self-medikasie of oor-die-toonbank-medisyne), entstowwe of mediese toestelle kan almal newe-effekte veroorsaak. 'n Mediese toestel is enige toestel wat op sy eie of in kombinasie vir 'n mediese doel gebruik word. Voorbeelde hiervan is verbande, swangerskaptoetse, gehoorstukke en ventilators.

Die navorsingsentiteit Medicine Usage in South Africa (MUSA) aan die **Noordwes-Universiteit** is besig met 'n studie oor volwassenes se bewustheid van ongewenste medisyne-ervarings, asook vorige ervarings met die aanmeld daarvan. Die bevindings van hierdie studie kan die veiligheid van medisyne in Suid-Afrika help verbeter.

Enige persoon wat tans in Suid-Afrika woon en ouer as 18 is, mag aan die studie deelneem. Jy word genooi om 'n Engelse aanlyn vraelys in te vul, wat nie langer as 10–15 minute sal neem om te voltooi nie. Stuur gerus ook die skakel aan enigiemand wat jy dink vrywillig sal wil deelneem. Klik [hier](#) vir meer ligting oor die studie en om daaraan deel te neem.

Dit is MUSA se doel om die toepaslike gebruik van medikasie in Suid-Afrika te bevorder deur middel van hoëgehalte-navorsing en nagraadse opleiding. Lees [hier](#) meer oor hul werk.

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LEES MEER OOR:

OOR-DIE-TOONBANK-MEDISYNES

MEDIKASIE

NOORDWES-UNIVERSITEIT

MUSA

SELF-MEDIKASIE

NEWE-EFFEKTE

## ANNEXURE D : DATA COLLECTION TOOL

### SECTION A: SOCIO-DEMOGRAPHIC INFORMATION

1. Do you currently reside in South Africa?

Yes		No	
-----	--	----	--

(If the response to this question is no, survey participation will be stopped.)

2. Are you 18 years of age or older

Yes		No	
-----	--	----	--

(If the response to this question is no, survey participation will be stopped)

3. Sex at birth

		Indicate (x)	
		Yes	No
3.1	Female		
3.2	Male		

4. Indicate your age (in years)

--

5. Province, you reside in

		Indicate (x)	
		Yes	No
5.1	Eastern Cape		
5.2	Free State		
5.3	Gauteng		
5.4	KwaZulu-Natal		
5.5	Limpopo		
5.6	Mpumalanga		
5.7	Northern Cape		
5.8	North West		
5.9	Western Cape		
5.10	Prefer not to say		

6. Do you reside in a rural or urban area?

		Indicate (x)	
		Yes	No
6.1	Urban (Area that is located in the cities, towns and suburbs)		
6.2	Rural (Area that is located outside towns and cities.)		

7. What is the highest level of education you have completed?

		Indicate (x)	
		Yes	No
7.1	No formal education		
7.2	Primary school		
7.3	Secondary school		
7.4	Tertiary education		

8. Are you a qualified healthcare professional or are you currently studying to become one?

Yes		No	
-----	--	----	--

9. If you answered yes to question 8, please select your profession or field of study from the following options:

- Clinical associate
- Medical doctor
- Nurse
- Pharmacist
- Allied health professional
- Other.
- if "other", please specify \_\_\_\_\_

10. Where do you usually go if you are sick, or to treat a general health problem? Select all that apply

		Indicate (x)	
		Yes	No
10.1	Private family doctor		
10.2	Private specialist physician		
10.3	Public hospital		
10.4	Public clinic		
10.5	Pharmacy		
10.6	None of the above		
10.7	If "none of the above " please specify:		

**SECTION B: AWARENESS OF ADVERSE DRUG EVENTS**

1. Have you heard about the term adverse drug events?

Yes		No	
-----	--	----	--

2. Do adverse drug events have to be reported?

Yes		No	
-----	--	----	--

3. If you answered yes to question 2, where did you hear about the reporting of adverse drug events?

		Indicate (x)	
		Yes	No
3.1	Healthcare professional		
3.2	Social media		
3.3	Internet		
3.4	Television		
3.5	Radio		
3.6	Family		
3.7	Friends		
3.8	I cannot remember		
3.9	Other		
3.10	If "other" please specify:		

4. Which age groups can experience adverse drug events

		Indicate (x)	
		Yes	No
4.1	Children only		
4.2	Adults only		
4.3	Elderly only		
4.4	Any age		
4.5	I do not know		

5. Who can report adverse drug events?

		Indicate (x)
5.1	Anyone can report adverse drug events	
5.2	Only healthcare professionals can report adverse drug events	

6. Have you heard of the Med Safety App, a mobile application that can be used to report suspected adverse drug events?

Yes		No		I cannot remember	
-----	--	----	--	-------------------	--

7. Have you heard of the South African Health Products Regulatory Authority (SAHPRA)?

Yes		No		I cannot remember	
-----	--	----	--	-------------------	--

**SECTION C: ATTITUDES REGARDING ADVERSE DRUG EVENTS AND ADVERSE DRUG EVENTS REPORTING**

1. Have you or anyone you look after ever used medication?

Yes		No		I do not remember	
-----	--	----	--	-------------------	--

2. If yes, when obtaining the medicines:

		Indicate (x)		
		Yes	No	I cannot remember
2.1	Did you ask your healthcare professional about the potential side effects of your medication?			
2.2	Did your healthcare professional inform you about the potential side effects of your medication?			
2.3	I did not get the medicine from a healthcare professional			

3. Do you ever read the patient information leaflet that comes with your prescription medication?

Yes		No		There was no leaflet packaged with my medicine	
-----	--	----	--	--	--

4. Do you believe it is important or necessary to report adverse events that you may experience after taking medication?

Yes		No		I don't know	
-----	--	----	--	--------------	--

5. How much do you agree or disagree with the following reasons why it is important to report adverse drug events?

		Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
		1	2	3	4	5
5.1	To protect only oneself from harm					
5.2	To make the healthcare professional aware of what the medicine has caused					
5.3	To make sure the medicine is not fake					
5.4	To ensure that the healthcare professional is reprimanded					
5.5	To avoid a repeat of the reaction in other people					
5.6	To ensure that the report reaches the medicine's manufacturer					
5.7	To make sure the medicine's manufacturer stops making the medicine					
5.8	To ensure that you get compensated for the experienced adverse drug event					

6. Do you feel well informed about the adverse effects that your medication may cause?

Yes	1	No	0	I am not sure	0
-----	---	----	---	---------------	---

7. Do you wish you could get more information about the adverse effects of your medication?

Yes		No		I am not sure	
-----	--	----	--	---------------	--

8. Have you ever experienced an adverse drug event?

Yes		No		I cannot remember	
-----	--	----	--	-------------------	--

If your answer to question 8 is **Yes** – continue to question 9

If your answer to question 8 is **No** or **I cannot remember** – end of questionnaire

9. If you answered yes to question 8, did this event occur after: (Select all that apply)

		Indicate (X)	
		Yes	No
9.1	Using or taking medicine		
9.2	Vaccination /immunisation		
9.3	Using a medical device		

10. If you answered yes to question 8, did you report this to anyone?

Yes		No		I cannot remember	
-----	--	----	--	-------------------	--

If your answer to question 10 is **Yes** – please complete **Section D**

If your answer to question 10 is **No** – please complete **Section E**

If your answer to question 10 is **"I cannot remember"** – end of questionnaire

**SECTION D: PRACTICES AND EXPERIENCE WITH REPORTING ADVERSE DRUG EVENTS**

1. When was the adverse drug event reported?

		Indicate (X)
1.1	Less than a year ago	
1.2	1-2 years ago.	
1.3	3-5 years ago.	
1.4	6-10 years ago.	
1.5	More than 10 years ago.	

2. To whom did you report the adverse drug event?

		Indicate (X)	
		Yes	No
2.1	Doctor		
2.2	Nurse		
2.3	Pharmacist		
2.4	Other healthcare workers		
2.5	SAHPRA (South African Health Products Regulatory Authority)		
2.6	Family member or friend		

3. To what extent did the below motivate your decision to report?

		Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
		1	2	3	4	5
3.1	I was told by my healthcare professional to report					
3.2	I wanted a refund					
3.3	I was worried about what was happening					
3.4	I wanted additional information					
3.5	Reporting is easy					
3.6	I wanted to share my experience					
3.7	I was upset about the situation					
3.8	Reporting can help to keep others safe.					
3.9	It is my responsibility to report					

## **SECTION E: BARRIERS TO REPORTING ADVERSE DRUG EVENTS**

1. To what extent did the below influence your decision not to report?

		Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
		1	2	3	4	5
1.1	Did not know it had to be reported					
1.2	Did not know where to report it					
1.3	Reporting is too difficult					
1.4	Belief that all medications have side effects therefore not necessary to report.					
1.5	I assumed that once I stopped taking the medication, the side effects would go away					
1.6	No need to report because I stopped taking the medicine and the effect stopped.					
1.7	Read that the event I had was a side effect.					
1.8	Did not realise the event was related to medicine					

2. Are you likely to report any adverse drug events you may have in the future?

Yes	1	No	0	I am not sure	0
-----	---	----	---	---------------	---

# ANNEXURE E : AUTHOR GUIDELINE - PHARMACOEPIDEMOLOGY AND DRUG SAFETY (PDS)

**PDS** Pharmacoepidemiology  
& Drug Safety

**ispe** Official Journal of the  
International Society for  
Pharmacoepidemiology

3. After Acceptance
4. Manuscript Transfer Programme

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- Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
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- A statement about prior postings and presentations, name(s) of any sponsor(s) of the research contained in the paper, along with grant number(s);
- Abstract structured (Purpose/Methods/Results/Conclusions)
- Up to seven keywords;
- Five key points (up to five bullet points, of around 100 words only, explaining the importance of the paper's findings. These points will be published with article in a box entitled 'Key Points')
- The Plain Language Summary (PLS) should convey the same information as the Abstract for a lay audience. It should summarize your scientific study, its results, and their broader relevance without using jargon so that it is understandable by scientists from outside of your discipline, as well as science journalists and science educators. The PLS should be a single paragraph no more than 200 words long
- Main body: formatted as Introduction, Methods, Results, Discussion,
- Ethics Statement
- Acknowledgements (Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor; financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate);
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- Tables (each table complete with title and footnotes);
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<b>Commentaries</b>	Commentaries are evidence-based opinion pieces that cover a variety of topics of current interest in pharmacoepidemiology and pharmacovigilance, and the intersection between these disciplines and society.	1,500 limit (commissioned and submitted); no more than 15 references	No abstract	Five Key Points
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		publication as Brief Reports		
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- the rationale for important aspects of the research design is discussed in more depth than could be accommodated in a paper reporting the results, and in more detail than would usually be included in the protocol that would be posted on ClinicalTrials.gov or the ENCePP database.
- the description will serve as an instructive teaching example
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**Units of measurement:** Measurements should be given in SI or SI-derived units (see <http://www.bipm.fr>)

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**Genetic Nomenclature:** Sequence variants should be described in the text and tables using both DNA and protein designations whenever appropriate. Sequence variant nomenclature must follow the current HGVS guidelines; see <http://varnomen.hgvs.org/>, where examples of acceptable nomenclature are provided.

Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL and GenBank on a daily basis. The suggested wording for referring to accession-number information is 'These sequence data have been submitted to the DDBJ/EMBL/GenBank databases under accession number U12345'. Addresses are as follows:

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**[Research article](#)**

[Database article](#)

[Software article](#)

[Study protocol](#)

[Review](#)

[Matters Arising](#)

[Comment](#)

[Prepare supporting information](#)

[Conditions of publication](#)

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[Peer-review policy](#)

[Manuscript transfers](#)

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Three to ten keywords representing the main content of the article.

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- the type of statistical analysis used, including a power calculation if appropriate

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- Consent for publication
- Availability of data and materials

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*Book chapter, or an article within a book*

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. *International review of cytology.* London: Academic; 1980. p. 251-306.

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

*Online document*

Doe J. Title of subordinate document. In: *The dictionary of substances and their effects.* Royal Society of Chemistry. 1999. <http://www.rsc.org/dose/title of subordinate document>. Accessed 15 Jan 1999.

*Online database*

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. <http://www.healthwise.org>. Accessed 21 Sept 1998.

*Supplementary material/private homepage*

Doe J. Title of supplementary material. 2000. <http://www.privatehomepage.com>. Accessed 22 Feb 2000.

*University site*

Doe, J: Title of preprint. <http://www.uni-heidelberg.de/mydata.html> (1999). Accessed 25 Dec 1999.

*FTP site*

Doe, J: Trivial HTTP, RFC2169. <ftp://ftp.isi.edu/in-notes/rfc2169.txt> (1999). Accessed 12 Nov 1999.

*Organization site*

ISSN International Centre: The ISSN register. <http://www.issn.org> (2006). Accessed 20 Feb 2007.

*Dataset with persistent identifier*

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (*Sorghum bicolor*). GigaScience Database. 2011. <http://dx.doi.org/10.5524/100012>.

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- JPEG (suitable for photographic images, less suitable for graphical images)
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- BMP (suitable for images)
- CDX (ChemDraw - suitable for molecular structures)

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2/8

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3/8

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5/8

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Student No. 44459564 at North-West University

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21 November 2023

Jennifer Ludwig's qualifications:

- Bachelor of Arts Degree majoring in Languages.  
University of Port Elizabeth (Nelson Mandela Bay), South Africa;  
and
- Postgraduate Diploma in Translation  
Rhodes University, Grahamstown, South Africa.