South African Health Products
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GUIDELINE FOR ADVERSE DRUG REACTIONS (ADRs) REPORTING FOR HEALTHCARE PROFESSIONALS

This document has been prepared to serve as a guideline for healthcare professionals reporting adverse drug reactions and product quality problems. It represents the South African Health Products Regulatory Authority's (SAHPRA)'s current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, quality, and efficacy of medicines and may make amendments in keeping with the current knowledge at the time of consideration of safety data.

Guidelines and ADR Reporting & Quality Problem Forms are available from the SAHPRA website. The ADR Reporting Form is also available as Appendix A of this document.

Document History

Version	Reason for Amendment	Effective Date
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Contents

Glossary

Term	Meaning
Adverse Drug Reaction (ADR) or Adverse Reaction	An adverse drug reaction (ADR) means a noxious and unintended response to a medicine, including lack of efficacy, and which occurs at doses commonly 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 and over-the-counter (OTC) medicines. All such adverse effects should be reported. 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 or a reviewing healthcare professional/provider. The fact that the healthcare professional/provider is making a report serves as an indication that the observed event may be caused by the medicine.
Adverse Event	An adverse event is 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.
Adverse Effect	An adverse effect is a harmful patient outcome that seems to be associated with treatment, including the absence of any effect.
Causality assessment	Causality assessment is defined as the evaluation of the likelihood that a medicine was the causative agent of an observed adverse drug reaction.
Congenital Anomalies	Congenital anomalies are defined as structural and/or functional abnormalities, usually irreversible, that develop/occur during the period of conception and/or embryo-foetal development during one or more trimesters of pregnancy, affecting one or more of the following domains: genetic material, histology, anatomy, organ system, development, growth, differentiation, physiological function and/or metabolic function and/or homeostatic mechanisms which may be identifiable either prenatally and/or at birth or later in life. Congenital anomalies are also known as birth defects, congenital disorders, congenital defects or congenital malformations.
Consumer	A consumer in relation to healthcare means a person who uses or is a potential user of health services, as well as their family and caregivers.
Counterfeit or falsified medicines	Counterfeit or falsified medicine means a medicine in respect of which deliberate false representation has been made about its contents, identity or source by any means, including its labelling and packaging.
Substandard medicines	Substandard medical products are those that fail to meet quality standards and specifications, typically due to poor manufacturing practices or inadequate

	quality control.
Clinical Trial	A study is performed to investigate the safety or efficacy of a medicine. For human medicines, these studies are conducted with human participants.
Drug overdose	A drug overdose is the accidental or intentional use of a drug or medicine in an amount that is higher than is usually used.
Dechallenge	Dechallenge means a withdrawal /reduction in the dose of a medicine from the patient's therapeutic regimen. Negative dechallenge means the continued presence of an adverse experience after withdrawal of the medicine. Positive dechallenge refers to the partial or complete disappearance of an adverse event after the withdrawal of the medicine.
eReporting	eReporting is a module of the VigiFlow® system that allows for seamless electronic reporting of an individual case safety report (ICSR) directly from the source into the VigiFlow® system. It reduces the workload of manual data entry from ADR paper forms into VigiFlow® system.
Essential Medicines List (EML) Clinical Guide	The EML Clinical Guide is a National Department of Health Mobile Application (App) that contains the Primary Healthcare Standard Treatment Guidelines, Hospital Level Adult Guidelines, Tertiary and Quaternary Level EML Recommendations, and the Essential Medicines List for 2015. It includes an ADR reporting module which is used to report ADRs.
Healthcare Professional/Provider	Healthcare professional or healthcare provider means a person providing health services in terms of any law, including in terms of the: • Allied Health Professions Act, 1982 (Act No. 63 of 1982) • Health Professions Act, 1982 (Act No. 56 of 1982) • Nursing Act, 1978 (Act No. 50 of 1978); • Pharmacy Act, 1974 (Act No. 53 of 1974) • Dental Technicians Act, 1979 (Act No. 19 of 1979)
Hypothesis	A hypothesis is an idea which is suggested as a possible explanation for a particular situation or condition, but which has not yet been proved to be correct.
Holder of a certificate of registration/applicant	A holder of a certificate of registration is a person/company in whose name a registration certificate has been granted, and who is responsible for all aspects of the medicine, including quality, safety, effectiveness, and compliance with the conditions of registration.
Individual Case Safety Report (ICSR)	ICSR is a detailed record of all relevant data associated with the use of a medicine in a subject or patient. An individual case safety report is the information provided by a primary source to describe suspected adverse reactions or adverse events following immunisations related to the administration of one or more medicines to an individual patient at a particular point in time.
In vitro diagnostic (IVD)	IVD means a medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the

	human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.
Lack of efficacy	Lack of efficacy is defined as failure to produce the expected outcome for which the medicine was indicated. Lack of efficacy applies to registered medicines, including when used for an unapproved indication.
Medical device	Medical device means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, including Group III and IV Hazardous Substances contemplated in the Hazardous Substances Act, 1973 (Act 15 of 1973) - intended by the manufacturer to be used, alone or in combination, for humans or animals, for one or more of the following: • diagnosis, prevention, monitoring, treatment or alleviation of disease; • diagnosis, monitoring, treatment, alleviation of or compensation for an injury; • investigation, replacement, modification or support of the anatomy or of a physiological process; • supporting or sustaining life; • control of conception; • disinfection of medical devices; or • providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body; and • which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on human or animal body, but which may be assisted in its intended function by such means.
Medication error	Medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is under the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including: • prescribing errors; • dispensing errors; • medicine preparation errors; • administration errors and • monitoring errors. Medication errors and medicine-related adverse events have important implications – from increased length of hospitalisation and costs to undue discomfort and disability or increased mortality. Thus, minimising of medication errors, through early detection and clinical audit, is of paramount importance in healthcare by promoting compliance, adherence, recovery and the general well-being of patients.
Medicine	Means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in - • the diagnosis, treatment, mitigation, modification or prevention of

	disease, abnormal physical or mental state or the symptoms thereof in humans; or • restoring, correcting or modifying any somatic, psychic or organic function in humans; and • includes any veterinary medicine.
Med Safety App	The Med Safety App is a smartphone app for reporting of suspected ADRs to Regulatory Authorities, and it is developed by the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA) as part of the Innovative Medicines Initiative WEB-Recognising Adverse Drug Reactions (WEB-RADR) project.
Misuse of medicine	Misuse of medicine is defined as the use of a medicine outside label directions or in a way other than prescribed or directed by a healthcare practitioner. This includes patients using a medicine for a different condition than that for which the medicine is prescribed, patients taking more medicines than prescribed or at different dosing intervals, and individuals using a drug not prescribed for them, although for therapeutic purposes.
Minimum information required for a report	It is information required for a case to be deemed meaningful for data capturing and it includes the following: • information about the patient, • which medicine is suspected to have caused the reaction, • the reaction that has occurred, and • information about the reporter. A report may be nullified if it lacks the minimum information. For further information required to ensure the report is clinical meaningful, see point 4.4.1.
Pharmacovigilance	Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions (and adverse events following immunisation) to medicines/vaccines. The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.
Post-marketing surveillance	Post-marketing surveillance is the practice of monitoring the safety of a medicine, medical device or IVD after it has been released on the market. It is a crucial aspect of the science of pharmacovigilance. Medicines are approved/authorised to be used by the public on the basis of clinical trials, which involve relatively small numbers of participants who have been selected for such purposes. Post-marketing surveillance is used to confirm or disprove the safety of a medicine after it is used in the general population by large numbers of people who have a wide variety of medical conditions, by using approaches such as spontaneous ADR reporting procedures, pregnancy registries, etc.
Product Quality Problem	Product quality problems include concerns about the quality, authenticity, performance, or safety of any medical device or IVD. Problems with product

	quality may occur during manufacturing, distribution, or storage and include a suspect counterfeit product; product contamination; defective components; poor packaging or product mix-up; questionable stability; medical device malfunctions and labelling concerns.
Rechallenge	Rechallenge refers to the reintroduction of a product suspected of causing an adverse event after a successful dechallenge. Negative rechallenge means that, when reintroduced, the medicine fails to produce signs or symptoms similar to those observed when it was initially introduced. Positive rechallenge means reoccurrence of similar signs and symptoms upon reintroduction of a medicine.
Serious Adverse Drug Event or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: • results in death; • is life-threatening; • requires patient hospitalisation or prolongation of existing hospitalisation; • results in an abortion, premature delivery, congenital anomaly/birth defects; • results in persistent or significant disability/incapability; or • is a medically significant/ important event or reaction. The term "life-threatening" in the definition of "serious" refers to a reaction/event in which the patient was at risk of death at the time of the reaction/event; it does not refer to an event that, hypothetically, might have caused death if it were more severe. Medical and scientific judgement should be exercised when deciding whether other situations are serious or not. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse. The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious, which is based on patient/event outcome or action criteria.
Signal	A signal refers to 'reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.
Spontaneous ADR report	A spontaneous report is a communication to a pharmaceutical company, regulatory authority or other organisation that describes a suspected ADR in a

	patient given one or more medicines, and which does not derive from a study.
Teratogen	A teratogen is any substance/agent (e.g. medicine) that can harm/damage the sperm, ovum, the conceptus, developing embryo and/or foetus during one or more trimesters of pregnancy, affecting structure and/or function across one or more of the following domains: genetic material, histology, anatomy, organ system development, growth and differentiation, physiological function and/or metabolic function and/or homeostatic mechanisms which may be detectable prenatally, at birth or later in life.
Unlisted adverse reaction	An adverse reaction that is not included explicitly as a suspected adverse effect in the professional information (previously known as package insert) or other scientific reference. This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the professional information or other scientific reference.
Uppsala Monitoring Centre (UMC)	UMC is the WHO Collaborating Centre for International Drug Monitoring. UMC works by collecting, assessing, and communicating information from member countries' national pharmacovigilance centres concerning the benefits, harm, effectiveness, and risks of medicines. UMC is responsible for: • co-ordination of WHO Programme for International Drug Monitoring and its member countries; • collection, assessment and communication of information from member countries about the benefits, harms and risks of medicines and other substances used in medicines to improve patient therapy and public health worldwide; • collaborating with member countries in the development and practice of the science of pharmacovigilance.
VigiAccess®	VigiAccess® is a web application that allows the public to access VigiBase® database and retrieve statistical data on the suspected ADRs to medicines reported to the World Health Organization (WHO) Programme for International Drug Monitoring (PIDM).
VigiBase®	VigiBase® is the WHO global database of individual case safety reports (ICSRs). It is developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of WHO and its member countries. It consists of reports of ADRs to medicines received from member countries since 1968. It is updated with incoming case reports continuously. The purpose is to ensure that early signs of previously unknown medicine-related safety problems are identified as rapidly as possible. Contrary to VigiAccess®, consumers and healthcare professionals/providers do not have access to VigiBase® database.
VigiFlow®	VigiFlow® is a web-based ICSR management system that is available for use by national pharmacovigilance centres, e.g. SAHPRA, used by the WHO Programme for International Drug Monitoring. VigiFlow® supports the collection, processing and sharing of data of ICSRs to facilitate effective data analysis.

Vigilance	Vigilance in relation to a medicine, medical device, or IVD means the continuous monitoring and evaluation of its safety, efficacy, and performance profile, as well as the management of any risks throughout its life cycle.
VigiLyze	VigiLyze® is the search and analysis tool used to retrieve global ICSR data from VigiBase® database. Consumers and healthcare professionals/providers do not have access to this tool.
Web-Recognising Adverse Drug Reactions (WEB-RADR) project	Web-RADR project, launched in September 2014, sought to utilise the powers of social media and new technologies for pharmacovigilance purposes. The project developed mobile applications (apps) enabling patients, caregivers, and healthcare professionals/providers to report ADRs and receive up-to-date information and news alerts.
World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM)	The PIDM was established in 1968, to ensure that evidence about harm to patients was collected from as many sources as possible. This would enable individual countries to be alerted to patterns of harm that were emerging across the world, and which might not be evident from their local data alone. The PIDM consists of a group of more than 150 member countries (South Africa became a member in 1992) that share the vision of safer and more effective use of medicines. They work nationally and collaborate internationally to monitor and identify the harm caused by medicines, to reduce the risks to patients and to establish worldwide pharmacovigilance standards and systems. UMC has been responsible for the technical and operational aspects of the programme since 1978.

Abbreviations and Acronyms

ADRs	Adverse Drug Reactions
AIDS	Acquired Immune Deficiency Syndrome
DHCPLs	Dear Healthcare Professional Letters
DoH-PvPHP	Department of Health Pharmacovigilance Centre for Public Health Programmes
DRC	Directorate of Radiation Control
DTC	Drug and Therapeutic Committee
EML	Essential Medicines List
EPI	Extended Programme for Immunisation
HCR	Holder of Certificate of Registration
HCP	HealthCare Professional
HIV	Human Immunodeficiency virus
ICSR	Individual Case Safety Report
IVD	In vitro diagnostics
NADEMC	National Adverse Drug Event Monitoring Centre
MCC	Medicines Control Council
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OTC	Over the counter
PHP	Public Health Programmes
PI	Professional Information
PIDM	Programme for International Drug Monitoring
SAHPRA	South African Health Products Regulatory Authority
SOP	Standard Operating Procedure
TB	Tuberculosis
UMC	Uppsala Monitoring Centre
WEB-RADR	WEB-Recognising Adverse Drug Reactions
WHO	World Health Organisation

For the purpose of this guideline:

1 the terms “holder of certificate of registration” and “applicant” are used interchangeably.

2 the terms “medicine”, “drug”, “therapeutic agent” and “causative agent” are also used interchangeably.

3 the terms “pharmaceutical product”, “health product” and “product” are also used interchangeably.

4 the terms “adverse drug reaction”, “reaction” and “adverse event” are used interchangeably.

5 the terms “Authority” and “South African Health Products Regulatory Authority” are used interchangeably.

1. INTRODUCTION

This guideline is intended to assist healthcare professionals/providers in the participation in the very important process of continuous surveillance of safety and efficacy of the medicines, which are used in their clinical practice. Continuous evaluation of a medicine's benefit and harm helps achieve the ultimate goal of providing safe and effective treatments to patients.

The guideline is intended to assist healthcare professionals/providers in the reporting of suspected adverse drug reactions (ADRs) and product quality issues associated with the use of medicines.

1.1 The South African Health Products Regulatory Authority (SAHPRA)

This SAHPRA is a Section 3A public entity formed by the South African government to oversee the regulation of all health products, including medicines, medical devices, in vitro diagnostics (IVDs), and radiation-emitting products used in healthcare and industry. SAHPRA replaced the Medicines Control Council (MCC) and the Directorate of Radiation Control (DRC).

The Medicines and Related Substances Act mandate SAHPRA, 1965 (Act No. 101 of 1965) as amended, to regulate (i.e., monitor, evaluate, investigate, inspect, register and review) all health products and their use in South Africa.

SAHPRA has also been delegated the task of overseeing radiation control in South Africa. This function is governed by the Hazardous Substances Act (Act 15 of 1973) which aims to protect the public (workers, patients, etc.) against radiation used in both health settings and industry.

SAHPRA's function is therefore to promote public health and safety by ensuring that all medicines, medical devices, and IVDs available and used in South Africa are safe, effective, of good quality, and of acceptable performance.

2. The Pharmacovigilance obligation of the healthcare professional

According to Regulation 40 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended: A healthcare professional /provider, veterinarian or any other person should inform the Authority, in the manner as determined by the Authority, of any:

- suspected ADRs; or
- new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance.

3. PHARMACOVIGILANCE

3.1 Why is pharmacovigilance and reporting of ADRs important?

When a health product is first registered and made available in South Africa, information about its safety and effectiveness is usually only available from clinical trials. Clinical trials, through different test phases, provide information about many of the possible adverse events associated with a health product, but do not detect all possible adverse events because they:

- usually do not continue for long enough to detect adverse events that take a long time to develop,
- do not include enough patients to detect adverse events that occur rarely and
- do not include all of the different types of people who might eventually use the product and who might be more vulnerable to some adverse events, such as older people, children, pregnant women or people with other medical conditions.

Rare ADRs, occurring in only a small percentage of cases, after a long period of use or when a medicine interacts with a particular combination of other medicines or conditions, may not be detected during clinical trials. For ADRs that were not discovered during clinical trials to be detected, investigated, and communicated, and for the appropriate action to be taken, it is therefore vital that post-marketing pharmacovigilance of all medicines is comprehensive. Effective pharmacovigilance should take into account trends in use, as well as the occurrence of ADRs, enabling more effective advice to be given to those prescribing and using medicines and should ensure better standards of safety and efficacy.

SAHPRA, like other Regulatory Authorities around the world, monitors the safety of health products to contribute to a better understanding of their potential adverse events when used outside the controlled conditions of clinical trials. Continuous reporting by health professionals/providers and consumers provides important information for the pharmacovigilance system in South Africa.

3.2 Pharmacovigilance System in South Africa

To prevent undesirable effects in patients resulting from substandard health products and the inappropriate or unsafe use of health products, an ADR monitoring system was established in South Africa in 1987. The regulatory pharmacovigilance unit of SAHPRA coordinates this system. The regulatory pharmacovigilance unit works in collaboration with programmatic units based at the

National Department of Health (NDoH) head office in Pretoria. The programmatic units are:

- the Extended Programme on Immunisation (EPI) unit
- the Department of Health Pharmacovigilance Centre for Public Health Programmes (DoH-PvPHP).

Table 1: Overarching Pharmacovigilance Bodies

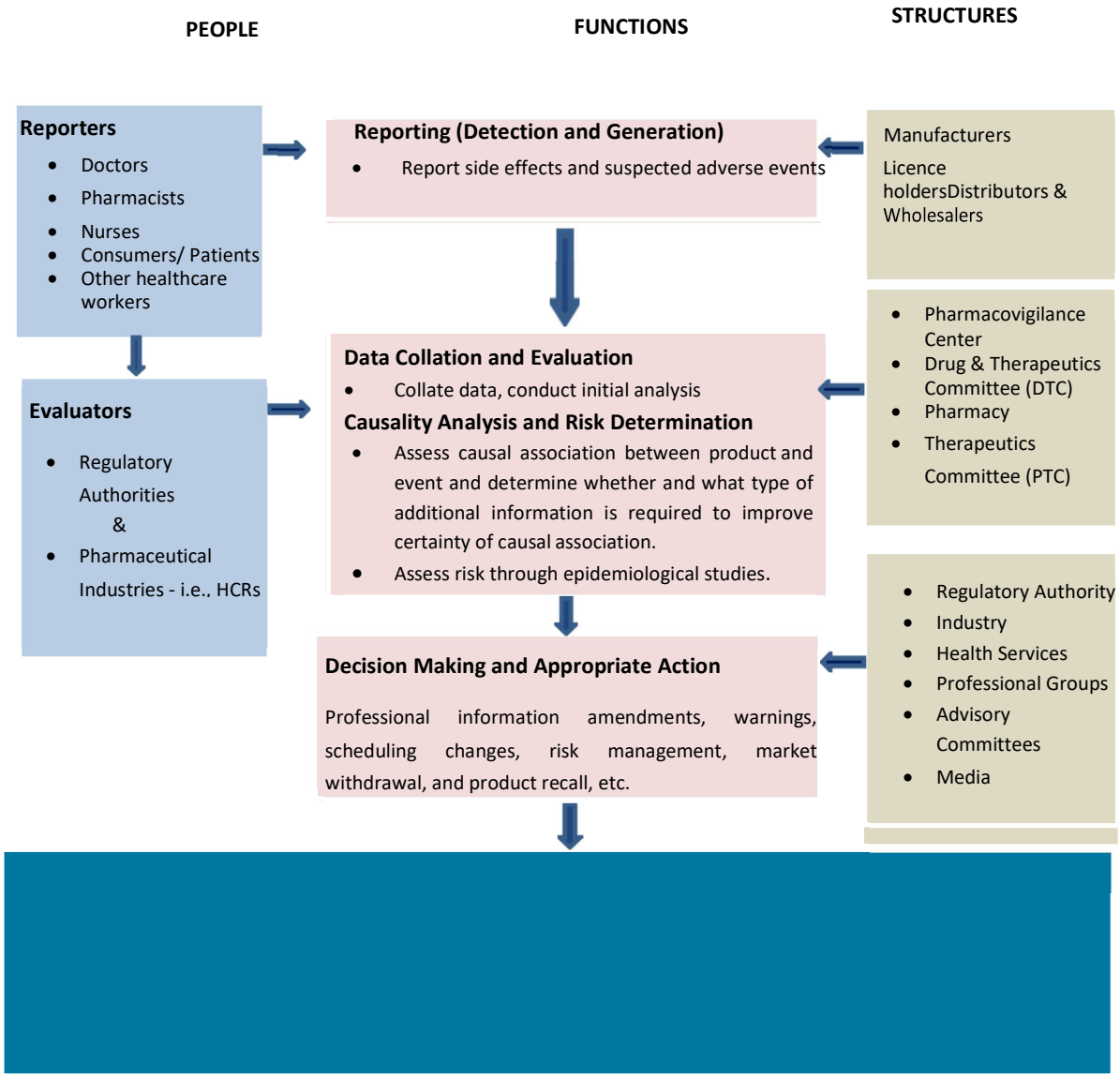
Characteristic	Regulatory	Public Health		Manufacturer/HCR
Focal Point	SAHPRA	DoH-PvPHP	EPI	Company Pharmacovigilance Programme
Medicines under focus	All medicines available in the country	HIV/AIDS and TB medicines	Vaccines	All medicines registered or authorised for marketing by the particular company.
Objectives	Ensure marketed medicines are safe, effective and of good quality in the interest of the public.	Minimise preventable harm and maintain public trust in the programmes and the medicines it employs		Ensure that marketed medicines are safe, effective, and of good quality, as per the product conditions of registration. Minimise preventable harm and maintain public safety with the medicines marketed.
Communication of results and corrective actions	Through regulatory decision-making, market withdrawal, labelling changes, Public Health Advisories, Dear Healthcare Professional Letters (DHCPLs) Press Statements and medicines safety alerts	Epidemiological newsletters, press statements, guidelines, training and educational materials, local or international publications, infrastructural changes and changes in conditions of drug use		Through reporting to the Authority, decision-making, labelling and professional information changes, market withdrawal, dear healthcare professional letters (DHCPLs), guidelines, training and educational materials, local or international publications.

Developed by Dr Ushma Mehta

The regulatory pharmacovigilance unit's key role is safety monitoring of all medicines available in the South African market. Its core activity is the collection and evaluation of ADR reports submitted by healthcare professionals/providers, consumers, and HCRs in the country. The ultimate goal of this activity is to contribute to the rational and safe use of medicines and to continuously monitor the risks and benefits of all medicines available at every level of healthcare. Ensuring safety of medicines is the responsibility of all stakeholders involved in the medicines chain.

The diagram below illustrates the various stakeholders involved in pharmacovigilance and their respective key responsibilities.

Diagram 1: Professional groups/associations and their functions



4. PROCEDURES FOR REPORTING

4.1 How do healthcare professionals/providers identify ADRs?

4.1.1 Obtain patient history and perform an appropriate examination

i) Take a proper history

- A full medical history should be appropriately performed.
- Can this ADR be explained by other causes, e.g., the patient's underlying disease, other prescription medicine/s or OTC medicines, toxins or foods?
- It is essential that the patient is thoroughly investigated to establish the actual cause of any new medical problem. A medicine-related cause should be considered, especially when other causes do not explain the patient's condition.

ii) Where necessary, perform a thorough physical examination with appropriate laboratory, imaging and other relevant investigations,

- Few medicines produce distinctive physical signs (exceptions include fixed drug eruptions, steroid-induced dermal atrophy, and acute extrapyramidal reactions).
- Laboratory tests are critical if the medicine is considered essential in improving patient care or if the laboratory test results will improve management of the patient.
- Describe the reaction as clearly as possible. Where possible, provide an accurate diagnosis and/or supply pictures.

In summary, some reactions occur immediately after a medicine is administered, while other responses take time to develop. Thus, the time from the start of therapy to the time of onset of the suspected reaction must be logical.

4.1.2 Effect of dechallenge and rechallenge should be determined (when necessary)

- Positive dechallenge (partial or complete disappearance of a reaction when dechallenge is instituted) is a strong, although not conclusive, indication of a medicine-induced reaction.
- Rechallenge (reintroducing the medicine after a dechallenge) is justifiable when the benefit of reintroducing the medicine to the patient outweighs the risk of recurrence of the reaction. This is rare. In some cases, the reaction may be more severe on repeat exposure.

4.1.3 Where possible, check the known pharmacology of the medicine

- Is the reaction known to occur with the particular medicine as stated in the Professional Information (PI)/ medicine labelling or other scientific reference?
- If the reaction is not documented in the PI, it does not mean that the reaction cannot occur with

that particular medicine.

4.2 What to report?

ADRs resulting from prescription medicines or OTC medicines should be reported. All ADRs should be reported. Most importantly, serious, undocumented and unexpected ADRs are to be reported. If there is any doubt about whether the ADR should be reported, it is always best practice to submit a report, as causality does not need to have been established.

i) ADRs in children

All suspected ADRs occurring in children under the age of 18 should be reported regardless of whether the medicine is registered for use in children.

ii) ADRs in the elderly

Healthcare professionals/providers should be particularly aware that the elderly may be more susceptible to ADRs. It is therefore important to monitor drug safety in this age group. Elderly patients are more likely to be taking multiple medicines and may also metabolise them less effectively or be more sensitive to their effects.

iii) ADR reports on lack of efficacy

Lack of efficacy for medicines used in the treatment of life-threatening diseases (e.g., antimicrobial agents), vaccines, contraceptives or other classes of medicines where lack of efficacy could result in serious consequences, requires reporting. The normal progression of disease does not imply a lack of efficacy. The batch/lot number of the suspected medicine for a report of lack of efficacy must be included in the report.

iv) Delayed drug effects

Some reactions may become manifest months or years after exposure. Any suspicion of such an association should always be reported. Examples of delayed reactions that might need to be reported include:

- kidney disease from long-term usage of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs);
- disabling and potentially permanent side effects which involve tendons, muscles, joints, nerves and the central nervous system (i.e., tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste and smell) following the use of fluoroquinolone antibiotics.

v) Interactions

If an adverse effect is suspected to be related to an interaction between two or more medicines, it should be reported as an ADR.

vi) Medication errors

Medication errors, whether resulting in an adverse drug reaction or not, should be reported.

vii) Overdose

Suspected ADRs associated with an overdose should be reported, as well as other reactions that may have occurred due to the overdose.

viii) Reports relating to pregnancy and breastfeeding

The healthcare professional/provider should report suspected ADRs related to pregnancy or breastfeeding regardless of whether the medicine is contraindicated in pregnancy and/or lactation.

ix) Serious adverse drug reactions

All serious suspected reactions should be reported within seven calendar days of identification, while non-serious ADRs should be reported within 15 calendar days. The side effects of an established medicine may be well known but if a severe reaction occurs it should always be reported regardless of whether it is expected or not.

x) Product quality problem

Healthcare professionals/providers are encouraged to report product quality problems, whether or not they result in an adverse drug reaction. The batch/lot number of the suspected medicines must be included in the report.

xi) Teratogenicity and congenital anomalies

The following information should be provided for reports on congenital anomalies or teratogenicity:

- age and sex of the infant,
- the birth date or the date on which the pregnancy was ended; (duration of pregnancy/gestational age of foetus/baby),
- date and/or duration of exposure to teratogen/substance/medicine in the preconception period, and/or any or all trimesters of pregnancy,
- the teratogen/substance(s) or medicine(s) exposed to and the dose in case of a medicine and reason(s) for exposure or treatment with the medicine(s),
- the type of congenital anomaly/malformation/adverse event/ reaction noticed at or after birth, and the seriousness thereof,
- whether the congenital anomaly/malformation/adverse event/reaction resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, was a medically significant/important reaction/event or would have persistent and/or significant disability/incapability consequences, and

- any adverse reactions experienced by the mother must be considered a new initial case report and should be reported separately.

Suspected ADRs should also be reported in cases where a baby is born with a congenital abnormality or where a pregnancy results in a malformed or aborted foetus. The report should include details of all medicines taken during pregnancy.

4.3 When to report an ADR?

A healthcare professional/provider should report when they have identified an ADR suspected to have been caused by a medicine. Healthcare professionals/providers are encouraged to report suspected ADRs even when they do not have all the facts or are uncertain that the medicine is definitely responsible for causing the reaction.

4.3.1 Minimum information required

Healthcare professionals should note that even if all the facts are not available at the time of reporting, the minimum information required for a meaningful case (i.e., information about the patient, suspected medicine, the reaction and information about the reporter) should always be included in the report. However, it is important that healthcare professionals/providers make every effort to ensure that all facts are included in the report to provide a meaningful assessment.

4.3.2 Reporting timelines

Serious adverse drug reactions should be reported within 24 hours of identification, while non-serious adverse drug reactions should be reported within 15 calendar days of identification.

4.4 Information to consider when reporting?

4.4.1 What to consider?

When completing the form, the healthcare professional/provider should include the minimum information required for a case to be deemed meaningful, which is as follows:

- information about the patient:
    - patient's initials,
    - local identification/ reference number [any number or code that identifies the patient to the reporter, but not to SAHPRA (e.g., hospital number; file number)],
    - gender,
    - age at the time of the ADR or date of birth and

- weight (if known),

- which medicine is suspected to have caused the reaction,
  - name (preferably proprietary name),
  - dose, frequency and route used,
  - therapy date,
  - indication for use,
  - batch/lot number,
  - expiration date,
- the reaction that has occurred,
  - description of the reaction,
  - onset date of the reaction,
  - outcome of the reaction after use of the medicine was stopped or reduced,
  - information about the reaction, in instances where there is repeat exposure of the medicine,
- information about the reporter,
  - name or initials, email address and telephone number,
  - occupation,
  - health institution/facility.

Further information that is required to ensure that the report is clinically meaningful is as follows, but is not limited to:

- concomitant medicines, therapy dates,
- other relevant patient information/ history,
- date of the report and
- relevant tests/laboratory data (if available).

These are important points to note when reporting an ADR:

- It should be noted that by supplying these anonymised details, a healthcare professional/provider will not breach the confidentiality agreement they have with the patient. Although explicit consent from the patient is not required, it is best practice to inform the patient if a report will be submitted.
- Healthcare professionals/providers should submit ALL the relevant information available at the time of initial identification of an ADR, not only the minimum information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data and other additional clinical data is encouraged.
- Additional information, not available at the time of the initial report, should be provided when available, as a follow-up report (using the same reference number as the initial report).
- The healthcare professional/provider who initially reported the suspected ADR is required to submit

their names or initials, institution, email address, telephone number and qualifications.

4.4.2 Follow-up reports

Any follow-up information from the healthcare professional/provider relating to an initial ADR report submitted to SAHPRA, should be cross-referenced to the reference number (if applicable) on the initial report. The follow-up report, which follows a previous (first) communication to SAHPRA, should be clearly marked as a follow-up. This is the only reliable way to minimise duplication of reports submitted by reporters in the VigiFlow® system.

4.5 Who should report ADRs?

All healthcare professionals/providers, including doctors, dentists, pharmacists, nurses and other healthcare professionals/providers are requested to report all suspected adverse reactions severe ADRs and those related to new medicines. Consumers should be encouraged to report all suspected ADRs, preferably via their healthcare professionals/providers.

4.6 How to report?

All ADRs should be reported to SAHPRA's Pharmacovigilance Unit through one of the channels stipulated below:

4.6.1 Med Safety App

Med Safety App is a mobile application developed to engage both patients and healthcare providers on medicines safety issues. It was developed by the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA) as part of the Innovative Medicines Initiative WEB-Recognising Adverse Drug Reactions (WEB-RADR) project. The app is designed to simplify and promote the reporting of suspected adverse drug reactions (ADRs), including adverse events following immunisation (AEFIs), by both the public and healthcare providers. The App also allows the public and healthcare providers to learn about medicine safety news from SAHPRA, thereby creating an awareness of medicines, their potential adverse effects and pharmacovigilance. The Medsafety app is currently the most preferred tool for reporting suspected AEFIs and ADRs.

Where to find Med Safety app?

The Med Safety App is available for download from:

- App store (For iOS devices)
- Google Play (For Android devices)

How to download the Med Safety app:

- Open the Play Store (Android) or the App Store (IOS)
- Search for Med Safety icon
- Tap the Med Safety icon
- Tap to install to download the App
- Tap Open
- Select a region, in this case South Africa. Sometimes it selects automatically depending on the settings you already have on your phone
- Click continue as guest or create an account
- Report ADRs and/or product quality problems

Upon successful submission of the report, a message is displayed on the app to confirm submission, and an email acknowledgement is sent to the reporter. For more information about the Med Safety App, please visit the SAHPRA website, under the E-Services tab, there is more information, including the videos of how to use the app and recorded related trainings.

Why use Med Safety app?

- **The Medsafety app provides several benefits:**
  - The App facilitates reporting of ADRs by the **public** and **healthcare practitioners**.
  - The app provides feedback to reporters on a platform that is readily available to reporters.
  - Users can create a watch list which enables users to view information that is relevant to them by following products of interest.
  - The user can change the language within the app, and the language is automatically adapted to the language to which the device is configured.
  - Reports can be created and saved without an internet connection and submitted later when a connection becomes available.
  - View and submit updates to previously submitted reports.
  - See immediate acceptance of your reports.

4.6.2 Using eReporting link to VigiFlow®

- Healthcare professionals (and consumers) can report ADR through the eReporting module (accessible from the SAHPRA website) directly into VigiFlow®.
- eReporting allows for seamless electronic reporting of ADR reports, thus reducing the workload of manual data entry from ADR paper forms into VigiFlow®.
- Pharmacovigilance unit personnel need only to enter a small amount of data, which allows more time for the pharmacovigilance team to verify the coding and to conduct causality assessment of cases of interest.

4.6.3 Adverse Drug Reactions & Quality Problem Reporting Form

ADR reports should be sent via email at adr@sahpra.org.za or to the relevant pharmaceutical company (contact details can be found on the outer packaging of the health product).

4.7 What happens after reporting?

Once an ADR report has been received:

- SAHPRA (Pharmacovigilance Unit) staff capture the information onto the VigiFlow® system in a structured format.
- In turn, the VigiFlow® system assigns a unique identification number.
- The captured information for each report is checked for quality and completeness before being sent to the global database known as VigiBase®, where it is confidentially stored.
- An acknowledgement letter (which quotes the unique identification number assigned to the report and the local/reference number) is then sent to the reporter. Acknowledgement letters for reports that have been assessed to determine the causal link are prioritised.
- At any point during this process, the reporter may be asked by the SAHPRA Pharmacovigilance Unit to provide clarification or further information about the ADR report. SAHPRA's Pharmacovigilance Unit personnel, using referenced data from other sources (e.g. case reports in the literature; pre- and post-marketing clinical trials; epidemiological studies; record-linkage databases; data from other drug regulatory authorities), conduct preliminary causality assessments and prepare reports on ADR cases with emerging drug safety problems. The report reviews are then presented to the Pharmacovigilance Advisory Committee (PVC) and its sub-committee for expert advice in identifying the possible risk factors contributing to the reaction and causal association.

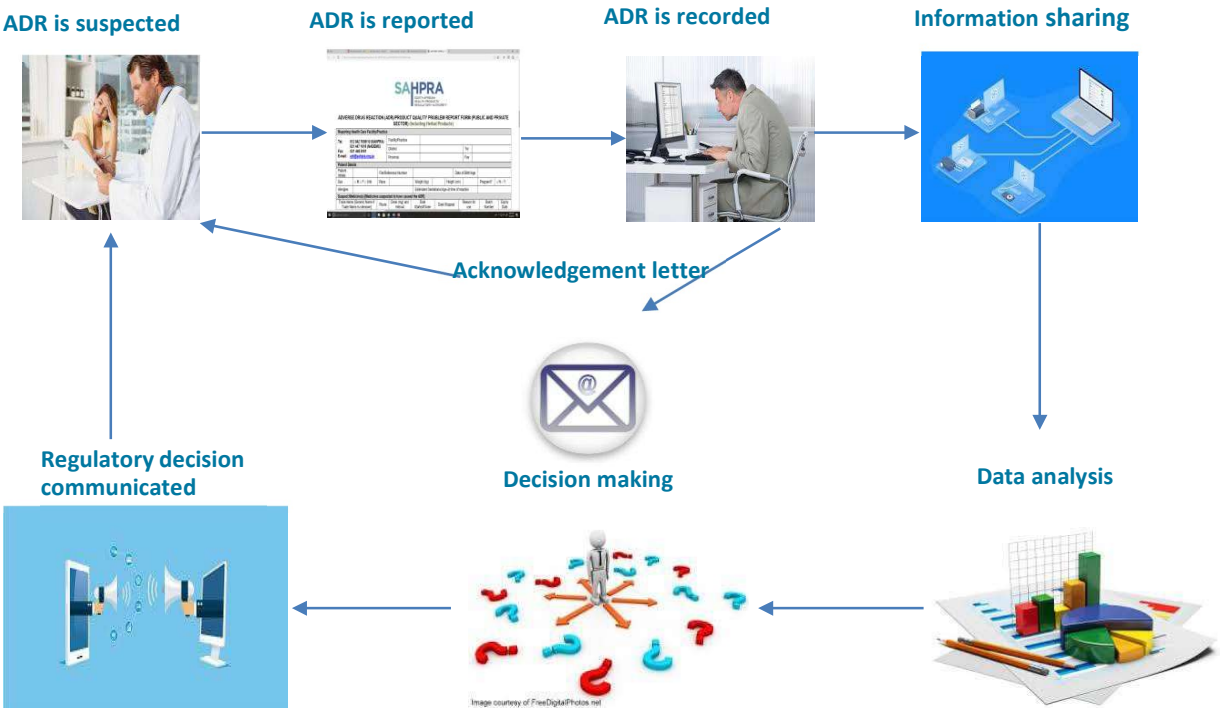
When safety concerns are identified, the overall ADR profile for the medicine is compared with the relevant therapeutic alternatives, and its benefits in terms of efficacy, the therapeutic indication, and target patient population(s). Again, the PVC advises the Authority on drug safety, enabling regulatory decisions to be made

on whether changes in the use of a medicine are necessary. The possible regulatory changes may include:

- product label change
- product withdrawal/suspension
- “Dear healthcare professional” letters (DHCPLs)
- press statements
- medicines safety alerts
- product restrictions (up-scheduling, limited packaging, limited prescribers)
- an educational programme

Following consideration of the advice provided by the PVC, the Authority engages with industry to alert the HCRs about safety concerns related to their products and communicate regulatory decisions related to products implicated as suspect medicines to ADRs.

Diagram 1: Flow diagram: ADR Form Life cycle



5. WHAT HAPPENS TO THE REPORTER?

5.1 Will reporting have any negative consequences on the healthcare professional or the patient?

The ADR report does not constitute an admission that the reporter or any other healthcare professional contributed to the ADR in any way. The details of the report will be stored confidentially in VigiBase® database. The names of the reporter or any other health professionals named on a report and the patient will be removed before any details about a specific ADR are used or communicated to others. The information obtained from the report will not be used for commercial purposes. The information is intended to enhance our understanding of safety in relation to the use of medicines in South Africa.

5.2 Confidentiality

SAHPRA will maintain strict confidentiality regarding the identities of the patient and the reporter.

6. VALIDITY

This guideline is valid for a period of five (5) years from the effective date of revision. It will be reviewed as and when required.

7. REFERENCES

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8. APPENDICES

APPENDIX A: ADR REPORTING FORM

Doc Number: GLF-CEM-PV-06A *[Old Doc no. 6.04]*	**ADVERSE DRUG REACTION (ADR)/ PRODUCT QUALITY PROBLEM REPORT FORM** (PUBLIC AND PRIVATE SECTOR) (Including Herbal Products)	SAHPRA South African Health Products Regulatory Authority
Revision: 3.0		Effective date: 11 October 2023

See Page 2 for CONSENT CLAUSE, more information regarding reporting of PRODUCT QUALITY PROBLEMS and ADVERSE EVENTS FOR VACCINES

Reporting Health Care Facility/Practice

Building A, Loftus Park 402 Kirkness Street, Arcadia, Pretoria Tel: (012) 501 0311 E-mail: adr@sahpra.org.za	Facility/Practice			
	District		Tel	
	Province		Fax	

Patient Details

Patient Initials		File/Reference Number			Date of Birth/Age		
Sex	☐M ☐F ☐Unk	Race		Weight (kg)		Height (cm)		Pregnant?	☐N ☐Y
Allergies				☐ Follow up report Reference number: _____			Estimated gestational age at time of reaction

Suspect Medicine(s) [Medicines suspected to have caused the ADR], Concomitant [Other medicines taken together with the suspect medicine(s)] OR Interacting [Other medicines taken together with the suspect medicine(s)] [Including over the counter and herbal products].

Trade Name [Active Ingredient if Trade Name is unknown]	Medicine role (Please tick the applicable box)	Route	Dose (mg) and Interval	Date Started/ Given	Date Stopped	Reason for use	Batch Number	Expiry Date
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							

Adverse Drug Reaction/Product Quality Problem

Date and time of onset of reaction		Date reaction resolved	

Please describe Adverse Event/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention (Tick all that apply)	**Patient Outcomes** (Tick all that apply)	**ADR seriousness criteria** (Tick all that apply)
☐ No intervention. ☐ Intervention unknown. ☐ Patient counselled/non-medical treatment. ☐ Discontinued suspect drug; **Replaced with:** _____ ☐ Decreased suspect drug dosage; **New Dose:** _____ ☐ Treated ADR – with: _____ ☐ Referred to hospital: **Hospital name** _____ ☐ Other intervention (e.g., dialysis): _____	☐ ADR recovered/resolved. ☐ Recovering/resolving. ☐ Not recovered/not resolved. ☐ Recovered with sequelae. ☐ ADR resolved after suspect medicine was stopped: ☐N ☐Y. ☐ ADR reappeared after restarting suspect drug/similar drug (rechallenge): ☐N ☐Y ☐ Not done ☐ Unknown	☐ Resulted in death. Date of death: _____ ☐ Patient hospitalised or hospitalisation prolonged. ☐ Life threatening. ☐ Impairment/disability. ☐ Congenital anomaly/ birth defect. ☐ Other medically important condition.

Laboratory Results			**Additional Laboratory Results**		
Lab Test	**Test Result**	**Test Date**	**Lab Test**	**Test Result**	**Test Date**

Co-morbidities/Other Medical Condition(s)

Reported by			
Name		E-mail	
Designation	☐Nurse ☐Pharmacist ☐Doctor ☐Other:	Telephone	
Date reported:		Signature	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR

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ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:
- medications (medicines and biologicals),
- complementary / alternative medicines (including traditional, herbal remedies, etc).

Please report especially:
- adverse drug reactions to newly marketed products,
- serious reactions and interactions with all products,
- adverse drug reactions which are not clearly reflected in the package insert.

Report Product Quality Problems such as:
- suspected contamination,
- questionable stability,
- defective components,
- poor packaging or labelling,
- therapeutic failures.

Report even if:
- you're not certain the product caused the event,
- you don't have all the details.

Report adverse events experiences with Medical Device via:
- phone: 012 501 0476
- mdvigilance@sahpra.org.za

Report Adverse Events Following Immunisation (AEFI) experienced with vaccines on:
- the dedicated Case Reporting Form accessed from SAHPRA portal: https://www.sahpra.org.za/health-products-vigilance/
- forward the dedicated form to AEFI@health.gov.za
- phone: 0800 02 9999.

Report Product Quality Problems via:
- phone: 0800 204 307

SAHPRA portal: https://www.sahpra.org.za/complaints-relating-to-medicine-and-medical-devices/

Other reporting tools available at SAHPRA include:

Med Safety Application

The Med Safety Application is a mobile application designed for the public and healthcare professionals to report suspected ADRs/adverse event following immunisations (AEFIs). It is the preferred reporting tool by SAHPRA and allows for a seamless electronic submission of ADR/AEFI reports directly from the source into SAHPRA's reporting systems. The app can be downloaded onto a smart mobile phone directly from the SAHPRA website, https://medsafety.sahpra.org.za.
For more reporting channels please visit SAHPRA website, https://www.sahpra.org.za

CONSENT CLAUSE

By the signature above, the reporter hereby provides consent to the processing of personal information provided for the purpose of reporting a suspected adverse reaction. The reporter acknowledges that this information may be used a) to access all medical and clinical records for the purpose of gathering additional information for a clinical meaningful data, when required; b) in the generation of statistics; and c) to make policy decisions relating to safe use of medicines.

SAHPRA's Vigilance unit undertakes to collate the personal information contained in this form and collected during the process of reporting of suspected adverse drug reaction in a manner that adheres to the Protection of Personal Information Act, so that your personal data is processed fairly, lawfully and transparently, adequate, relevant, and limited to what is necessary, processed for specific and legitimate purposes, accurate and kept up to date where necessary, kept in an identifiable form no longer than necessary for the purpose and processed securely . SAHPRA has placed appropriate technical and organisational measures to safeguard your information. The information will not be stored for any longer than is necessary to achieve the purpose for which it was collected, unless the unit has a lawful basis to do so. If the reporter wishes to access and/or rectify their personal information, they may do so by contacting SAHPRA's Vigilance unit at 012 501 0311 or via email: adr@sahpra.org.za.

Confidentiality:

Identities of the reporter and patient will remain strictly confidential.

Your support of the South African Health Products Regulatory Authority's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

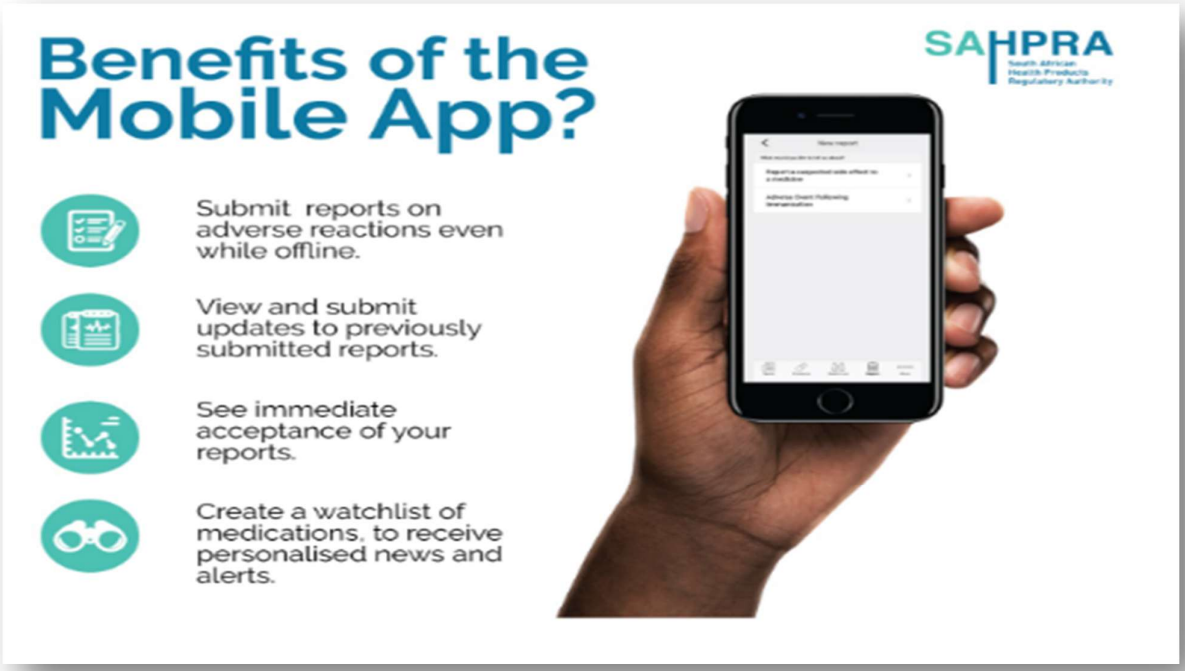
APPENDIX B: MED SAFETY APPLICATION

Other reporting tools available at SAHPRA include:

Med Safety Application

The Med Safety Application is a mobile application designed for the public and healthcare professionals to report suspected ADRs. It is the preferred reporting tool by SAHPRA and allows for a seamless electronic submission of ADR reports directly from the source into SAHPRA's reporting systems. The app can be downloaded onto a smart mobile phone directly from the SAHPRA website, https://medsafety.sahpra.org.za.

Figure 1: Benefits of the Med Safety App



Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the South African Health Products Regulatory Authority's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.