ZAMBIA MEDICINES
REGULATORY AUTHORITY

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PHARMACOVIGILANCE

REFERENCE MANUAL

Second Edition

March 2020

Republic of Zambia

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Pharmacovigilance Reference Manual

TheGlobalFund

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Foreword

Medicines have the potential to cause harm during their use. Adverse events associated with the use of medicines have considerable social and economic consequences. A system for continuous monitoring of the safety of medicines is therefore required. For such a system to be successful, there is need to engage all stakeholders in a well-structured system. In 2006, the Government of the Republic of Zambia established the National Pharmacovigilance Unit under the then Pharmaceutical Regulatory Authority (now Zambia Medicines Regulatory Authority) to coordinate the drug safety monitoring activities in the country.

Pharmacovigilance refers to the science and activities relating to the detection, assessment, understanding and prevention of drug adverse effects or any other medicine related problem. The aim of a pharmacovigilance system is to ensure rational and safe use of effective medicines.

Success of any pharmacovigilance system depends on active participation of healthcare workers and relevant stakeholders who are conversant with the principles of drug safety monitoring. It is for this reason that Zambia Medicines Regulatory Authority has developed this manual to serve as a reference document for the detection, management and reporting of adverse events caused by medicines and allied substances. The manual also gives guidance on reporting of medication errors and medicine quality problems.

I hope that this manual, a second edition, will serve as an important source of reference material for medicines safety monitoring, and will stimulate the active participation of all stakeholders in pharmacovigilance. I equally want to take this opportunity to thank all the organizations and individuals that provided both technical and financial support to ensure the successful revision of this manual.

Dr Kennedy Malama
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Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization
DHO	District Health Office
MAH	Market Authorisation Holders
MTC	Medicines and Therapeutics Committee
MoH	Ministry of Health
NPVU	National Pharmacovigilance Unit
PHO	Provincial Health Office
PHP	Public Health Programme
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
ZAMRA	Zambia Medicines Regulatory Authority

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Definitions

For the purposes of this document, the following terms are defined:

Active Surveillance
A system which proactively identifies and quantifies risks for adverse events.

Adherence
A patient's careful and willing observance of the guidelines for taking a medicine or managing a therapy. This term has largely replaced the term compliance.

Adverse drug event
Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.

Adverse drug reaction
A response to a medicine which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Adverse effect
A negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all.

Adverse event
Any negative or harmful occurrence that takes place during treatment that may or may not be associated with a medicine. Note. A fall could be such an event that may – or may not – have any association with a medicine.

Association
Events associated in time but not necessarily linked as cause and effect (temporal association).

Benefit
(a) positive therapeutic effects of treatment in an individual; (b) positive health, social or psychological effects of treatment from the patient's perspective.

Benefit-harm
A description or assessment of both positive and negative effects of a medicine (not necessarily expressed in quantitative terms) as far as they are known and as perceived by an individual. This is the critical information that health professionals and patients need to make wise therapeutic decisions. The perspectives of professionals and patients on the issues may differ.

Benefit-risk
'Benefit-risk' is a logically mismatched pair, the more accurate, benefit-harm, is preferable.

Causal relationship
Where there is a demonstrable cause-effect association between two events.

Cohort Event Monitoring
Cohort Event Monitoring (CEM) is a prospective, observational study of events that occur during the

use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment and for a defined period of time.

Common
In pharmacovigilance, an event with a probability between 1 in 100 and 1 in 10, or 1%-10%.

Compliance
Adherence to the recommended medication regimen.

Consumer
A consumer in a healthcare is anyone who uses, has used, or may use any health or health related service. It is not limited to those currently using a service. The terms "patients" and "users" generally apply only to those currently undergoing some form of treatment.

Dependence
The compulsion to take a drug repeatedly with distress (physiological and/or psychological) being caused if this is prevented.

Drug
See Medicine: commonly used as a synonym for this term.

Drug Abuse
The non-medical, self-administered use of a drug that is outside the limits considered acceptable by society.

Drug interaction
A drug interaction is a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect not produced on its own. Typically, interaction between drugs comes to mind (drug-drug interaction). However, interactions may also exist between drugs & foods (drug-food interactions), as well as drugs & herbs (drug-herb interactions).

Drug Misuse
The use of a medicine or allied substance for a purpose not consistent with legal or medical guidelines.

Drug Resistance
Reduction in effectiveness of a chemotherapeutic agent, for example antimicrobials and antineoplastic agents.

Effectiveness
A measure of the chances or odds (probability) of a medicine working positively as expected for patients.

Efficacy
A measure of the extent to which a chemical substance or medicine works positively under laboratory conditions and in a selected group of patients.

Falsified Product
Medical product that is deliberately and fraudulently misrepresents their identity, composition or source.

General public/the public
People collectively as members of the community.

Harm
The damage or injury that is or might be caused by a medicine, including death. The concept extends to social and psychological damage or impairment, especially from the patient's perspective.

Hazard
The intrinsic chemical or biological characteristics of a medicine or its use that have the potential to cause harm.

Health Facility
A health facility is any governmental, non-governmental or private institution that carries out promotion, preventive, curative and rehabilitative activities or medicine trade or services (refer to the Health Professions Act No.24 of 2009 Zambia). For the purposes of this document, a health facility shall also include Pharmacies and Health Shops according to the Medicines and Allied Substances Act No. 3 of 2013.

Healthcare professional
Person who is trained and licensed to provide health care.

Healthcare worker
Any person providing health care services at any of the health facilities defined above.

Herbal medicine
The use of plants for medicinal purposes; also known as botanical medicine.

Individual Case Safety Report (ICSR)
Reports sent by health professionals or patients when an adverse effect has occurred in a patient taking one or more medicines. These have also been referred to as adverse drug reaction (ADR) reports or adverse event (AE) reports.

Intensified Spontaneous Reporting (Stimulated Reporting)
a spontaneous reporting system in which health care professionals and medicine consumers are stimulated or encouraged to report adverse events associated with specific medicines that are deemed by the medicine regulatory authority to require intensive monitoring.

Lack of efficacy
Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

MedDRA
A code book of medical terminology developed by the International Conference on Harmonisation.

Media
Any channel of communication.

Medical device
Includes an instrument, apparatus, component, part or accessory manufactured or sold for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or the symptoms of the disease, or abnormal physical state in human beings or animals.

Medication errors
A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare provider, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medicine (Drug)
Means human medicine, veterinary medicine, medicinal product, herbal medicine or any substance or mixture of substances for human or veterinary use intended to be used or manufactured for use for its therapeutic efficacy or for its pharmacological purpose in the diagnosis, treatment, alleviation, modification or prevention of disease or abnormal physical or mental state or the symptoms of disease in a person or animal.

Member countries
Countries that have joined the WHO Programme for International Drug Monitoring, fulfilling the membership criteria.

National Centres
Organizations or entities recognized by government to represent their country in relation to pharmacovigilance in the WHO Programme for International Drug Monitoring.

Non-adherence
May be defined as the failure of a patient to take medications as prescribed by the attending health worker.

Patient Reporting Form
Refers to the Adverse Medicine Reaction Reporting Form for Patients, Non-Health Professionals and Practitioners of Traditional/ Alternative/ Complementary Medicine.

Patient
Person awaiting or under medical or health care treatment. This concept includes anyone taking medicines, also those who are self-medicating.

Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Post-marketing
The stage when a drug is approved and generally available on the market.

Pre-marketing
The developmental stage before a drug is approved and available for prescription or sale to the public.

Prescription
A written direction given by an authorised prescriber directing that a selected amount of a medicine specified in the direction be dispensed for the person or animal named in the direction.

Prescription event monitoring
System created to monitor adverse drug events in a population. Prescribers are requested to report

all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug.

Prescription Only Medicine (POM)
A medicine dispensed only on prescription.

Product quality problem
Quality problems of products i.e.; suspected contamination, questionable stability, defective components, poor packaging or labelling, or unexpected therapeutic ineffectiveness.

Prophylaxis
Prevention or protection.

Rare
n pharmacovigilance, an event with a probability between 1 in 10,000 and 1 in 1,000, or 0.01% and 0.1%.

Rational drug use
A visionary concept implying the achievement of optimal prescribing and use of drugs.

Regulatory authority
The legal authority in any country with the responsibility for regulating all matters relating to drugs.

Risk
The probability of harm being caused; the probability (chance, odds) of an occurrence. Note 1. The term risk normally, but not always, refers to a negative outcome. Note 2. Contrary to harm, the concept of risk does not involve any reference to the nature or severity of an outcome.

Serious adverse event
Any untoward medical occurrence that at any dose can result in any of the following: death, life-threatening event/reaction, hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or a medically important event or reaction.

Side effect
Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug. Essential elements in this definition are the pharmacological nature of effect, that the phenomenon unintended and there is no overt overdose.

Signal
Reported information on a possible causal relationship between an adverse event and a drug, 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 Report
An unsolicited communication to a company, regulatory authority, or other organisation that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organised data collection scheme.

Spontaneous reporting
System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

Stakeholder
Individual, or group of individuals, with a legitimate interest and responsibility in a human endeavour, e.g. pharmacovigilance. Their interest may be because they will have a role in implementing decisions, or because they will be affected by actions taken.

Substandard Product
Also called “out of specification”, these are authorised medical products that fail to meet their quality standards or specification, or both

Targeted Spontaneous Reporting (TSR)
Intensified spontaneous ADR reporting within a defined cohort.

Tolerance
Diminished response to a drug when given repeatedly at the same amount.

Traditional medicine
The sum of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Treatment failure
Occurs when the expected treatment outcome is not achieved despite the patient taking the prescribed medications correctly. Drug resistance, product failure, bioequivalence problems and the use of substandard or falsified products may cause treatment failure.

VigiBase®
The World Health Organisation (WHO) global database of Individual Case Safety Report (ICSRs).

VigiFlow®
A web-based data management tool for ADR data. It is a complete Individual Case Safety Report (ICSR) management system created and maintained by the Uppsala Monitoring Centre (UMC) based in Sweden and closely associated with WHO Collaborating Centre for International Drug Monitoring. It can be used as the national database for countries in the WHO programme as it incorporates tools for report analysisand facilitates sending reports.

VigiLyze®
The search and analysis tool used to retrieve global ICSR data from VigiBase®.

1. Introduction

1.1. The Concept of Pharmacovigilance

Medicines are beneficial to mankind. They have helped to bring improved health and longer life to the human race. They affect the lives of hundreds of millions of people every day. The use of medicines is, however, not without risks. Medicines have caused and continue to cause harm to many people. On one hand, there are many people who benefit from effects of medicines, while on the other hand others do not derive any beneficial effect at all. Furthermore, not all hazards of medicines can be known before a medicine is marketed. Neither tests in animals nor clinical trials will always reveal all the possible adverse effects of a medicine. These may only be known when the medicine has been administered to large numbers of people over considerable periods of time.

During the last decades, medicine-related morbidity and mortality have been among the major health problems recognised by healthcare providers and the public. This has been demonstrated by several studies. In the early 1960s, the World Health Organisation (WHO) recognised the need for developing effective systems for continuous monitoring of the effects of medicines in all countries. As at 2018,there were 134countries in the world which had developed drug safety monitoring (pharmacovigilance) systems. Zambia became a member of the WHO Programme for International Drug Monitoring in 2010.

As defined by WHO, Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

1.2. Evolution of Pharmacovigilance

The Thalidomide tragedy, which occurred from the late 1950's to the early 1960's, raised concerns regarding the safety of medicines and the potential dangers to public health associated with unexpected adverse reactions to medicines. In response, the Sixteenth World Health Assembly (1963) adopted a resolution (WHA 16.36) that reaffirmed the need for early action regarding the rapid dissemination of information on adverse drug reactions. The World Health Organization (WHO), following the World Health Assembly Resolution (WHA 20.51 of 1967), established an international drug monitoring scheme initially with 10-member countries in 1968 to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines. The initial activities of the pilot project culminated in the current WHO Programme for International Drug Monitoring (PIDM), which by the end of 2018 had grown to become a global network of national pharmacovigilance centres in over 134 countries. The Thalidomide tragedy demonstrated that seemingly safe drugs could have potentially serious adverse effects. World Health Organisation therefore called for closer monitoring of the adverse effects of all drugs.

1.3. Legal Basis for Pharmacovigilance in Zambia

According to the National Drug Policy of 1999, the objective of drug legislation and regulation in Zambia is to ensure that all drugs (medicines) and drug information conform to the required standards of quality, safety and efficacy throughout the chain of manufacture, importation/exportation, distribution/supply, storage and use.

Since all medicines have potential to cause harm during their usage, mechanisms to continuously monitor their safety are needed. This entails having in place a well-organized drug safety monitoring system.

The Zambian Government recognized this need and under the Pharmaceutical Act (No.14) of 2004, the Pharmaceutical Regulatory Authority (PRA) was established whose functions, among others, included post-marketing surveillance. The Authority established the National Pharmacovigilance Unit (NPVU) in 2006, which is responsible for Pharmacovigilance activities in Zambia. Since then, the Unit has conducted a number of activities aimed at medicines safety monitoring.

The main objectives of the NPVU include:

a) Early detection of drug/ product related safety problems to inform decision making;
b) Contributing to risk-benefit analysis of medicines and promoting safe, rational and cost-effective use of medicines;
c) Protecting public health and safety in relation to the use of medicines;
d) Promoting understanding, education and training in pharmacovigilance; and
e) Providing effective communication with health professionals and the general public.

The Medicines and Allied Substances Act, 2013 continued the existence of the Pharmaceutical Regulatory Authority which was then renamed Zambia Medicines Regulatory Authority (ZAMRA).

1.4. Importance of Pharmacovigilance

The information collected during the pre-marketing phase of a medical drug is inevitably in complete about possible adverse reactions for the following reasons:

a) Tests in animals are insufficiently predictive of human safety;
b) In clinical trials, patients are selected and limited in number. The conditions of use differ
from those in clinical practice and the duration of trials is limited;
c) Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available.

Pharmacovigilance is needed in Zambia because there are differences between countries (and even regions within countries) in the occurrence of adverse drug reactions and other medicine-related problems. This may be because of differences in:

a) Medicine production;
b) Distribution and use (e.g. indications, dose, availability);
c) Genetics, diet, traditions of the people;
d) Pharmaceutical quality and composition (excipients) of locally produced pharmaceutical products;
e) Use of herbal remedies which may pose special toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country or region may have greater relevance and educational value; and may encourage national regulatory decision-making. Information obtained in a certain country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may be different. When information from a region itself is not available, it may take longer before a problem becomes known to drug regulatory authorities, physicians, pharmacists, patients and pharmaceutical companies.

The WHO PIDM may provide information on possible safety issues which may not yet have emerged within the country's data. Pharmacovigilance is needed for the prevention of drug-induced human suffering and to avoid financial risks associated with unexpected adverse effects. Medicines available on the market therefore need continuous monitoring in every country.

Whereas the National Drug Policy acknowledges irrational medicine use as a problem, there is limited information on Adverse Drug Reactions (ADRs) in Zambia. Drug safety monitoring is therefore an important tool for detecting ADRs and medicine related problems. This will help ensure patients obtain safe and efficacious products.

1.5. Aims of Pharmacovigilance

The aims of pharmacovigilance are:

a) Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,
b) Improve public health and safety in relation to the use of medicines,
c) Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and
d) Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

1.6. Goals of Pharmacovigilance

The ultimate goals of pharmacovigilance are:

a) To promote the rational and safe use of medicines
b) To assess and communicate the risks and benefits of medicines on the market
c) To educate and inform the consumers on matters related to medicine safety

1.7. Goal of the Manual

This manual gives guidance on the detection, management and reporting of medicine related problems and is intended for all stakeholders involved in Pharmacovigilance. Its purpose is to help all involved to participate effectively in this very important process of continuous surveillance of the safety and efficacy of medicines and allied substances.

1.8. Scope of the Manual

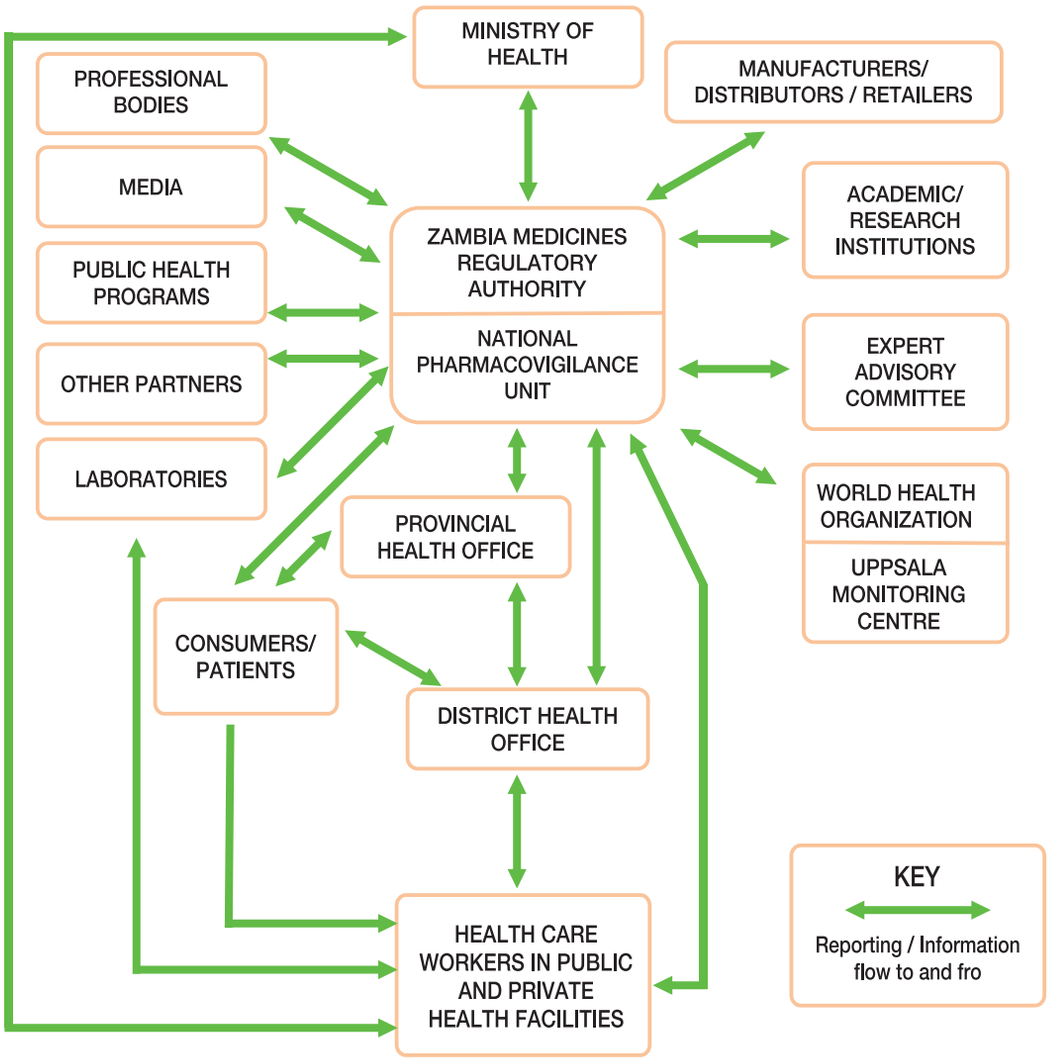
The scope of this manual extends to:

a) Promoting ADE monitoring and reporting.
b) Describing the Pharmacovigilance System in Zambia.
c) Outlining the various roles and responsibilities of stakeholders.
d) Describing various types of Adverse Drug Reactions (ADRs).
e) Describing the principles of diagnosing and managing ADRs.
f) Outlining various types of medicine related problems.
g) Providing guidance on the process of ADE monitoring and reporting.

2. Organization of the Pharmacovigilance System in Zambia

The Zambia Medicines Regulatory Authority (ZAMRA) is mandated by law to undertake pharmacovigilance activities in Zambia. The National Pharmacovigilance Unit (NPVU) under ZAMRAmanages the day-to-day activities of the pharmacovigilance programme. The Unit receives reports from healthcare workers, the pharmaceutical industry as well as members of the public. For the Unit to operate efficiently however, there is need for a well-established communication system among the stakeholders. The organization of the pharmacovigilance system in Zambia is illustrated in Figure 1 below.

Figure 1. Organizational and Operational Structure of the Zambia Pharmacovigilance System



2.1 Zambia Medicines Regulatory Authority (ZAMRA)

The primary role and mandate of ZAMRA is to ensure that marketed medicines consistently meet the required standard of quality, safety and efficacy throughout the distribution chain. The Authority has the responsibility to investigate safety concerns and acts to prevent and minimize medicine-related harm.

ZAMRA has established the National Pharmacovigilance Unit (NPVU) to undertake the pharmacovigilance functions.

The following are the functions of the NPVU:

a) Collection, collation, review and evaluation of all ADR, medication errors and product quality problem reports received.
b) Maintenance of databases for ADRs, medication errors and product quality problems
c) Provision of feedback to reporters.
d) Transmission of the assessed reports to the global database hosted at WHOUppsala Monitoring Centre.
e) Identification and investigation of signals.
f) Communication of relevant safety information to the national authorities, healthcare workers, pharmaceutical companies and other relevant stakeholders.
g) Advise healthcare providers and consumers on medicines safety issues.
h) Education and training of healthcare workers and the general public on medication safety.
I) Information sharing at regional and global levels. NPVU maintains contact with international regulatory bodies working in pharmacovigilance and exchange information on drug safety.
j) Assess the regulatory information relating to safety in order to determine what action, if necessary, needs to be taken to improve safe use of medical products. Based on the available data, the advisory committee shall make recommendations on appropriate regulatory actions.
k) Development/updating of Information Education Communication (IEC) materials, guidelines and training manuals.

The following are the steps NPVU takes in the management of ADR reports:

1) Report entry

Pharmacovigilance staff at the unit enter the incoming reports into the national pharmacovigilance database as per standard operating procedures. Each report is classified as an ADR, medication error or product quality problem. The recipient of the report will carefully review the report for the quality and completeness of the medical information.

The unit then provides feedback to the reporter and might request information in case of missing pertinent data. Causality assessment is performed and the report is classified as per WHO-UMC causality criteria.

The outcome of the report, together with any important or relevant information relating to the reaction will be communicated to the appropriate stakeholder.

Zambia Medicines Regulatory Authority conducts investigations on reported product quality problems. The Authority submits samples of the reported products to ZAMRA National Quality Control Laboratory (NQCL) for testing.

Medication errors are evaluated to determine whether preventative actions can be made. Depending on the nature of the safety concern, assessment will be performed in collaboration with the MAH or health facility. Product quality problems are communicated to the NQCL at ZAMRA for testing.

In case of a product quality problem, corrective actions are taken in collaboration with the MAH and ZAMRA.

2) Signal detection and assessment

The pharmacovigilance staff at ZAMRA review and assess each incoming report (ADR, medication error, product quality problem), and determine the course of action.

The Authority works towards detecting signals (new potentially causal drug and event associations, or new aspects of a known associations, including previously unknown ADRs and increases in frequency of known ADRs). A signal can initially be detected in a single incoming report. The Authority evaluates signals to determine the risk groups, risk factors and possible mechanisms underlying the ADRs.

The Authority regularly reviews WHO Pharmaceutical Newsletters and drug alerts to detect medicine-related problems relevant for the nation. Each year, a summary of the reports received during the previous year is produced and evaluated.

Each detected potential signal will undergo further evaluation. The national and WHO-ADR databases, published literature and information from the MAH are reviewed for similar cases. The Expert Advisory Committee is provided summary information for evaluation. The committee recommends what actions need to be taken.

2.2 The Expert Advisory Committee

The Expert Advisory Committee (EAC) is composed of health professionals and other experts appointed by the ZAMRA Board to advise or make recommendations on matters relating to drug evaluation, clinical trials, pharmacovigilance and other related issues. The Committee reviews risk assessment and risk management measures relating to medicines and allied substances. Following their assessment, the committee communicates their findings and recommendations to ZAMRA Board. They recommend containment measures, reporting mechanisms, remedial measures monitoring procedures and other appropriate conditions for medicines or allied substances.

2.3 Roles and Responsibilities of Stakeholders in the Pharmacovigilance System

For the pharmacovigilance system to operate efficiently, there is need for collaboration among various stakeholders. The roles and responsibilities of the key stakeholders are as follows:

2.3.1 Consumers

Consumers who suspect they have been affected by an ADR should report to any healthcare worker including the one that had prescribed, dispensed or administered the medicine that has caused the suspected ADR. This will then enable the healthcare worker to report the medicine-related problems to the ZAMRA. In addition, consumers can report directly to the ZAMRA.

2.3.2 Healthcare workers at the health facility

All healthcare workers in the nation have a very important role to highlight problems occurring when a marketed medicinal product is used. They need to report to ZAMRA about suspected adverse drug reactions, medication errors and product quality problems for the Authority to take action in preventing or minimizing the occurrence of the medicine-related injury for other patients in the future. These activities include:

a) Being vigilant and detect adverse drug events

Consumers and healthcare workers have the challenging task to monitor and be alert for possible medicine-related problems. It is important that clinicians are vigilant and perceptive towards any unexpected sign, symptom or complaint voiced by patients taking medicines, particularly in the early

phases of treatment.

Distinguishing between the natural progression of a disease and an adverse effect by a medicine can be difficult. When an unexpected event, for which there is no obvious cause, occurs in a patient taking a medicine, the possibility that it is caused by the medicine or its use must always be considered.

The possibility of an ADR should always be considered as the first differential diagnosis in patients taking medicines.

Healthcare workers should monitor for medication errors whilst prescribing, dispensing and administering medicines to patients.

Healthcareworkers should make physical inspections of the medicinal product to be dispensed or administered. Pharmacy personnel have an important role in the work of detecting product quality problems. Colour changes, separating components, powdering, crumbling, caking, moulding, change of odour, incomplete pack, suspected contamination, poor packaging/poor labelling should be acknowledged.

b) Assessing the patient

When a medicine-related problem is suspected, the clinician should carry out a thorough physical examination with appropriate laboratory tests and consider:

i) The patient's medical history, including history of a similar reaction or allergy
ii) The existence of any potential risk factors, such as hepatic or kidney insufficiency
iii) The existence of risk groups such as paediatric, elderly, pregnant and lactating patients

c) Managing the encountered adverse event

If an ADR is suspected, the clinician should treat the patient, and consider adjusting the dose, replace the medicine, or withdraw the medicine.

The patient should be informed about the suspicion of the ADR and what actions are planned. Careful documentation of the ADR in the patient's medical records should take place. Documenting and informing the patient is important to avoid future problems.

If a medicine has caused an allergy, the clinician should clearly document in the patient's medical file to prevent subsequent prescriptions of the same medicine. The healthcare worker should submit an ADR report to ZAMRA and notify the Medicine and Therapeutics Committee(MTC).

If the event is believed to be caused by a medication error, action should be taken according to the hospital or healthcare facility procedure in order to avoid similar problems in the future. If an ADR, medication error or product quality problem is suspected, it should be reported to ZAMRA immediately as described in the section below.

d) Reporting

Suspected ADRs, detected medication errors or product quality problems should be reported to the ZAMRA. See section 5.8.

All ADEs ranging from minor reactions to disability or death should be reported. However, there is a need to emphasize the reporting of suspected ADEs to new medicines, serious adverse drug reactions, unexpected reactions and drug interactions.

The reporter does not need to prove that there is a causal association between the medicine and the

event. Therefore, uncertainty of the cause and effect relationship should not be a reason for not reporting.

Reports relating to medication errors should specify information on the product, sequence of events up to the time of error, work circumstances during error and type of error.

Report as soon as possible

Any suspected ADR, medication error or product quality problem should be reported as soon as possible after all relevant information is compiled. Delay in reporting will reduce the beneficial effects of ADR reporting such as early signal detection and implementation of safety regulatory measures. Reporting while the patient is still in the health facilities will give chance to the reporter to clear any ambiguity by re-questioning or examining the patient. When reports are received, ZAMRA will acknowledge receipt and additional information may be requested.

Submission of additional information

If the reporter wishes to submit additional information for an event that has already been reported, the reporter should use a new ADR form. The reporter should clearly indicate that the report concerns follow-up information and should include the reference number so that the follow-up report can be matched with the original report. It is very important that follow-up reports are identified and linked to the original report to avoid duplications of reports in the pharmacovigilance database.

2.3.3 Medicines and Therapeutics Committee at the health facility

The MTC is a technical working group established at any health facility with representative members from each department with the aim of managing medication use problems. Using the information on medicine safety the MTC should revise the facility-specific medicine list and promote rational use of medicines. These activities include:

a) Processes to detect adverse drug reactions

The MTC should promote activities to monitor ADRs, medication errors and product quality problems and use the information to improve healthcare. Activities could involve review of ADRs, medication errors or near misses, patient chart review, or physical inspection of products. It needs the involvement of all health professionals as a team to identify problems with medicines and allied substances, setting standards and monitoring practice. The facility should also assign a focal person to coordinate all ADR monitoring activities in the facility and serve as a link between the facility activities and ZAMRA.

b) Assessing adverse drug reactions

The MTC should be involved in the processing and analysis of spontaneous reports arising from patients and healthcare workers. The evaluation to determine if an event is possibly related to a medicine can be performed by the MTC as follows:

i) Obtain a detailed history of the patient including current health status and medication, and past medical history. Use an ADR reporting form to organise reporting. (See Appendix 1.)
ii) Identify and document the ADR.
iii) Check the product information:

- Whether the reaction is known to occur with the medicine or not. If the reaction is not listed, it does not necessarily mean that the reaction cannot occur with that particular suspected medicine. Unlabelled and unexpected events are particularly important to acknowledge since these events could contribute to the detection of new ADRs that need to be further communicated.
- Whether the mechanism of action of the medicine can explain the reaction or not. Note

that a suspicion should not be discarded even if a mechanistic explanation cannot be found because complete knowledge on the pharmacokinetics and pharmacodynamics of a medicine does not always exist.

iv) Establish causality

- Use the WHO-UMC system (refer to Appendix 5)to assess the reaction and establish causality.
- Investigate the aesthetic quality of the product to rule out any adverse reaction occurring from a poor-quality product. This investigation should include the possibility of falsifying and overt contamination of the product.
- Consider the possibility of the underlying cause of the adverse event resulting from a drug interaction (including interactions with herbal and over-the-counter medicines) or a medication error. Note that these events should still be reported.
- Consider other more likely explanations for the event.

The MTC should also perform analysis of ADRs, medication errors and product quality problems to study the prevalence, severity and trends at their facility.

c) Action in health facility

The MTC should utilise the findings of their analyses to design interventions, methods, procedures that will prevent similar events from re-occurring at the facility. The following actions are required by the MTC after the evaluation of the event:

i) Educate the healthcare workers concerning ADRs using in-service training, mentorship and medicine information bulletins, etc.
ii) Change facility-specific medicine list if necessary, to use medicines of proven safety.
iii) Modify the way patient taking particular medicines are monitored.

The actions taken should be followed-up to determine if there is any improvement in reporting and management of ADRs at the facility. Medication errors observed at the healthcare facility should be reported to ZAMRA to determine the causes and recommend preventive measures.

These errors include:

i) Near misses such as administering the wrong medicine, strengths or dose;
ii) Confusion over look-alike and sound-alike medicines;
iii) Incorrect route of administration;
iv) Calculation or preparation errors;
v) Misuse of medical equipment; and
vi) Other errors in prescribing, transcribing, dispensing and monitoring of medicines.

All errors that necessitate regulatory action should be reported to ZAMRA. It is recommended that associated materials (e.g. product photographs, containers, labels, etc.) that would support the information are submitted together with the ADR report form.

If a detected medication error that has not caused patient harm can be traced to a specific underlying cause following MTC investigation, and that cause can be corrected at local level, e.g. stressing the importance of legible handwriting, or introducing routine procedures to prevent giving medicines to the wrong patient, it needs to be reported to ZAMRA and the summarised information needs to be used for educational purposes.

2.3.4 Laboratories

Laboratories are a source of information on drug resistance, for drug monitoring and other aspects of

a patient's health status. Such information will be forwarded to ZAMRA along with ADR reports.

2.3.5 District Health Office (DHO)

The District Health Office has roles and responsibilities, which may include:

a) Providing administrative, technical, capacity-building and logistical support to health centres and first level hospitals;
b) Coordinating the collection of reports and samples from health facilities within their jurisdiction;
c) Distributing blank ADR reporting forms, receiving and forwarding completed forms to ZAMRA;
d) Verifying or investigating ADR, medication error, and product quality problem reports whenever required;
e) Receiving feedback from ZAMRA.

2.3.6 Provincial Health Office (PHO)

The Provincial Health Office has roles and responsibilities which may include:

a) Providing administrative, technical, capacity-building and logistical support to DHOs and second level hospitals;
b) Distributing blank ADR reporting forms; and
c) Verifying or investigating ADR, medication error and product quality problem reports whenever required;
d) Providing feedback to and from ZAMRA.

2.3.7 Marketing Authorization Holders

Marketing authorization holders (MAH) such as pharmaceutical industry, importers, wholesalers and distributors have the prime responsibility to monitor safety of their marketed products from the start of drug development to post-marketing phase of the medicine.

The MAH is required to have an internal pharmacovigilance system in place, and be responsible for safety monitoring of its registered medicinal products in Zambia. The MAH should ensure that information on ADRs are collected, collated and communicated to ZAMRA.

2.3.8 Public Health Programmes

Public Health Programmes (PHP) serve to promote health, prevent spread of disease, premature death, and disease-related discomfort and disability in the population. Through the PHPs, large populations receive medicines for diseases such as HIV, tuberculosis, and malaria, as well as vaccines, and sexual and reproductive health products. This necessitates intensive monitoring of ADRs. These programmes should be actively involved in the following:

a) Monitoring medicines

ZAMRA and the PHP will jointly decide priorities regarding monitoring of medicines to be used in the PHP, how the medicines should be monitored, when adverse reactions should be reviewed, the time frames for reporting and actions to be taken if a safety concern emerges.

b) Reporting adverse drug events

Suspected ADRs, product quality problems and medication errors should be reported to ZAMRA. Treatment guidelines used by the PHP should include instructions on reporting ADRs. If the PHP independently detects safety issues, these should be communicated to ZAMRA.

2.3.9 Academic and Research institutions

The educational system plays an important role in pharmacovigilance by providing training on safe

and rational use of medicines, the nature of ADRs, the specifics of medication errors, and the importance of being vigilant to product quality problems.

Pharmacovigilance should be included in the training curriculum for all health professions' programmes. ZAMRA has developed a training manual which can be used as a teaching aid for pharmacovigilance training. Research and postgraduate studies in the field of pharmacovigilance should also be considered. The research institutions can participate in pharmacovigilance through conducting research in medicine-related issues and sharing their findings with ZAMRA.

2.3.10 Professional Bodies

Professional bodies play a valuable role towards the maintenance of drug safety by building the capacity of their respective members through various types of trainings on pharmacovigilance as part of continuous professional development. These trainings should be designed to make members aware of the importance of pharmacovigilance and the activities in the national pharmacovigilance system. This will enable them to participate actively in pharmacovigilance activities.

2.3.11 World Health Organization (WHO)-Uppsala Monitoring Centre (UMC)

The World Health Organisation has a programme for pharmacovigilance called Programme for International Drug Monitoring (PIDM). The PIDM is a group of more than 130 countries 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. Zambia is a member of PIDM.

The Uppsala Monitoring Centre (UMC) is one of five officially designated collaborating centres within the WHO-PIDM. UMC has been responsible for the technical and operational aspects of the programme since 1978. It is responsible for managing the technical and scientific aspects of the WHO's worldwide pharmacovigilance network. These activities are carried out following WHO policy and in close liaison with headquarters in Geneva. The activities include:

a) Collecting, assessing and communicating information from member countries about the benefits, harms, effectiveness and risks of medicines.
b) Analysing VigiBase® data and identifying signals of potential safety problems.
c) Collaborating with member countries in the development and practice of pharmacovigilance through consultation and training.
d) Pursuing research in all aspects of the science and practice of pharmacovigilance.
e) Broadening the scope of pharmacovigilance through debate, research and consultation.
f) Being a partner in the extended global patient safety network.
g) Developing and providing tailored data-entry, management, retrieval and analysis tools such as VigiFlow® and VigiLyze®.
h) Providing and maintaining the WHO Drug Dictionary portfolio and the WHO Adverse Reactions Terminology (WHO-ART) used for coding and analysis of VigiBase® and medicinal product data throughout the world.

2.3.12 Partners

Cooperating partners in pharmacovigilance, such as Non-Governmental Organisations (NGOs), and advocacy groups play a vital role. These partners can directly or indirectly facilitate the development of new and robust drug policies and systems.

a) Non-governmental organizations

Non-governmental organizations provide support to the national pharmacovigilance system through:

i) Capacity-building
ii) Health Systems Strengthening
iii) Mentorship
iv) Providing resources

b) Media and Advocacy groups

In many instances, these organisations or individuals have the capacity to voice, and often change public opinion. Their roles include:

i) Public sensitization on drug safety.
ii) Facilitating active public debate and discussion of issues, which have direct relevance to health.
iii) Highlighting deficiencies and weaknesses in existing drug safety policies.
iv) Engaging proactively with policy makers on important matters of public interest to facilitate the creation of policies and legislation on pharmacovigilance.

3. Diagnosis and Management of Adverse Drug Reactions

3.1 Types of Adverse Drug Reactions

The table below summarises the various types of ADRs.

Table 1: Classification of ADRs

Type of ADR	Description	Example
Type A (Augmented) reactions	- These reactions reflect the pharmacological action of the drug in an exaggerated way. - They are predictable, common (80%), dose-dependent and experimentally reproducible. - The reaction is treated by reducing the dose or withholding the medicine and considering alternative therapy.	Examples of such reactions include: - Bronchospasm from Propranolol (a beta-blocker) administration; Bleeding due to Warfarin, Heparin or NSAIDs, etc.
Type B (Bizarre) reactions	- They are rare (0.1-1%), unexpected, characteristically serious, have a low background frequency and no dose relationship. - Their mechanism is often uncertain.	Examples include: immune-allergic and autoimmune reactions e.g. to Sulphonamides, Penicillin, Aplastic anaemia caused by Chloramphenicol, etc.
Type C (Chronic) reactions	- These reactions occur often during chronic therapy and show a picture less typical for a drug reaction but mimic natural disease.	Examples include: Osteoporosis with Oral Steroids, Adrenal suppression by corticosteroids (i.e. patient develops buffalo hump, renal failure, etc.) Gynecomastia with Efavirenz
Type D (Delayed) reactions	- ADRs that present long after a treatment was completed or even skip a generation.	Examples include: Teratogenesis, Carcinogenesis e.g. the occurrence of vaginal carcinoma in young women whose mothers were treated with Diethylstilboestrol during pregnancy 20 years ago.
Type E (End of treatment) reactions	- Withdrawal reactions can occur after stopping treatment and have to be considered ADRs as well.	Examples include: Myocardial Ischemia after beta-blocker withdrawal, Benzodiazepine withdrawal effects
Type F (Unexpected failure of efficacy) reactions	- These reactions occur when there is a failure of efficacy of a drug. - Such reactions are common, may be dose-related and are often caused by drug interactions.	Examples include: Interactions with enzyme inducers, altered absorption, Resistance to antimicrobials, Inadequate dosage of oral contraceptives, particularly when used with specific enzyme inducers, Warfarin-induced bleeding when co-administered with Aspirin.
Type G (Genotoxicity)	- Many drugs can produce genetic damage in humans. Notably some are potential carcinogenic and genotoxic.	Alkylating agents e.g. Cyclophosphamide – an anticancer drug
Type H (Hypersensitivity) reaction	- These reactions are side effects caused by allergy or hypersensitivity, they are probably the most common adverse reaction after type A. - Immunologically mediated reactions. - They are not pharmacologically predictable and dose dependent. - Accordingly, dose reduction does not lead to amelioration of symptoms, so the drug must be stopped. - Some ADRs have a mechanism that is not	Hypersensitivity reactions to Sulphonamides, Penicillin, etc.
Type U (Unclassified) reaction	- Some ADRs have a mechanism that is not understood, and these must remain unclassified until more is known about them.	

3.2 Categories of Frequency of ADRs

The table below shows how frequency of ADRs is categorised:

Table 2: Frequency categories of ADRs

Category	Frequency	
Very common	≥1/10	≥10%
Common (frequent)	≥1/100 and < 1/10	≥1% and < 10%
Uncommon (infrequent)	≥1/1,000 and < 1/100	≥0.1% and < 1%
Rare	≥1/10,000 and < 1/1,000	≥0.01% and < 0.1%
Very rare	<1/10,000	<0.01%

Source: Council for International Organisation of Medical Sciences (CIOMS)

Why ADRs occur

The effects of any medical intervention cannot be predicted with absolute certainty. Any medicine or medical intervention has the potential to have a negative or undesirable effect on an individual. Information about rare events may not be available until they happen.

Traditional or herbal remedies, just like conventional medicines, may cause ADRs. It is not always easy to identify the responsible plant, plant constituent or animal material.
Some causes of ADRs are preventable while others are inevitable and unavoidable.

Preventable causes of ADRs include:

a) Diagnosis error
b) Prescription of the wrong medicine for the disease
c) Prescription of a wrong dose of the right medicine
d) Choice of the right medicine for the disease but maybe the wrong medicine for the patient because of genetic or ethnic predisposition, age, co-morbid conditions, concurrent medication, allergy or intolerance
e) Choice of appropriate medicine but without considering the potentially harmful interactive effects with other medicines or substances being taken by the patient
f) The full specification, indications, contraindications and risks of the medicine may not have been read or fully understood by the prescriber or dispenser
g) The patient may not comply with the doctor's advice or with the manufacturer's advice in the patient information leaflet
h) Self-medication
i) Polypharmacy (may lead to increased drug interactions)

Major factors predisposing to adverse reactions

It is well known that different patients can respond differently to a given treatment regimen. In addition to the pharmaceutical properties of the drug therefore, there are characteristics of the patient which predispose to ADRs.

The following can be predisposing factors of ADRs: -

i) Extremes of Age

The very old and the very young are more susceptible to ADRs. Medicines which commonly cause problems in the elderly include: hypnotics, diuretics, non-steroidal anti-inflammatory, antihypertensive, and psychotropic drugs and digoxin.

Young children and particularly neonates, differ from adults in the way they respond to medicines. Some medicines which are likely to cause problems in neonates include: morphine, valproic acid, chloramphenicol (grey baby syndrome), antiarrhythmics (worsening of arrhythmias), sulphonamides (Kernicterus) and aspirin (Reye syndrome).

ii) Sex

Several studies have shown that for some medicines, safety profiles may differ in males and females. For instance, females (women) are more likely to suffer from ADRs than men and vice versa due to pharmacokinetic and or pharmacodynamic sex-related factors. For example, Spironolactone can cause gynaecomastia in men and Methyldopa lowers men's libido.

iii) Co-morbidities

If the patient also suffers from another disease, such as kidney, liver or heart disease besides the condition being treated, special precautions are necessary to prevent ADRs. There is reduced elimination of medicines in conditions of renal insufficiency, hepatic disease and heart failure, resulting in increased medicine toxicity.

iv) Drug Interactions

When two medicines are administered to a patient, they may either act independently of each other, or interact with each other. Interaction may increase or decrease the effects of the medicines concerned and may cause unexpected toxicity.
Interactions may occur between drugs which compete for the same receptor or act on the same physiological system.

They may also occur indirectly when a drug-induced disease or a change in fluid or electrolyte balance alters the response to another medicine.
Interactions may occur when one medicine alters the absorption, distribution or elimination of another medicine, such that the amount which reaches the site of action is increased or decreased e.g. rifampicin increases the elimination of protease inhibitors thereby reducing their efficacy, antacids reduce the absorption of a number of medicines such as Ciprofloxacin, Amoxicillin, etc.

As newer and more potent medicines become available, the number of serious drug interactions is likely to increase.

In addition, interactions which modify the effects of a medicine may involve non-prescription medicines, non-medicinal chemical agents, and social drugs such as alcohol and herbal/traditional remedies, as well as certain types of food e.g. grapefruit juice.

v) Race and Genetic Factors

The genetic make-up of the individual patients may predispose to ADRs. Genetic polymorphism results in inter-individual variations in metabolic enzymes. E.g. some individuals are slow acetylators of drugs such as isoniazid and hence predisposed to ADRs, 3435C-T polymorphism at the multidrug resistance gene 1 is associated with increased risk of hyperbilirubinaemia with atazanavir, HLA-B5701 genotype is associated with abacavir hypersensitivity.

Variation in genes involved in the absorption, distribution, metabolism and excretion of a drug will lead to changes in its pharmacokinetics and thereby in overall drug exposure, which in some cases may be profound enough to lead to ADRs.

Variation in genes that encode drug targets such as receptors, ion channels, and enzymes could lead to changes in the pharmacological effects of the drug and its interaction with the target, altering

benefits and harms.

vi) Prolonged Treatment and Amount of Administered Medicines

An excessive exposure to medicines or prolonged therapy may be a predisposing factor for ADRs.

Response to amount of medicines varies from one individual to another. Example: prolonged use of drugs like stavudine in HIV/AIDS patients causes lipodystrophy (body fat maldistribution), Statins (e.g. Simvastatin) can cause muscle damage, efavirenz can cause gynaecomastia, corticosteroids can cause growth retardation in children, etc.

vii) Previous History of Allergy

Patients who have previously suffered an allergic drug reaction appear to be more susceptible than others to allergic ADRs in general, e.g. penicillin and sulphonamide allergies.

Heredity may make some people more susceptible to the toxic effects of certain drugs.

viii) Multiple Drug Therapy (Polypharmacy)

The incidence of ADRs increases with the number of drugs given due to risk of drug interactions.

ix) Incompatibilities between medicines, IV fluids and packaging material

Medicines may be incompatible when mixed with each other and IV fluids or when they come in contact with certain packaging material. This may result in loss of potency and formation of toxic chemicals. Certain medicines, when added to IV fluids, may be inactivated by pH changes, by precipitation or by chemical reaction. For example, benzyl penicillin and ampicillin lose potency after 6 – 8 hours if added to dextrose solutions, due to the acidity of these solutions.

Some medicines bind to plastic containers and tubing, for example diazepam and insulin. Aminoglycosides are incompatible with penicillins and heparin. Hydrocortisone is incompatible with heparin, tetracycline and chloramphenicol. Medicines should not be added to blood, amino acid solutions or fat emulsions because they may interact with these products.

3.3 Diagnosis of Adverse Drug Reactions

Diagnosis of ADRs may be undertaken using the following steps:

Step 1

Verify that the suspected medicine was the one consumed. Consider all medicines possibly taken by the patient including general sale (GS) medicines, contraceptives, herbal/traditional medicines, drugs of abused, alcohol and drugs being taken on a long-term basis.

Step 2

Verify that the onset of the suspected ADR was after the medicine was taken, not before. Discuss carefully observations made by the patient. Determine the time interval between beginning of treatment and onset of reaction.

- Was the event present before the patient began the medicine?
- Did the event occur within a plausible time period of starting the medicine?

Step 3

Consider whether the event is pharmacologically plausible?

- Is it a side effect of the medicine(s) in question or the class to which the medicine belongs?
- Is it a known allergic reaction the medicine(s) in question or the class to which the medicine

belongs?

Step 4

Evaluate suspected ADR after discontinuing medicines or reducing dose and monitor patient's status.

- Dechallenge and then assess whether the time to recovery is consistent with the action taken.
- Rechallenge and observe whether the reaction recurs or not.

Dechallenge: Withdrawal of a medicine from the patient's therapeutic regimen

Positive dechallenge: Improvement of an adverse reaction when medicine is withdrawn. Resolution of suspected ADR when the medicine is withdrawn is a strong, although not conclusive indication of drug-induced reaction.

Negative dechallenge: Non-resolution of an adverse reaction after withdrawal of the medicine.

Rechallenge: Re-introduction of a medicine suspected of having caused an adverse reaction following a positive dechallenge.

Negative rechallenge: Failure of a medicine to produce similar signs or symptoms to those observed when the medicine was previously administered.

Positive rechallenge: Re-occurrence of similar signs and symptoms upon re-introduction of the medicine.

Rechallenge is only justifiable when the benefit of re-introducing the medicine to the patient outweighs the risk of recurrence of the reaction, however, this is rare. In some cases, the reaction may be more severe on repeated exposure. Rechallenge therefore requires serious ethical considerations.

Step 5

Consider the possibility of a drug interaction with GS medicines, contraceptives, herbal/traditional medicines, drugs of abuse, alcohol, long term medicines

No problems observed with the first drug but problems occur when a second drug is commenced

- Is it the second drug causing the ADR or is it an interaction?
- Has the patient taken the second drug before?
- Is the reaction resolving after the first drug is withdrawn?

Pharmacokinetics of the two drugs should also be considered

Step 6

Consider alternative factors (other than the medicine) that could on their own have caused the reaction.

Step 7

Use relevant up-to-date literature and personal experience on medicines and their ADRs. Verify if there are previous conclusive reports on this reaction. The National Pharmacovigilance Unit is one resource for obtaining information on ADRs. The manufacturer of the medicine can also be a source of information (caution: information from manufacturers may be biased).

3.4 Management of Adverse Drug Reactions

Decisions on management of ADRs are made by considering the following:

a) Seriousness/Severity of ADR

If the reaction is serious, consider withdrawing all suspected medicines and treat urgently.
If the reaction is mild:

i) Continue treatment if necessary;
ii) Stop unnecessary medicines;
iii) Consider dose reduction;
iv) Reassure the patient and continue monitoring;
v) Treat symptoms if warranted.

b) Seriousness of disease

If the disease is serious consider:

i) The effect of not having treatment;
ii) Continuing treatment and treat symptoms of reaction if necessary;
iii) Alternative medicines;
iv) Stopping unnecessary medicines.

Take note that the term **'severe'** is not synonymous with serious. **'Severe'** is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). **Seriousness** (not severity), which is based on patient/event outcome or action criteria, serves as guide for defining regulatory reporting obligations.

c) Benefit/Risk Assessment

Whenever a medicine is given to a patient, the prescriber should have a clear idea of what is to be achieved, the likelihood of success and the chance of doing harm and try to balance these factors.

Although general knowledge about a medicine may not be sufficient to cover a patient's situation, the benefits and risks of the medicines would be determined from available literature including the enclosure with the medicine produced by the manufacturer.

For each medicine prescribed the prescriber should ask the following questions:

For benefit:

i) What is the seriousness of the disease and how much will the drug do in reducing the seriousness?
ii) How long will the disease last and how much reduction in the duration of the disease can be expected from the medicine?
iii) In the case of prophylaxis, how prevalent is the disease and what reduction in prevalence can be expected?

For risk:

I) How serious are the adverse reaction(s)?
ii) How long is the reaction expected to last i.e. days, weeks or months?
iii) What is the frequency of the reaction(e.g. refer to Table1 for categories of ADRs)?

3.5 Prevention of Adverse Drug Reactions

The following measures would help to reduce the incidence of ADRs:

Good prescribing practice

a) Refer to textbooks and other reference materials providing information on ADRs and drug interactions.

b) Prescribe medicines that you know very well so that you know which risks to anticipate. Then use the drugs in a way that minimizes the risks.

c) Avoid changing therapy from known medicines to unfamiliar ones without good reasons.

d) Always consider the risks and benefits of any medicine that you plan to use. Make comparisons among medicines for the same indication before deciding what is most appropriate to use for a patient.

e) Consider the predisposing factors to ADRs and individualise drug therapy according to patients' needs. Be particularly careful when prescribing for children, the elderly, the pregnant and lactating, the seriously ill and patients with hepatic and renal diseases. Careful ongoing monitoring is essential in these patients. Where available, pharmacogenetic testing should be done.

f) Consider possible interactions of medicines with certain foods, alcohol and non-therapeutic chemicals.

g) Avoid polypharmacy. Use few medicines whenever possible. The incidence of adverse reactions increases with the number of medicines concomitantly used.

h) Avoid prescribing medicines that are prohibited or have been officially withdrawn from the market.

i) Always inquire about known medicine allergies before prescribing medicines and avoid classes of medicines that the patient has previously reacted to.

Good dispensing practice

a) Sensitize the patient on known or established risks of medicines.

b) Encourage patients to disclose any known allergies to medicines.

c) Dispense medicines of the best possible quality.

Education and training of healthcare workers

a All healthcare workers should have adequate basic education in pharmacotherapy.

b) All healthcare workers should have some training in the recognition and reporting of ADRs.

Monitoring and reporting of ADRs

a) Closely monitor patients on medicines that are known to exhibit a large variety of interactions and adverse effects (e.g. anti-coagulant, anti-epileptic, anti-arrhythmic and anti-hyperglycaemic medicines).

b) Suspect ADRs in patients who show signs and symptoms not clearly explained by the course of their disease.

c) Review all medicines that the patient takes on a regular basis, taking special note of those bought without a prescription (e.g. GS medicines and herbal preparations).

d) If you suspect an ADR, consider stopping the medicine or reduce dosage as soon as possible and report the ADR to ZAMRA.

4. Medicine Related Problems

4.1 Medication Errors

Medication errors and medicines-related adverse events have important implications from increased length of hospitalization and costs to undue discomfort and disability or increased mortality. Minimizing medication errors, through early detection and clinical audit, is of paramount importance as it contributes to the general well-being of patients and promotes patient confidence in the healthcare system.

4.1.1 Common Medication Errors

Table 3.Examplesof Medication Errors

Category of source of medication error	Sources of medication error	Common medication error
Prescriber error	Illegible writing	Wrong drug regimen dispensed (dose, dosage form, formulation, duration)
	Wrong diagnosis	Inappropriate drug selection
	Incomplete patient information	Failure to alter therapy when required Insufficient Monitoring of Patient
	Irrational prescribing	Unnecessary medication
	Miscommunication of medication order	Wrong drug regimen dispensed
	Environmental conditions that distract health care workers e.g. overcrowding, noise, poor lighting	Wrong drug prescribed
Dispensing error	Misinterpretation of prescription, illegible writing and use of abbreviations	Wrong drug dispensed(route, dose, formulation, duration)
	Confusion between medicines with similar names or appearance	Wrong drugs dispensed
	Environmental conditions that distract health care workers	Incomplete/wrong instruction Wrong dosage calculation
Manufacturer error	Poor labelling and packaging	Wrong drug dispensed
	Inadequate drug information (warnings)	Consumer given contraindicated medication
Patient error	Inadequate counselling	Wrong frequency of administration Wrong administration technique Inappropriate storage conditions
	Transferring of medicines from original containers	Wrong frequency of administration
	Inappropriate self-medication	Wrong medication taken for ailment

4.1.2 Medication Error Monitoring and Reporting

a) Evaluate the medication use process in collaboration with other healthcare workers. This can be done through the MTC.
b) Establish a process for identifying and tracking medication errors.
c) Define categories of medication errors, e.g., prescribing, dispensing, administration, monitoring and compliance errors.
d) Increase awareness of medication errors through education and the importance of reporting ALL medication errors, regardless of their significance.
e) Establish systems for detecting medication errors at the facility, e.g. random sampling of prescriptions, medication storage survey, etc.
f) Involve healthcare workers, patients, and care givers in the medication error detection and reporting process.
g) Encourage reporting that focuses on the medication error (not the personnel who committed the error) and ultimately improve the processes and systems.
h) Respect the confidentiality of the patient, facility and personnel involved with the medication error.

4.1.3 Role of the Medicines Therapeutic Committee in Assessment of Medication Errors

a) Examine and evaluate causes of medication errors.
b) Analyse aggregate data to determine trends, significance, frequency, and outcomes of medication errors.

4.1.4 Prevention Strategies

a) Interventions
   i) Examine processes and develop interventions for reducing medication errors. Some examples of interventions are production changes, instituting bar coding, using different distribution systems, training personnel, standard prescription format, developing protocols for recording and transmission of prescription orders, and developing policies and procedures for proper storage and administration of medication.
   ii) Establish goals and measurable standards for the interventions.
   iii) Monitor interventions and make necessary changes.

b) Reporting

   i) Communicate the results of the medication error program to healthcare workers, patients, and care givers as appropriate.
   ii) Promote reporting of medication errors to ZAMRA for review and analysis.

c) Strategies to Prevent Medication Errors
   i) The healthcare worker managing the patient should obtain adequate and accurate patient information.
   ii) The facility should provide healthcare worker with up-to-date drug references and treatment guidelines.
   iii) Establish effective communication among healthcare workers.
      - Share information about patient's treatment plans
      - Improve handwriting
      - Avoid potentially confusing abbreviations and symbols
      - Be aware of similar drug names
      - Consider using electronic prescribing systems
   iv) Improve labelling and storage

- Do not store drugs with look-alike names or similar packaging in close proximity to each other in medicine storage area
- Keep the storage area well organized
- Control access to medicines

v) Use proper devices and provide training to health personnel on the use of the devices e.g. use of the appropriate syringes.

vi) Educate patients on the proper way to take medication.

4.2 Product Quality Problems

With new safety concerns, such as illegal sale of medicines, potentially unsafe medicinal products, poor drug donation practices, widespread manufacture and sale of falsified and substandard medicines, the vigilance for product quality problems is important. Suspected contamination, questionable stability, defective components, poor packaging or labelling and unexpected therapeutic ineffectiveness could be indicative of product quality problems. Medicines that have lost their potency after being stored at high temperatures would also fall under this category.

4. 3 Drug Interactions

A drug interaction occurs when the response of a patient to a medicine is changed by the presence of another medicine, food, drink or by some environmental chemical agent.

Medicines associated with greatest risk include:

a) Medicines that induce hepatic cytochrome P450 enzymes (e.g. phenytoin, rifampicin, carbamazepine, phenobarbitone) or inhibit the enzymes (e.g. ciprofloxacin, erythromycin, ketoconazole).

b) Medicines with narrow therapeutic index e.g. aminophylline, quinine, phenytoin, warfarin, digoxin and immuno-suppressants.

Drug-Food Interactions

Some foods interact with drugs due to chemicals they contain e.g. foods containing tyramine such as cheese will cause reactions in patients given monoamine oxidase inhibitors, dairy products reduce the absorption of tetracycline and ciprofloxacin, grapefruit juice induces cytochrome P450 enzymes (increases the metabolism of a number of medicines such as statins and calcium channel blockers).

Patients at risk of significant drug interactions include:

a) Patients at extremes of age
b) Seriously ill patients
c) Patients with hepatic or renal disease
d) Patients on long-term therapy for chronic disease (HIV infection, epilepsy, diabetes mellitus)
e) Patients with more than one prescriber
f) Patients on concurrent drug therapy

To minimize the risk of harmful drug interactions, healthcare workers:

a) Must have adequate knowledge of the pharmacological mechanisms involved in drug interactions.
b) Should be aware of the medicines associated with greatest risk and the most susceptible patient groups.
c) Must be alert to the possible involvement of non-prescribed medicines and other substances in drug interactions.

4.4 Treatment Failure

There are several reasons why a patient may not respond well to medication given:

a) Incorrect diagnosis, hence incorrect drug

b) Incorrect dose, strength, formulation
c) Drug interactions that result in reduced efficacy
d) Poor compliance
e) Pharmaceutical manufacturing defects
f) Substandard and falsified medicines
g) Drug resistance
h) Tolerance
I) Metabolic insensitivity of the patient (e.g. in hereditary coumarin resistance, a rare autosomal dominant condition).

4.5 Drug Misuse, Abuse and Dependence

Healthcare workers should be aware that drug misuse, abuse and dependence, may result in ADRs. Almost all psychotropic drugs have a misuse or abuse potential. Commonly abused substances include cannabinoids, benzodiazepines, opioids, cocaine, amphetamines, barbiturates, hallucinogens, alcohol and nicotine. Other drugs that have a propensity for misuse include antihistamines, cough mixtures, nasal decongestants, laxatives and non-opioid analgesics.

ADRs that are suspected to result from drug misuse or abuse should be reported to ZAMRA in the same way as all other ADR cases.

Reporting of Drug Dependence

The cardinal features that indicate dependence and should be reported are:

a) Unexpected neuropsychiatric symptoms which are regarded as pleasurable by the patient, and particularly if their use is associated with objective changes in mood or behaviour
b) The development of tolerance indicated either by reducing drug efficacy or tendency to increase dose
c) Withdrawal symptoms

Strong suspicions of dependence should always be reported to ZAMRA.

4.6 Overdose

Overdose constitutes excessive pharmacological effects. This may result in harm to the consumer. Overdose may be:

a) Relative or absolute
b) Recreational
c) Iatrogenic
d) Intentional or accidental
e) Acute or chronic

All cases of overdose should be reported as medication errors using the ADR reporting form.

5. Reporting Adverse Drug Reactions

5.1 Importance of reporting ADRs

The purpose of ADR reporting is to detect new information about the drugs that could not be identified during clinical trials.

Information from pre-marketing phase of drug development is incomplete due to:

a) Pre-clinical trials (animal tests) are insufficient to predict human safety
b) Clinical trials have limitations: patients used in clinical trials are limited in number, clinical trial conditions differ from clinical practice and duration of trials is limited.

Limitations of Clinical Trials

a) Limited number of patients

By the time a drug receives market authorization, not more than 5000 individuals would have been exposed to it. At least 30,000 exposures are needed so as not to miss at least one patient with an ADR of incidence of 1 in 10,000. Therefore, only more common ADRs are detected during clinical trials. Furthermore, the events detected in clinical trials will be incompletely identified and understood since they are few.

b) Limited population

Clinical trials usually include a small number of healthy, male volunteers and highly selected patients. In general, they tell us how well a drug works for a defined disease and what potential harm it may cause. However, clinical trials provide only limited information for larger populations with different characteristics from the trial group (e.g. age, gender, state of health, ethnic origin, etc.).

Susceptible patients are usually not included in clinical trials and the effects of inter-current disease or medication are little assessed.

Information on rare but serious ADRs, chronic toxicity, use in special groups (such as children, elderly, pregnant women) is therefore not available or incomplete from pre-marketing trials.

c) Limited duration

With most drugs, some hazards may only be known when the drug has been administered to large numbers of patients over considerable periods of time.
For instance, effects of aspirin (gastric ulceration and bleeding), prolonged use of phenacetin (renal papillary necrosis) and thalidomide (phocomelia) were only realized after long periods of time.

Reporting ADRs is one of the key activities in Post-marketing surveillance which serves the following purposes:

i) Detection of unexpected ADRs and drug interactions
ii) Identification of risk factors for ADRs
iii) Quantitative measurement of risk of ADRs
iv) Determination of long-term safety/toxicity

Benefits of reporting ADRs

a) Helps to identify rare ADRs
b) Prevents medicine-associated tragedies
c) Exposure of substandard and falsified medicines when healthcare personnel are alert to unexpected and apparently inexplicable adverse reactions, or to lack of effect.

d) Leads to improvement of information in labelling
e) Contributes to the development of a database on ADRs that would serve as a useful and relevant educational source

5.2 Pharmacovigilance Reporting Methods

5.2.1 Passive Surveillance Methods:

a) **Spontaneous Reporting System**
This is a system whereby case reports of adverse drug events are voluntarily submitted from healthcare workers and pharmaceutical manufacturers to the national regulatory authority.

A spontaneous report is an unsolicited communication by healthcare workers or consumers to a national pharmacovigilance centre, pharmaceutical company, regulatory authority or other organisation (e.g., WHO, Regional Centres, Poison Control Centre) that describes one or more suspected adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme.

Spontaneous reporting is the most common way of performing pharmacovigilance today. The aim is to monitor the safety of all medicines on the market. The pharmacovigilance system in Zambia utilizes spontaneous reporting as the main method for collecting information on ADRs.

Spontaneous reports play a major role in the identification of signals of medicine related problems once a drug is marketed. They can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions.

Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since product was granted marketing authorisation, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.

Spontaneous reporting requires two initial steps:

i) A reporter suspects that an undesirable medical event may have been caused by exposure to a medicine
ii) The reporter reports the suspicion to the national pharmacovigilance centre

What to report?

iii) Serious ADRs
iv) Severe ADRs
v) Suspected ADRs to new drugs
vi) Unknown ADRs (unlabelled reactions)
vii) ADRs in vulnerable groups (children, pregnant women, elderly)

Advantages of Spontaneous Reporting

I) Covers the whole population
ii) Includes all medicines
iii) Continual monitoring throughout life-cycle of a medicine
iv) Detects signals of new, rare or serious ADRs

v) Most commonly used method
vi) Easiest method to establish
vii) Least labour intensive
viii) Relatively inexpensive

Disadvantages of Spontaneous Reporting

i) Inherent under-reporting
ii) Captures only suspected ADRs
iii) Reporting bias: seriousness, severity, new medicines, advertising of products and publicity of specific ADRs
iv) Denominator unknown
v) Difficult to detect some ADRs: delayed ADRs, ADRs with high background incidence

b) Intensified Spontaneous Reporting (ISR)

Intensified Spontaneous Reporting (ISR) is an extension of the spontaneous reporting program. ISR is a spontaneous reporting system in which health care professionals and medicine consumers are stimulated or encouraged to report adverse events associated with specific medicines that are deemed by the medicine regulatory authority to require intensive monitoring.

The aim is to enhance ADR reporting of specific medicines in the early marketing phase. Example of ISR: Black Triangle Scheme in UK

Certain medicines are targeted for intensive monitoring. Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and summary of product characteristics together with a short sentence explaining what the triangle means.

The intent of the Black Triangle Scheme is to provide a simple means for health care practitioners and patients to identify medicines that require intensive monitoring. The scheme encourages the reporting of adverse events associated with the use of these medicines.

For medicines showing the black triangle symbol, the Medicines and Healthcare products Regulatory Agency (UK medicines regulatory authority) asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme (UK spontaneous reporting system).

Medicines under additional monitoring include:

i) Medicines containing a new active substance
ii) Biological medicines
iii) Medicines given conditional approval or approved under exceptional circumstances
iv) Medicines that require additional studies (e.g. more data on long term use or on rare side effect seen in clinical trials)

The medicines are monitored intensively for a specified period of time or up to when the conditions for approval have been met (e.g. five years for medicines containing a new active substance). The list of medicines under additional monitoring is reviewed monthly. The European Union and Australia have similar schemes.

c) Targeted Spontaneous Reporting (TSR)

Targeted Spontaneous Reporting (TSR) is intensified spontaneous ADR reporting within a defined cohort and is intended to complement ordinary spontaneous reporting. TSR was developed by WHO in 2010 and was piloted in Kenya, Vietnam and Uganda. TSR focuses on the collection of information on specific ADRs with specific medicines, in defined patient groups.

Healthcare workers in charge of the patients in the cohort are sensitized and facilitated to investigate and report adverse effects they encounter in the patients.

Patients in the cohort are systematically followed up to record the ADRs they experience. TSR uses the same forms used in spontaneous reporting but specific guidance is given to the healthcare workers on completion of the forms. TSR may be adapted either to report all suspected ADRs in the defined population or to focus only on specific ADRs of particular concern.

Example of TSR

TSR of suspected renal toxicity in patients undergoing HAART in two public health facilities (Masaka and Mbale) in Uganda:

From April 2012 to March 2014, cases of suspected renal toxicity in 10,225 patients on tenofovir were targeted for monitoring. Healthcare workers managing the patients were trained on renal toxicity monitoring and ADR reporting. To facilitate renal toxicity monitoring and ADR reporting, they were provided with job aids and regular technical supportive supervision.

Specific population: patients with HIV infection

Specific clinics: Masaka and Mbale

Specific medicine: Tenofovir

Specific ADRs: Renal toxicity

Advantages

i) Can utilise existing ADR reporting infrastructure
ii) Targets specific medicines of interest
iii) Possible to implement monitoring programme that targets specific issue of concern (ADR, medicine, patient group)
iv) Captures useful information (less 'background noise')
v) Denominator known

Disadvantages

i) Under- reporting remains a problem
ii) Captures only suspected ADRs or known toxicities
iii) May limit reporting only to specific ADRs
iv) Relies on diagnostic capability of reporter

d) Analysis of patient records

This method involves analysing data from patient records. The clinical information available includes prescriptions, laboratory test results, symptoms and signs, and diagnoses. In comparison with individual case reports, patient records carry more complete information on the medical history, potential susceptibility factors and other medications taken before and after the event of interest.

One of the most widely used is longitudinal electronic patient records. This involves tracking electronic records over a period of time. Information is extracted directly from the computer systems in which patients' data is stored. The advantage is that no extra effort is required to obtain the information and omissions are minimised. The drawback of this method is that electronic patient records are not available in all settings and there is under-reporting of events where medical care is not sought for.

5.2.2 Active Surveillance Methods

a) Cohort Study

In a cohort study, a population-at-risk for the event is followed over time for the occurrence of the

event. Information on exposure status is known throughout the follow-up period for each patient. Since the population exposure during follow-up is known, incidence rates can be calculated.

Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a medicine that is rarely used or to study very rare events.

b) Cohort Event Monitoring (CEM)

CEM is an example of a cohort study. In a CEM, patients are enrolled into a cohort and actively followed up during treatment to record all adverse events (not just suspected ADRs). Adverse events monitored in CEM do not necessarily have a causal relationship with the treatment, in contrast to established adverse drug reactions and a causality assessment will thus be required.

CEM encourages healthcare professionals to report adverse events and solicits information about events that may not otherwise be reported. The well-specified cohorts, together with encouragement to report all events, ideally allow incidence rates to be estimated and compared across medicinal products.

CEM is not intended to replace spontaneous reporting but to complement it. Some countries (e.g. New Zealand and United Kingdom) have implemented CEM systems for intensified follow-up of selected medicinal products in order to complement individual case reports.

Objectives of CEM

The aim of CEM is to gather more information on the safety profile of a new chemical entity in early post-marketing phase. The objectives of CEM include:

i) To characterise known reactions
ii) To measure risk
iii) To detect signals of unrecognised reactions
iv) To detect interactions with other medicines
v) To identify risk factors for ADRs like age, gender, dose etc.
vi) To assess safety in pregnancy & lactation
vii) To detect inefficacy of the medicine

CEM is used in cases of:

i) New class of medicine
ii) Medicine related to class of medicine that has previously caused problems
iii) Potentially significant adverse event observed during pre- or post-marketing surveillance spontaneous reports

Limitations of CEM

i) Restriction to a small subset of medicinal products
ii) Relatively small fraction (globally) of the population covered
iii) Lack of data from unexposed patients

c) Cross-sectional Study

In a cross-sectional study, data is collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status. These studies are best used to examine the prevalence of an event at one time point or to examine trends over time. These studies can also be used to examine the association between exposure and outcome. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed.

d) Case-control Study

In a case-control study, cases of events are identified. Controls, or patients without the event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of the event in the two groups.

e) Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. Such studies include:

i) Pharmacodynamic and pharmacokinetic studies
ii) Genetic testing (to identify the group of patients that might be at an increased risk of adverse reactions)
iii) Specific studies to investigate potential drug-drug interactions and food-drug Interactions.

How ADR reporting can prevent medicine-associated tragedies

The following are examples of drugs that have been withdrawn as direct result of ADR reporting. This shows how ADR reporting has helped prevent development of drug morbidity and mortality:

	Year of marketing	Year withdrawn	Reason for withdrawal
Bromfenac	1997	1998	Hepatotoxicity
Benoxaprofen	1982	1982	Liver necrosis
Encainide	1987	1991	Excessive mortality
Mibefradil	1997	1998	Multiple drug interaction
Terfenadine	1985	1998	Fatal cardiac arrhythmias
Cerivastatin	1997	2001	Rhabdomyolysis
Rofecoxib	1999	2004	Myocardial infarction and stroke

These drugs were withdrawn in a relatively short period following introduction to the market. This was due to existence of drug safety monitoring systems. This is in comparison to drugs such as phenacetin (marketed 1887 and withdrawn in 1983 due to nephropathy) and dipyrone (marketed 1922 and withdrawn in 2010 due to agranulocytosis) which were only withdrawn after many years of use due to lack of an effective drug safety monitoring system.

The success of spontaneous reporting in preventing medicine tragedies is dependent on cooperation of healthcare providers and consumers.

How voluntary reporting on ADRs can influence labelling

a) Cyclophosphamide – an anticancer drug has been on the market for several years in many countries. In January 2001, there were some new reactions included in the product information: Stevens Johnson Syndrome and toxic epidermal necrolysis.
b) Losartan was marketed in the USA since 1995. Some of the new reactions that have been discovered after launch and included in the Physician Desk Reference are: vasculitis, allergic purpura (including Henoch-Schoenlein purpura), anaphylactic shock and anaphylactoid reaction.
c) Levofloxacin was launched in the USA in 1997. In February2000,Torsade de pointes was included as one of the ADRs listed on the product information leaflet.

5.3 Case report

A case report, also called an Individual Case Safety Report(ICSR) in pharmacovigilance can be defined as a notification relating to a patient with an adverse event (or laboratory test abnormality) suspected to be induced by a medicine

5.4 Events to be reported

a) Suspected reactions, including minor ones, in the case of "new" (<5 years on the market) medicines.
b) All serious or unexpected or unusual ADRs, in the case of established or well-known medicines.
c) If an increased frequency of a given reaction is observed.
d) Suspected ADRs associated with drug-drug, drug-food or drug-nutritional supplements interactions.
e) ADRs in special cases or conditions such as drug abuse, and drug use in pregnancy and during lactation.
f) When suspected ADRs are associated with drug withdrawals.
g) ADRs attributed to an overdose or medication error.
h) Medication errors - Th ese reports should specify information on the product, sequence of events up to the time of error, work circumstances during error, and type of error.
I) When there is a non-response, therapeutic ineffectiveness or when suspected pharmaceutical defects are observed.
j) All medicine-related problems for example, substandard and falsified medicines.
k) Any concerns about product presentation e.g. confusing labeling, packing or presentation.
l) Adverse events following the ingestion of herbal or traditional medicines.
m) A malfunction or deterioration in the characteristics or performance of in-vitro diagnostics.
n) False positive or false negative test result falling outside the declared performance of the test.
o) Report even if you are not certain the product caused the adverse drug reaction or adverse event and whether or not you have all the details.

Any of the above events should be reported to the ZAMRA using the Adverse Drug Reaction Reporting Form, see Appendix1.

Adverse Events Following Immunisation (AEFI) should be reported as per the Zambia "National Manual for Surveillance of AEFIs".

5.5 Product quality problems that should be reported

a) Suspected contamination e.g. present of foreign particles or unusual smell
b) Defective medical devices and supplies
c) Separation of components
d) Reduced or lack of efficacy
e) Poor packaging or labelling
f) Mislabelling
g) Incomplete pack
h) Colour change
i) Caking
j) Change in odour

k) Moulding
l) Crumbling of tablets

5.6 Types of medicines and allied substances that should be reported

a) Conventional medicines (including general sale medicines)
b) Traditional medicines
c) Herbal medicines
d) Nutritional supplements
e) Cosmetics
f) Biological products such as vaccines and blood products
g) Diagnostic products, Medical devices and radio-contrast media
h) Investigational medicines
I) Medical supplies

5.7 When to report an ADR

Any suspected ADR should be reported upon observation of the adverse eventor as soon as possible.

Adverse events should be reported even if it is not certain the product caused the event or one does not have all the details.

5.8 Who should report?

a) Patients and caregivers can report all suspected ADRs experienced or observed during treatment.
b) Associations and interest groups (e.g. Diabetic Association of Zambia) can report all suspected ADRs and product quality problems experienced or observed by their members.
c) All healthcare workers in Zambia as part of their professional responsibility
d) All government hospitals, private hospitals, health centres, dispensaries, private clinics, private pharmacies and private nursing homes have obligation to report all ADR cases encountered or reported to them by the patients.
e) Manufacturers and Marketing Authorization Holders: These should develop systems for ADR follow-up and assessment of impact of notification of significant safety data on their products.
f) Members of the Public: It is vital for members of the public to report a suspected ADR to ZAMRA even if they are doubtful about the precise relationship with the given medication or they do not have all the facts. What is required is to report '**ALL SUSPECTED ADRs'.**
g) Public health programmes, including Research Institutions, NGO's/Partners implementing health programmes, are obligated to report ADRs encountered by participants on their programmes.

Why healthcare workers have a professional obligation to report

a) They have the right training to identify and correctly report adverse events
b) Healthcare workers are in the best position to report suspected ADRs observed in their everyday patient care because they are the people who diagnose, prescribe, dispense and monitor the patients' response to the medicines
c) Patients with ADRs are most likely to see healthcare workers for intervention
d) All healthcare workers should report ADRs as part of their responsibility, even if they are doubtful about the precise relationship with the given medication.

5.9 What happens to reported ADRs

a) The report submitted is entered into the national database of adverse drug reactions and be analysed by expert reviewers on a regular basis.
b) The report submitted is also added to the global database.
c) The information obtained from the report is used to promote safe use of medicines.

A well-completed and duly submitted ADR report may result in:

a) Additional investigations into the use of the medicine in Zambia
b) Appropriate changes to the package insert
c) Change of the category of distribution of the medicine
d) Enhancing educational initiatives to improve the safe use of that medicine
e) Other regulatory and health promotion interventions as the situation may warrant including withdrawal / recall of the medicine from the market.

5.10 Benefits of ADR reporting

a) Improved quality of healthcare.
b) Reduction of medicine-related problems leading to better treatment outcomes
c) Improved public confidence in the healthcare system
d) Improved knowledge on drug safety
e) Provides information on medicine related problems for decision-making

5.11 Where to report

Completed ADR reporting forms should be submitted as soon as possible to:

The National Pharmacovigilance Unit
Zambia Medicines Regulatory Authority
P.O Box 31890, Lusaka, Zambia
Email: pharmacy@zamra.co.zm
Tel: +260211220429/ 269410

In the event one is unable to submit directly to NPVU at ZAMRA, forms can be submitted through the following:

a) ZAMRA regional offices
b) District Health Office
c) Provincial Health Office
d) Responsible officer/In-charge for a retail pharmacy, health shop and pharmacy in private health facility(hospital/clinic)
e) Free postage at the nearest post office (Zambia Postal Services)

5.12 How to report

Reporters should complete the relevant ADR form and send accurate information to achieve a better and efficient outcome of the Pharmacovigilance system in Zambia.

The following can be used to report an ADR:

i) Hard-copy ADR Report Forms available at the health facility (Appendix 1)
ii) Telephone: +260 211 220429/ +260 211 269410/+260 212 622111
iii) Online e-reporting form on the ZAMRA website (www.zamra.co.zm) and select report online(https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZM)
iv) Mobile App (“Med Safety” available on Play Store® (Android devices) or iStore® (iOS devices)

v) Email to pharmacy@zamra.co.zm (preferably with attachment of a copy of the completed ADR report form)
vi) Forms can be downloaded from the ZAMRA website (http://www.zamra.co.zm/wp-content/uploads/2016/08/NPVF-Form.pdf)
vii) Forms can be completed on the ZAMRA website (http://www.zamra.co.zm/adr-reporting-form)

The ADR report form

Refer to the form in Appendix 1 for healthcare workers and Appendix3 for non-health professionals. The main features on the ADR report form are:

a) Patient information: initials, File No, age, weight, sex, date of birth, height
b) Details of Adverse Drug Reaction or Product Quality Problem: date of reaction; category
c) Medicines/vaccines/medical device (Suspected and concomitant)
d) Adverse Drug Reaction Outcome
e) Product Quality Problem
f) Details of Reporter (Name, Profession, Signature, Date, Contact address, phone no. and email address)

The reporter's details are considered confidential and are to be used only for data verification, completion of case report, case follow-up and feedback. Refer to the JobAid in Appendix 2 for instructions on how to fill in the report form

Patient Reporting Form

The Patient reporting form is meant for use to report ADRs by non-health professionals. The form is distributed via health shops, community pharmacies and health posts. This form can be sent to ZAMRA directly by the reporter or through the nearest health facility. Refer to Appendix 3

Characteristics of a Good Case Report

A Report should have the following essential data elements:
For ADRs:

a) Patient information
b) Description of suspected ADR
c) Date of onset of ADR
d) Date of commencement of medication(s)
e) Details of the medicine/product (i.e. name, dosage, reasons for use)
f) Outcome of the ADR
g) Details of the reporter (i.e. name, contact address, contact number)

For Product Quality Problems:

a) Name of product (Trade/brand and generic name)
b) Description of suspected product quality problem
c) Batch/lot Number
d) Name of manufacturer
e) Details of the reporter (i.e. name, contact address, contact number, email address)

For medication errors:

a) Patient information
b) Description of medication error
c) Date of commencement of medication(s)
d) Details of the medicine/product (i.e. name, dosage, reasons for use)
e) Outcome of the error if known

f) Details of the reporter (i.e. name, contact address, contact number)

5.13 What happens to Reports

All reports:

a) Verbal reports will immediately be transcribed onto the ADR Report Form.
b) Reports from health facilities (private or public) can be sent directly to ZAMRA or through District Health Office or the Provincial Health office.
c) Reports from consumers, can be sent directly to ZAMRA or through the nearest health facility.

National Pharmacovigilance Unit at ZAMRA:

a) Receives all reports
b) Acknowledges receipt of all reports
c) Requests for additional information and samples when necessary.
d) Carries out case Causality Assessment.
e) In the case of product quality problems, the unit submits the report to the Post Marketing Surveillance Unit for further investigations.
f) Refers reports to Expert Review Committee.
g) Advises the reporter on action to take.
h) Provides feedback to the reporter on action taken.
i) May recommend regulatory action.
j) Adds report to the national database(Vigiflow®).
k) Submits the report to the global database (VigiBase®) at UMC.

Refer to Appendix 4 for Schematic presentation of the ADR reporting system.

6. Causality Assessment

An inherent problem in pharmacovigilance is that most case reports concern suspected adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice, few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e.'possible' or 'probable'. To solve this problem many systems have been developed for a structured and harmonized assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Sometimes epidemiological studies are needed to confirm causality. We work with imperfect data and our conclusions are those of probability. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance

6.1 What is Causality Assessment?

Causality assessment is the systematic review of data about a suspected ADR to determine the likelihood of a causal association between the event and the medicine received.

Determination of causality requires that the following information is derived from the report:

a) Medicines taken and their indications
b) Time to onset of the event
c) Reaction type
d) Results of dechallenge & rechallenge
e) Co-morbidity
f) Outcome information

Information sources for causality assessment

a) Information available on the report
b) Pharmacological knowledge
c) Previous reports received
d) WHO global database
e) Any literature reports
f) Product information

Importance of Case Causality Assessment

Case Causality Assessment is an essential discipline. It ensures:

a) Careful review of report details
b) Standardised assessment
c) An in-depth understanding of the data
d) Standardised data for signal assessment
e) The ability to sort reports by quality

6.2 The WHO-UMC causality assessment system

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment considering the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognized that the semantics of the definitions are critical and that individual judgments may therefore differ. There are other algorithms that are either very complex or too specific

for general use. This method gives guidance to the general arguments which should be used to select one category over another. Refer to Appendix 5.

6.3 WHO causality categories

a) Certain

A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

i) Event with plausible time relationship
ii) No other explanation – disease or drugs
iii) Response to withdrawal plausible
iv) Event definitive – specific problem
v) Rechallenge required

b) Probable/likely

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

i) Event with reasonable time relationship to drug intake
ii) No other explanation
iii) Response to withdrawal clinically reasonable
iv) No rechallenge required

c) Possible

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

i) Event with reasonable time relationship to drug intake
ii) Could also be explained by disease or other drugs
iii) Information on drug withdrawal lacking or unclear

d) Unlikely

A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanations.

i) Event with duration to onset that makes a relationship improbable (but not impossible)
ii) Diseases or other drugs provide plausible explanations

e) Conditional/unclassified

A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

i) An adverse event has occurred, but there is insufficient data for adequate assessment, or
ii) Additional data is awaited or under examination

f) Unassessable/unclassified

A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

6.4 The process of Causality Assessment

6.4.1 Objective evaluation

From the report the assessor should be able to derive the following:

a) Dates of use of drug(s)
- To establish whether the event occurred before the commencement of the drugs

b) Date of onset of event
- To establish the duration to onset of the event (timeframe between taking the medication and onset of the ADR)

c) Nature of event
- Apply ADR terminology from MedDRA

d) Response to withdrawal of medicines(dechallenge)

e) Response to reintroduction of the same medicines (rechallenge)

f) Outcome of the ADR

6.4.2 Subjective assessment

To determine whether the reaction is plausible; the assessor should consider the following:

a) Indications for use of the medicine
b) Past medical and drug history
c) Pharmacology of the medicines
d) Prior knowledge of similar reports with the suspect drug or related drugs
e) Consultations with literature, experts etc.

6.4.3 Decision making

Based on the assessments in (1) and (2) above decide on causality.

7. Importance of Communication in Pharmacovigilance

The Erice Declaration – On Communicating Drug Safety Information

The following declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily, 24-27 September 1997. It was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organizations.

Preamble

Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties – consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organizations – working together. High scientific, ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements set forth the basic requirements for this to happen, and were agreed upon by all participants from 34 countries at Erice:

a) Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.

b) Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.

c) All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal must be recognized and overcome.

d) Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to

all. Adequate non-partisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

e) A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated.

These ideals are achievable and the participants at the conference commit themselves accordingly. Details of what might be done to give effect to this declaration have been considered at the conference and form the substance of the conference report.
Erice, 27 September 1997

It is against this background that ZAMRA places importance on communication in Pharmacovigilance. The findings collected through pharmacovigilance activities are used to educate and promote rational, safe and more effective use of medicines by healthcare workers and consumers.

Depending on the safety issue, ZAMRA will use circulars, newsletters, letters to healthcare workers, the website, and on occasion, the media to communicate medicine safety concerns and regulatory decisions taken. The MAH and PHP should submit any new safety knowledge about their products in use to ZAMRA so that collaborative actions can be taken.

Research and academic institutions, healthcare workers and other partners can conduct health research to improve the quality, effectiveness and safety of medicines in the country. Reports generated through pharmacovigilance studies provide evidence base for decision making with the ultimate goal of providing quality, safe and efficacious medicines and care to consumers. Findings from these studies need to be communicated and disseminated effectively to influence optimal and timely practice and healthcare policies.

8. Confidentiality

The data collected by ZAMRA will only be used for prevention of ADRs and promotion of rational and safe use of medicines. The information obtained from the report will not be used for commercial purposes. The reports do not constitute an admission that the healthcare worker contributed or caused the event in any way. The information will not be available to support any legal, administrative or other actions to the detriment of the reporting healthcare worker or consumers. In this regard, the identity of patients and reporters will be kept confidential. Publications will not disclose trade names unless regulatory actions have been taken. The names of the reporters or any other healthcare worker named on the report will be removed before any details about a specific adverse reaction is used or communicated to other parties.

Details of the report are entered in the national pharmacovigilance database and the original report form kept in a secure place. The database can only be accessed by authorized personnel. Report details are also electronically sent to Uppsala Monitoring Centre (UMC) - the WHO Collaborating Centre for International Drug Monitoring. The UMC regularly screens compiled case reports for medicine safety concerns at international level. The UMC also provides web-based access to all internationally collected reports via the WHO-ADE database (VigiBase®) to member countries.

9 Training and Capacity Building

Under reporting of suspected ADRs is a common problem in spontaneous reporting systems. The reasons for not reporting include but are not limited to; the lack of awareness among healthcare workers about the need to monitor the safety of medicines and the existence of a system to do so. Therefore, on-the-job training is required for healthcare workers so that they may consider ADRs as one possible cause of their patients' ailment.

Training modules for Pharmacovigilance have been prepared for on-the-job training of healthcare workers. Newly graduated healthcare workers need to have the skills to make evidence-based decisions about patient safety. Pharmacovigilance has been incorporated in health professions' training programmes to improve ADR diagnosis, management, prevention and reporting skills.

Pharmacovigilance trainings are conducted as part of Continuous Professional Development (CPD) programs through professional bodies and associations.

Trainings of Trainers (TOTs) in Pharmacovigilance are conducted in order to have trainers throughout the country that are able to train healthcare workers. Healthcare workers that are trained serve as focal point persons at their respective institutions to spearhead Pharmacovigilance activities as well as provide sensitisation and advocacy in Pharmacovigilance.

APPENDICES

Appendix 1: ADR Reporting Form

ZAMRA/NPVU/FORM/0001 version 00

ADVERSE DRUG REACTION, MEDICATION ERROR AND PRODUCT QUALITY PROBLEM REPORTING FORM

(Identities of reporter and patients will remain strictly confidential)

Republic of Zambia

NATIONAL PHARMACOVIGILANCE UNIT (NPVU)

The Director General
The Zambian Medicines Regulatory Authority
Plot No. 6903, Tuleteka Rd, Off Makishi Rd,
P.O. Box 31890, Lusaka, Zambia.

Telephone: +260211220429
Telefax: +260211238458
Email:pharmacy@zamra.co.zm

PATIENT INFORMATION

Patient initials: ..... File No..... Age:..... Weight (kg):.....

Sex: Male ☐ Female ☐ Date of birth:..... /...../..... Height (cm):.....

DETAILS OF ADVERSE DRUG REACTION OR PRODUCT QUALITY PROBLEM

I am reporting on :1) an Adverse Drug Reaction ☐ Date of onset of reaction: ...../...../.....

2) a product Quality Problem ☐ Category: medicine ☐ medical device ☐

Description of Adverse Drug Reaction or Product Quality Problem: .....

.....

.....

1. MEDICINES / VACCINES / MEDICAL DEVICES: (✓) *Tick against the **suspected** medicine/ vaccine*

Indicate all Medicines the patient is taking

(✓)	Trade/Generic Name & Batch Number	Dosage & dosing Frequency	Rounte of Administration	Start date (dd/mm/yy)	Stop date (dd/mm/yy)	Reasons for use

ADVERSE DRUG REACTION OUTCOME: *(Tick all that apply)*

Outcome: ☐ **Death** ☐ Life threatening ☐ Disability ☐ Hospitalization ☐ Congenital abnormality

☐ Other *(Specify)*: .....

Recovered: ☐ Yes ☐ No If YES, date of recovery: ...../..... /.....

Additional information *(e.g. Relevant medical history, medicines taken in the last 28 days, allergies, previous exposure, baseline test results/lab data)*.....

.....

2. PRODUCT QUALITY PROBLEM

Trade Name	Batch Number	Registration Number	Dosage Form & Strength	Expiry Date (mm/yyyy)	Size/Type of container

Product sample(s) have been submitted for evaluation: ☐ **Yes** ☐ **No** **Number of submitted samples:** ☐

DETAILS OF REPORTER

Name: ..... Profession:..... Signature:..... Date (dd/mm/yyy):.....

Contact address: ..... Phone: ..... Email:.....

ADVICE ABOUT VOLUNTARY REPORTING

Responsibility to report
The onus is on al members of the public, in particular healthcare professionals to report all suspected Adverse Drug Reactions or Product Quality.
Problems to the National Pharmacovilance Unit (NPVU) of the Zambia Medicines Regulatory Authority.

Report even if:
- You are not certain the product caused the event.
- You do not have all the details.

Report adverse events with:
- Medications (drugs, vacccines, bilogicals,blood and blood products)
- Medical devices including in vitro diagnostics)
- Traditional and herbal medicines (give local name and /or botanical name)
- Medications errors
- Treatment failure or reduced efficacy

Report product quality problems such as:
- Suspected contamination
- questionable stability (e.g. not working properly or leaking)
- Poor packaging or labeling
- Therapeutical failures

If there is need for additional information please attach an extra page.

Where to sent the report
This report may be sent to NPVU through your health facility, nearest ZAMRA Office,by faxing,email or mailed to the address given below.

Fold here

Note:
It if your professional responsibility to report all suspected adverse drug reactions and quality problems of medicines and allied substances. This report will contribute to the improvement of drug safety monitoring in Zambia

Fold here

PLEASE USE THE ADDRESS PROVIDED BELOW - JUST FOLD TAPE AND MAIL

Postage will be paid by addressee

No postage stamp is required if posted within the Republic of Zambia

NATIONAL PHARMACOVIGILANCE UNIT (UPVU)
THE ZAMBIA MEDICINES REGULATORY AUTHORITY
PLOT NO. 6903,TULETEKA ROAD, OFF MAKISHI ROAD,
P.O BOX 31890,
LUSAKA,
ZAMBIA.

Appendix 2: Job Aid For Completing An ADR Report Form

The following instructions are for completing the ADR Report Form.

Task:	Filling in an ADR Report Form
Completed by:	Healthcare Worker
Purpose:	To report a suspected ADR/Medication Error/Product Quality Problem
When to Perform Task:	Immediately a suspected ADR/Medication Error/Product Quality Problem is encountered
Materials Required to Perform Task:	ADR Report Form, Blue/Black Pen

Notes:

- If you are reporting an ADR or Medication Error, skip Step 14.
- If you are reporting a product quality problem, go to Steps 8 to 10 and 13 to 15.

Step	Action	Notes	Example
1.	**Patient Initials:** Enter the initials of the patient name	Abbreviate the patient name using initials only. This is required to maintain confidentiality.	Andrew Bwalya = A.B.
2.	**File Number:** Enter the patient file number (if available at the health facility as indicated on the patient file)	A file number is usually assigned to a patient's file at the Health facility	00010-08-18
3.	**Age:** Enter the patient's age in digits	Indicate the age at the last birthday	42 years
4.	**Weight:** Enter the patient's weight (if available or indicated in the patient's file)	Indicate weight in kilogram (kg) units	58 kg
5.	**Sex:** Tick the sex of the patient		Male or Female
6.	**Date of Birth:** Enter the patient's date of birth	Indicate the date of birth using the format: DD/MM/YYYY	05/08/1976
7.	**Height:** Enter the patient's height (if available or indicated in the patient's file)	Indicate the height in centimetre (cm) units	172 cm

8.	**Details of ADR / Medication Error/ Product Quality Problem** : Tick the appropriate box depending on the category being reported.	If reporting an ADR, Tick the first box in part (1) and indicate the date of onset of reaction: DD/MM/YYYY If reporting a Product Quality Problem, Tick the second box in part (2) and then tick the category of product being reported: Medicine/Medical Device	
9.	**Description of ADR/Medication Error/ Product Quality Problem:** Write a brief description of the ADR or Product Quality Problem encountered	Note down anything unusual. Limit your description of the ADR/Product Quality Problem to the main key features of the problem in the line spaces provided on the Form. A Medication Error can also be described in this section.	Generalised rash on face, trunk and upper limbs after first dose of Amoxicillin capsules OR Broken tablets in a sealed medicine container
10.	**Medicines/Vaccines/Medical Devices:** In the box provided, indicate the generic name & batch number, Dosage & dosing frequency, route of administration, start date, stop date and reasons for use.	Use this section to provide details of all medicines/products the patient is taking (including those not suspected to be causing the ADR).	Amoxicillin; 500mg three times daily; Oral capsule; Started: 01/08/2018; Stopped: 06/08/2018; Respiratory tract infection.
11.	**Outcome:**Tick the outcome(s) that apply to the ADR situation encountered. If ticked 'Other', indicate/specify the outcome in the space provided.	When reporting an ADR, use this section to indicate the outcome of the ADR encountered. If outcome unknown, tick 'Other' and specify.	
12.	**Recovered:** Tick the appropriate box to indicate the status of the patient. If 'YES', indicate the date of recovery	When reporting an ADR, use this section to indicate and provide information on the status of the	

	(DD/MM/YYYY). Provide additional information (e.g. relevant medical history, medicines taken in last 28 days, allergy, previous exposure, baseline lab results, etc.) if available	patient.	
13.	**Additional Information:** Indicate relevant medical history medicines taken in the last 28 days allergies previous exposure baseline test results/lab data	If reporting a Medication Error, any other information relating to the case should be reported under the section for 'Additional Information'. Manufacturer information can also be included here.	Allergic to Sulphonamides
14.	**Product Quality Problem:** Indicate in the table the Generic/Trade Name; Batch Number; Product Registration Number; Dosage Form & Strength; Expiry Date; and Size/Type of container. Tick the appropriate box indicating the status of the product (i.e. whether product submitted for evaluation or not). If submitted for evaluation, use the box provided to indicate the box provide to indicate the number of sample submitted.	When reporting a Product Quality Problem, use this section to provide details of the product	Amoxicillin, Batch No. XXXX, Reg. No. 000/000, Capsule 250mg, Exp. Date: 20/08/2022, Pack of 1000 Capsules.
15.	**Details of Reporter:** Complete the form by indicating name of person completing the report, profession, signature and date. Indicate your contact address (name of the Health Facility), phone number and email address.	The date, contact address, phone number and email address are required for ZAMRA to follow -up the report.	Jane Banda, Registered Nurse, JaneB., 05/08/2018, Lusaka Health Centre, 09066105678, janebanda@email.com

Form is complete when:-

- The necessary fields and above steps are completed correctly.
- The patient information (initials, age, sex, etc.), details of ADR/Product Quality Problem, details of the medical product and Contact information of Reporter are indicated on the form
- Report Form dated

Report should be sent/submitted to ZAMRA

Appendix 3: Patient Reporting Form

ADVERSE MEDICINE REACTION REPORTING FORM

FOR PATIENTS, NON-HEALTH PROFESSIONALS AND PRACTITIONERS OF TRADITIONAL/ ALTERNATIVE/ COMPLEMENTARY MEDICINE

(Identities of reporter and patient will remain strictly confidential)

NATIONAL PHARMACOVIGILANCE UNIT (NPVU)

The Director General
Zambia Medicines Regulatory Authority
Plot No. 6903, Tuleteka Rd, Off Makishi Rd,
P.O. Box 31890, Lusaka, Zambia.

Telephone: +260211220429The
Telefax: +260211238458
Email: pharmacy@zamra.co.zm

INFORMATION ON THE PERSON WHO HAD THE SIDE EFFECT(S)

Patient initials: …… File No. …… Age: …… Weight (kg): ……

Sex: Male Female Date of birth: …. /…. /…… Height (cm): ……

INFORMATION ABOUT THE SUSPECTED SIDE EFFECT(S)

1. Describe the symptoms of the suspected side effect? ……
   ……
2. How long did the suspected reaction last? …….day(s) Start date: …./…/…. End date: …./…/…
3. How serious was the side effect? (tick)
   Mild (did not affect everyday activities)

   Affected everyday activities but did not consult a health professional

   Had to seek treatment services

   Got admitted to hospital
4. How were the symptoms managed?
   Suspected medicine was discontinued as a result of the side effect

   No action was taken
5. What was the outcome? Death Disability others (specify): ……

INFORMATION ABOUT THE MEDICINE(S) BEING TAKEN

Name of the medicine(s)	
Name of manufacturer	
Expiry date (mm/ yyyy)	
Where were the medicine(s) obtained from?	
When was the medicine pack opened?	
How were the medicine(s) being taken? At what dose?	
What were the medicine(s) taken for?	
Start date (dd/mm/yyyy): …./…./…….	End date (dd/mm/yyyy): …./…./……
What other medicine(s) or herbal remedies have been taken in the past 30 days?	

DETAILS OF REPORTER

Name: …… Signature: …… Date (dd/mm/yyyy): …./…./……

Contact address: …… Phone: …….. Email: ……

ADVICE ABOUT VOLUNTARY REPORTING

Responsibility to report:
The onus is on all members of the public, in particular healthcare professionals to report **all suspected** Adverse Drug Reactions or Product Quality Problems to the National Pharmacovigilance Unit of the Zambia Medicines Regulatory Authority.

Report even if:
- You are not certain the product caused the event.
- You do not have all the details.

Report adverse events with:
- Medications
- Traditional and herbal medicine (local name and/or botanical name)

Report product quality problems such as:
- Suspected contamination
- Questionable stability (e.g. visual signs of possible microbial growths, cracking)
- Defective components (e.g. not working properly or leaking)
- Poor packaging or labelling
- Therapeutic failures

If there is need for additional information please attach an extra page.

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

Importance of reporting:
Your support to the Zambia Medicines Regulatory Authority's role in monitoring the quality, safety and efficacy of medicines and allied substances is much appreciated. This report will contribute to the improvement of drug safety monitoring in Zambia.

PLEASE USE THE ADDRESS PROVIDED BELOW – JUST FOLD, TAPE AND MAIL

Postage will be paid by addressee

No postage stamp is required if posted within the Republic of Zambia

NATIONAL PHARMACOVIGILANCE UNIT (NPVU)
THE ZAMBIA MEDICINES REGULATORY AUTHORITY
PLOT No. 6903, TULETEKA ROAD, OFF MAKISHI ROAD,
P.O. BOX 31890,
LUSAKA,
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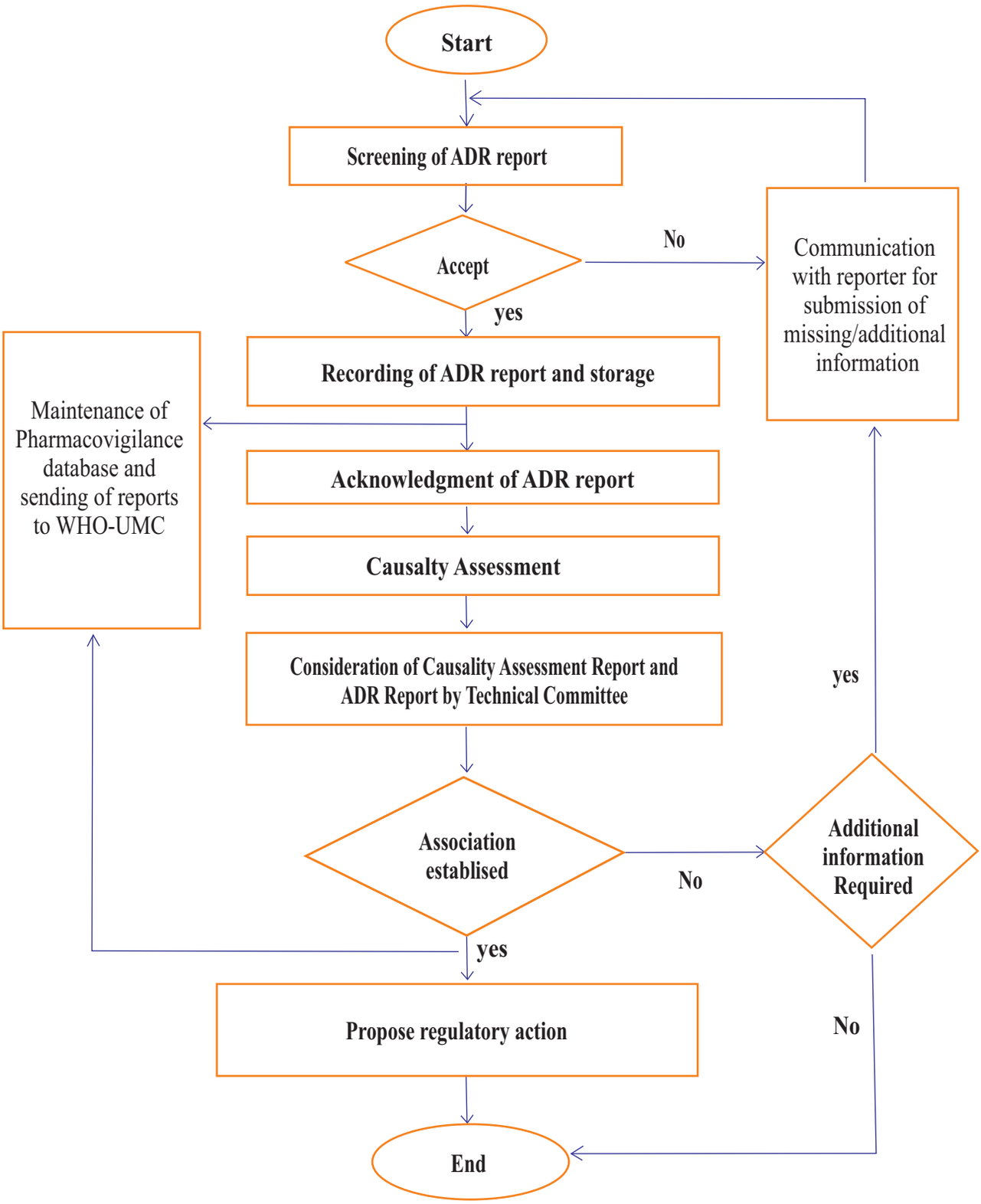
Appendix 4: Schematic presentation of the ADR reporting system



Appendix 5: WHO Causality Assessment Criteria

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

Appendix 6: Naranjo Algorithm for Assessing Probability of an ADR

The Adverse Drug Reaction (ADR) Probability Scale was developed in 1991 by Naranjo and co-workers from the University of Toronto and is often referred to as the Naranjo Scale. This scale was developed to help standardize assessment of causality for all adverse drug reactions and was not designed specifically for drug induced liver injury. The scale was also designed for use in controlled trials and registration studies of new medications, rather than in routine clinical practice. Nevertheless, it is simple to apply and widely used.

The ADR Probability Scale consists of 10 questions that are answered as either Yes, No, or "Do not know". Different point values (-1, 0, +1 or +2) are assigned to each answer. A simplified version of the 10 questions is provided in the table below:

Adverse Drug Reaction Probability Scale

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

Score	Interpretation of Scores
Total Score ≥9	Definite. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
Total Score 5 to 8	Probable. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	Possible. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	Doubtful. The reaction was likely related to factors other than a drug.

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Opposite Shoprite Chipata
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COPPERBELT REGIONAL OFFICE
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