Zimbabwe National Pharmacovigilance Policy Handbook

2nd Edition, December 2016

Medicines Control Authority of Zimbabwe

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FOREWORD

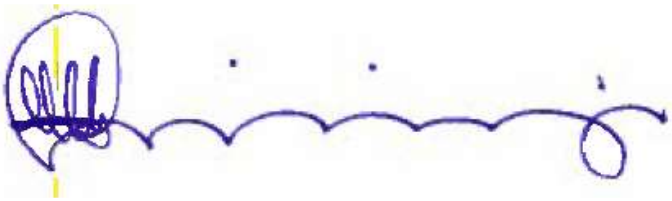
The Medicines Control Authority of Zimbabwe (MCAZ) is a statutory body established by an Act of Parliament, The Medicines and Allied Substances Control Act (MASCA) [Chapter 15.03]. MCAZ is a successor of the Drugs Control Council (DCC) and the Zimbabwe Regional Drug Control Laboratory (ZRDCL). DCC was established by an Act of Parliament in 1969: Drugs and Allied Substances Control Act [Chapter 15.03] following which ZRDCL became operational in 1989.

The mandate of the MCAZ is to protect public and animal health by ensuring that accessible medicines, vaccines and medical devices are safe, effective and of good quality through enforcement of adherence to standards by manufacturers and distributors

The national pharmacovigilance centre under the MCAZ, was set up in 1998. Zimbabwe, through the national PV centre is a participating country to the international drug monitoring programme. The first edition of the Pharmacovigilance policy handbook, November 2013 was written in consultation with the Ministry of Health and Child Care (MoHCC) public health programmes and all provincial management, including some private health stakeholders and the pharmaceutical industry. This revised edition, of the national PV policy, July 2016 was done in-line with current international and local medicines safety requirements, and in consultation with MoHCC public health programmes, private health stakeholders and the pharmaceutical industry.

The aims of the PV policy handbook are to firstly provide a framework for a national pharmacovigilance system in Zimbabwe. Secondly, to define the pharmacovigilance activities undertaken by the Pharmacovigilance centre and stakeholders. Thirdly to delineate the trends and signals of adverse events with medicines used in the country and help policy makers utilize evidence based practice in patient safety and therapeutics.

I urge both private and public health programmes to set up sustainable pharmacovigilance systems in collaboration with the national Pharmacovigilance Centre, and promote medicines safety data sharing and communication in a way that promotes patient safety and therapeutics.



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PREFACE

The Zimbabwe National Pharmacovigilance Policy Handbook, 2nd Edition updates the November 2013 version to indicate the Zimbabwe National Pharmacovigilance (PV) Centre's compliance with the WHO Pharmacovigilance Indicators Handbook 2015. This edition also includes the revised Adverse Drug Reaction (ADR) reporting form, the revised joint Medicines Control Authority of Zimbabwe-Medical Research Council of Zimbabwe Serious Adverse Event (SAE) reporting form, the revised World Health Organization (WHO) definition of an Adverse Event Following Immunization (AEFI) and causality assessment of an AEFI as per the WHO Aide-memoire on AEFI Causality Assessment, 2013 and the MCAZ Guidelines for the Notification of a Medicinal Product Problem/Defect and Recall Procedure.

CONTENTS

ACRONYMS

ACTs	Artemisinin-based Combination Therapies
AD	Auto Disabled Syringe
ADE	Adverse Drug Events
ADR	Adverse Drug Reaction
AEFI	Adverse Events Following Immunization
AFP	Acute Flaccid Paralysis
AIDS	Acquired Immuno Deficiency Syndrome
AMRHI	African Medicines Regulatory Harmonization Initiation
ANTI-TB	Anti-Tuberculosis
ARV	Antiretroviral
ATC	Anatomical Therapeutic Chemical Classification
BCG	Bacilli Calmette Guerin
CEM	Cohort Event Monitoring
DPS	Directorate of Pharmacy Medicines
DTP	Diphtheria Tetanus and Pertussis
DTP-HepB-Hib	Diptheria, Tetanus, Pertussis, Hepatitis B and Haemophillus Influenza Type B
DT	Diphtheria Tetanus
EDLIZ	Essential Medicines List of Zimbabwe
EPI	Expanded Programme on Immunization
GBS	Guillain-Barre Syndrome
GMP	Good Manufacturing Practices
HBV	Hepatitis B Virus
Hep B	Hepatitis B
HF	Health Facility
HIB	Haemophilus Influenza Type B
HIV	Human Immuno-deficiency Virus

HMTC	Hospital Medicines and Therapeutics Committee
IC	Information Component
ICSR	Individual Case Safety Report
IMMP	Intensive Medicines Monitoring Programme
IPAT	Indicator-Based Pharmacovigilance Assessment Tool, Manual for Conducting Assessments in Developing Countries
ISO	International Organization for Standardization
MASC	Medicines and Allied Substances Bill
MASCA	Medicines and Allied Substances Control Act
MCAZ	Medicines Control Authority of Zimbabwe
MCHIP	Maternal and Child Health Integrated Programme
MoH	Ministry of Health
MoHCC	Ministry of Health and Child Care
NEPAD	New Partnership for Africa's Development
NIDs	National Immunization Days
NNT	Neonatal Tetanus
OPV	Oral Polio Vaccine
PCV	Pneumococcal Conjugate Vaccine
PEM	Prescription Event Monitoring
PHP	Public Health Programme
PICS	Pharmaceutical Inspection Co-operation Scheme
PMTCT	Prevention of Mother to Child Transmission
PV	Pharmacovigilance
PVCT	Pharmacovigilance and Clinical Trials
RCORE	Regional Centers of Regulatory Excellence
SADCAS	Southern African Development Community Accreditation Service
SAE	Serious Adverse Event
S.I 150	Statutory Instrument 150 of MASCA Chapter 15:03
SOP	Standard Operating Procedure

TSR	Targeted Spontaneous Reporting
TT	Tetanus Toxoid
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
WCBA	Women of Child Bearing Age
WHA	World Health Assembly
WHO	World Health Organization
WHO-PQ	World Health Organization Pre-qualification

1. INTRODUCTION

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 in regard to 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 Programme and has grown to become a global network of national pharmacovigilance centres in over 140 countries in 2013 (see www.who-umc.org).

Zimbabwe, through the Medicines Control Authority of Zimbabwe (MCAZ), became a participating country to the WHO International Drug Monitoring programme in 1998. The mandate of the MCAZ as a National Drug Regulatory Agency (NDRA) is to ensure that medicines that can be accessed by the public are safe, effective, and of good quality. The MCAZ also serves as the national pharmacovigilance centre. The operations of the centre are based on the WHO guidelines for setting up and running a national pharmacovigilance centre. The Zimbabwe National Centre, along with all other member countries of the WHO Programme, are displayed on the following pages: https://www.who-umc.org/global-pharmacovigilance/members/

https://www.who-umc.org/global-pharmacovigilance/members/who-programme-members/

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicines-related problem. It aims at getting the best outcome from treatment with medicines. Good pharmacovigilance will identify the risks within the shortest possible time, and will help to establish or identify risk factors for adverse drug reactions. When communicated effectively, this information allows for intelligent, evidence-based prescribing with the potential for preventing many ADRs. Such information will ultimately help each patient to receive optimum therapy at a lower cost to the health system. Adverse drug events (ADEs) from poor product quality, adverse drug reactions (ADRs), and medication errors contribute significantly to morbidity and mortality. Although most cases go undetected, particularly in developing countries, data from the US shows that ADEs are the fourth to sixth leading cause of death. ADEs constitute a huge cost to the health system, estimated in the US at $177.4 billion in 2000. Economic consequences of adverse events that are not frequently reported include the impact of adverse events on patient adherence to treatment, resistance to medicines, and treatment outcomes. Besides the economic consequences, cases of adverse events affect the credibility of the

health system leading to loss of confidence. On the UMC website, under the tab “Safer use of medicines”, useful content for raising awareness of pharmacovigilance can be found and the link below leads you directly to the PV glossary.

https://www.who-umc.org/global-pharmacovigilance/global-pharmacovigilance/glossary/

The Zimbabwe National Pharmacovigilance Policy serves as a handbook for pharmacovigilance activities in the country. The pharmacovigilance activities are coordinated by the MCAZ in collaboration with the Ministry of Health and Child Care (MoHCC) and all key stakeholders both in the public and private health sector including the pharmaceutical industry. The handbook also serves as a tool for providing an enabling environment for effective planning, implementation, monitoring and evaluation of the pharmacovigilance system by all key stakeholders. The handbook address issues related to the systems and structures required for pre- and post-authorization monitoring of safety and effectiveness of medicines in Zimbabwe.

If successfully implemented, the pharmacovigilance system will lead to early detection of adverse reactions, interactions and other medicine-induced problems as well as the detection of previously unknown adverse reactions (signals). Furthermore, the system ensures communication of changes in risk/benefit balance to stakeholders with a view of promoting patient safety including rational and safe use of medicines, vaccines and complimentary medicines.

2. GUIDING PHILOSOPHY AND PRINCIPLES OF THE NATIONAL PHARMACOVIGILANCE POLICY:

The policy is based on the following guiding principles:

a. Good quality healthcare is assured through application of pharmacovigilance principles and practice in private and public healthcare systems at all levels in order to ensure patient safety.
b. Patients' access to safe and rational use of medicines and vaccines.
c. Healthcare professionals are to consider pharmacovigilance practice as a professional responsibility.
d. Integration of pharmacovigilance into the overall health system both public and private.
e. Existence of consistent and effective partnerships and collaboration with all stakeholders.
f. Existence of financial commitment at all levels for sustained safety monitoring of medicines and other medicine related issues.
g. Use of current WHO and ICH guidelines for different types of methods of pharmacovigilance activities including causality assessment and pharmacovigilance training tools.
h. The National Pharmacovigilance Centre will work in close collaboration with the WHO International Drug Monitoring Programme including submitting ICSRs to the VigiBase database.
i. The National Pharmacovigilance Centre will collect patient ADRs in an ethical and confidential manner, analyse and communicate the information in a way that improves therapeutics and patient safety through the use of bulletins, alert notices, circulars, dear doctor letters, and publications in international medicines safety journals.
j. Inclusion of pharmacovigilance training curriculum and modules at academic institutions for both undergraduate and post graduate biomedical degrees, medicine, pharmacy, and nursing, physiotherapy and occupational health training programs using the WHO pharmacovigilance toolkit.
k. Recognition of national and international treatment guidelines.
l. Requirements for a national pharmacovigilance centre as per the WHO Pharmacovigilance Indicators Handbook 2015, and Indicator-Based Pharmacovigilance Assessment Tool (IPAT); Manual for Conducting Assessments in Developing Countries, Strengthening Pharmaceutical Systems (SPS) Program 2009.
m. AEFI surveillance in collaboration with the Zimbabwe Expanded Programme on Immunization; EPI Unit – Ministry of Health and Child Care (MoHCC).

3. FUNCTIONS OF THE ZIMBABWE NATIONALPHARMACOVIGILANCE CENTRE

The functions of a national pharmacovigilance system are numerous and varied. Through consultation between WHO, the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) and The Global Fund, the minimum functions of a national pharmacovigilance system have been defined as follows:

a. To promote pharmacovigilance in the country, collect and manage Individual Case Safety Reports (ICSRs) as well as reports of medication errors and suspected counterfeit/substandard medicines

b. To collaborate and harmonize with other ICSRs collection activities within the country (e.g. national disease control programmes, poison control centres, etc.) and international ICSRs monitoring programmes.

c. To identify signals of medicines safety such as unknown or poorly characterised adverse events in relation to a drug.

d. To undertake assessment of risk and options for risk management.

e. To identify if there are quality problems in medicines resulting in ICSRs and more generally, support the identification of medicine quality issues.

f. To provide effective communication and feedback on aspects related to medicines safety, including dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines.

g. To apply information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines.

h. To set up and collaborate with regional/sentinel centers country wide, in line with the terms of reference, pharmacovigilance indicators including current legislation and guidelines.

i. To encourage conduct of medicines utilization studies.

j. To be an active participating member of the WHO International Drug Monitoring Programme through the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Uppsala, Sweden. The WHO headquarters is responsible for all policy issues relating to the WHO Drug Monitoring Programme whilst UMC focuses on technical issues and the day to day running of the WHO Programme.

k. Reporting ICSRs to the WHO medicines safety database; VigiBase and sharing safety data for analysis and signal detection.

l. Conduct surveillance of AEFI, classification of causality of AEFI as per the WHO Aide-memoire on Causality Assessment of AEFI, 2013.

4. PHARMACOVIGILANCE METHODS

Several methods can be used to collect safety information in pharmacovigilance. In all national pharmacovigilance systems, spontaneous reporting forms the bedrock of the system despite its well-known limitation of under-reporting. It is relatively inexpensive and provides a life-time monitoring of all medicines in all patients in any healthcare system. There are other systems including active patient follow-up e.g. Cohort Event Monitoring (CEM). Brief highlights of the various pharmacovigilance methods are given below (adapted from the ICH E2E Guidelines. The full document can be downloaded from the ICH website using this link

http://www.ich.org/products/guidelines/efficacy/efficacysingle/article/pharmacovigilance planning.html

Pharmacoepidemiologic studies provide valuable information about the health effects of healthcare products, Guidelines for Good Pharmacoepidemiology Practice, 2015.

4.1 Spontaneous Reporting

Spontaneous reports are those adverse drug events/reactions that are voluntarily reported either to pharmaceutical manufacturers, to national or regional pharmacovigilance centers, or to national regulatory authorities by healthcare professionals, other professionals or consumers (ICH definition). Spontaneous reporting is sometimes referred to as passive reporting. A spontaneous report is an unsolicited communication by health-care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme (WHO definition). It is designed to detect ADRs not previously observed in preclinical or clinical studies, to improve understanding of the potential risks, including reactions resulting from medicines interactions or effects of medicines in particular populations, and to help provide a basis for effective medicines regulation, education and consequent changes in practices by prescribers and consumers.

Spontaneous reporting is the most common method of surveillance worldwide. It has played a major role in the identification of safety signals throughout the marketed lifetime of medicines in general. It is the easiest system to establish and the cheapest to run. However, reporting is generally very low and subject to strong biases; and there is no database of all users or information on overall medicine utilization. It is possible to identify risk factors with spontaneous reports, however it is not possible to calculate incidence and compare safety profiles of difference medicines. A new term has been introduced that will replace “spontaneous reports”: this is individual case safety reports (ICSRs). ICSRs play a major role in the identification of signals of risk once a medicine is marketed. ICSRs can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs.

4.2 Case Series of Spontaneous Reports

Series of case reports can provide evidence of an association between a medicine and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between medicine exposure and outcome. There are certain distinct adverse events known to be associated frequently with drug therapy, such as anaphylaxis, aplastic anaemia, toxic epidermal necrolysis and Stevens Johnson syndrome. Therefore, when events such as these are spontaneously reported, it is important that pharmacovigilance centres place emphasis on these reports for detailed and rapid follow-up.

4.3 Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings), for new products or for limited time periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete information.

4.4 Targeted Spontaneous Reporting (TSR)

Targeted spontaneous reporting is a variant of spontaneous reporting. It focuses on detecting ADRs in a well-defined group of patients on treatment. Targeted spontaneous reporting (TSR) builds on the principles of both spontaneous reporting (described above) and cohort event monitoring (CEM, [described below]). Health professionals in charge of a well-defined group of patients would be sensitized to report specific safety concerns suspected to be medicine related. It provides a comprehensive monitoring method which is affordable, feasible and sustainable in settings with limited financial and human resources and promotes the role of pharmacovigilance as a best practice that improves quality of care. This focused approach has the same objectives and flow of information as spontaneous reporting. The reporting requires no active measures to look for particular syndromes.

TSR may be adapted either to measure all adverse reactions in the defined population or to focus only on specific reactions of particular concern. It is suitable for monitoring of patients on ARVs, anti-TBs and other essential medicines. The monitoring of ADRs can be integrated as a standard of care, to accompany the routine practice of monitoring success, death, default or failure of treatment within the cohort. One benefit of monitoring for safety within a treatment cohort is that the number and profiles of the exposed patients are known. To measure the burden of medicine related problems accurately, recording and reporting of observed events needs to be as complete as possible.

4.5 Active Surveillance

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is achieved by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. It is best done prospectively. Active pharmacovigilance is sometimes very descriptively referred to as “hot pursuit”. The most comprehensive method is the cohort event monitoring (CEM). It is an adaptable and

powerful method of getting good comprehensive data. Other methods of active monitoring include the use of registers, record linkage and screening of laboratory results in medical laboratories.

4.6 Cohort Event Monitoring

CEM is a prospective, observational, cohort study of adverse events associated with one or more medicines. An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment. CEM is sometimes referred to as prescription event monitoring (PEM), but this term is inappropriate when individual prescription with subsequent dispensing by pharmacists is not part of the process of supplying medicines to patients. In most resource limited countries, the treatment of TB and other important diseases is not provided on a prescription basis. A CEM programme is essentially an observational study in normal clinical practice of a new medicine in the early post-marketing phase, but it can be used for older medicines. Its basic function is to act as an *early warning system* of problems with new medicines, although it will provide much more information.

CEM records all clinical events and not just suspected ADRs. It involves actively and systematically asking for reports of any and all events and provides a method that facilitates reporting. An event is any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgment on its causality. Favorable events may be recorded as an indication of an unexpected therapeutic effect.

4.7 Prescription Event Monitoring (PEM)

Prescription event monitoring is a method of active pharmacovigilance surveillance. In prescription event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

4.8 Sentinel Sites

Active surveillance can also be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient sub-groups that would not be available in a spontaneous reporting system. Further, information on the use of a medicine, such as abuse, can be

targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.

4.9 Registries

A patient registry is a list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry), a specific exposure (medicines registry) and death (death registry). In each type of registry, information can be collected through a battery of standardized questionnaires in a prospective fashion.

4.10 Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. A number of observational study designs are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

4.11 Cross-Sectional Study

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

4.12 Case-Control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or 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 disease in the two groups.

4.13 Cohort Study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicine at one time during followup, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving medicines exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. 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 of interest or to study very rare outcomes.

4.14 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. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicine in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

4.15 Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with medicine exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

4.16 Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

4.17 Drug Utilization Study

Drug utilization studies (DUS) describe how a medicine is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

5. REPORTING OF ADVERSE DRUG REACTIONS (ADRs) BY HEALTHCARE PROFESSIONALS, PATIENTS AND CONSUMERS

5.1 Reporters of Suspected ADRs

All health care workers, including doctors, dentists, pharmacists, nurses, other health professionals and the patients are requested to report all suspected adverse reactions to medicines (including vaccines, X-ray contrast media, complementary medicines), especially when the reaction is unusual, potentially serious or clinically significant. It is vital to report an adverse drug reaction to the Medicines Control Authority of Zimbabwe pharmacovigilance programme even when all the facts are not available or there is uncertainty that the medicine definitely caused the reaction.

Adverse drug reaction reports do not constitute an admission that a health professional contributed to the event in any way. The outcome of the report, together with any important or relevant information relating to the reaction that has been reported, will be sent back to the reporter as appropriate. The details of the report will be stored in a confidential database. The name of the reporter or any other health professionals named on a report and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. The information obtained from the report will not be used for commercial purposes. The information is only meant to improve understanding of the medicines used in Zimbabwe.

5.2 Reporting a Suspected ADR

5.2.1 Obtain Patient History and Do a Proper Examination

a. A full medicine and medical history should be done.
b. Determine if the adverse reaction can be explained by other causes e.g. patient's underlying disease, other medicine/s, over-the-counter medicines or complementary medicines; toxins or foods
c. The patient should be appropriately investigated to decide what the actual cause of any new medical problem is. A medicine-related cause should be considered, especially when other causes do not explain the patient's condition.
d. Few medicines produce distinctive physical signs. Exceptions include fixed medicine eruptions, steroid-induced dermal atrophy, acute extra pyramidal reactions
e. Laboratory tests are especially important if the medicine is considered essential in improving patient care or of the lab test results will improve management of the patient
f. Try to describe the reaction as clearly as possible and where possible provide an accurate diagnosis.

5.2.2. Establish Time Relationships

a. Some reactions occur immediately after being given a medicine while other reactions take time to develop.
b. The time from the start of therapy to the time of onset of the suspected reaction must be logical.

5.2.3. Dechallenge and Rechallenge (when necessary)

a. Resolution of suspected ADR when the medicine is withdrawn is a strong, although not conclusive, indication of medicine-induced reaction.
b. In cases where a withdrawal reaction is experienced, a rechallenge is when the medicine is again given to the patient. Rechallenge is only justifiable when the benefit of re-introducing the medicine to the patient outweighs the risk of recurrence of the reaction. This is rare. In some cases the reaction may be more severe on repeat exposure
c. "Positive" dechallenge is resolution of an ADR after withdrawing the medicine.

5.2.4 Check the Known Pharmacology of the Medicine.

a. Is the reaction known to occur with the particular medicine as stated in the package insert or other reference?
b. If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine.

5.2.5 ADRs Reportable to the MCAZ

a. All suspected adverse events regardless of severity

5.2.6 Reportable Product Quality Problems to MCAZ

a. Suspected contamination
b. Questionable stability
c. Defective components
d. Poor packaging or labeling
e. Therapeutic failures

5.3 Characteristics of a Complete Case Report

Complete case reports include the following elements:

a. Description of the adverse events or disease experience, including time to onset of signs or symptoms;
b. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;
c. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use

of concomitant medications, relevant family history of disease, and presence of other risk factors;

d. Documentation of the diagnosis of the events, including methods used to make the diagnosis;
e. Clinical course of the event and patient outcomes (e.g., hospitalization or death)
f. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
g. Information about response to dechallenge and rechallenge; and
h. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, a complete case report also includes full descriptions of the following, when such information is available:

a. Products involved (including the trade (proprietary) and generic name, manufacturer, dosage form, strength, concentration, and type and size of container);
b. Sequence of events leading up to the error;
c. Work environment in which the error occurred; and
d. Types of personnel involved with the error, type(s) of error, and contributing factors.

A medication error form should be completed and submitted to the MCAZ.

5.4 Minimization of Occurrence of Suspected ADRs

Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines that are described as follows:

a. Use few medicines, whenever possible
b. Use medicines that you know well
c. Do not change therapy from known medicines to unfamiliar one without good reasons.
d. Use text books and other reference material providing information on medicine reactions and interactions.
e. Take extra care when you prescribe medicines known to exhibit a large variety of interactions and adverse reactions (anticoagulants, hypoglycemic, and medicines affecting the CNS) with careful monitoring of patients with such reactions.
f. Beware of the interaction of medicines with certain food stuffs, alcohol and even with house hold chemicals.

g. Review all the medicines being used by your patients regularly, taking special notice with those bought without prescription (over the counter, complementary).

h. Be particularly careful when prescribing to children, the elderly, pregnant and nursing women, the seriously ill and patients with hepatic and renal diseases. Careful ongoing monitoring is also essential in these patients.

i. If the patient shows signs and/or symptoms not clearly explained by the course of their illness, think of adverse drug reaction.

j. If you suspect an adverse reaction, consider stopping the medicine or reduce the dosage as soon possible and please report the adverse drug reaction to the Medicines Control Authority of Zimbabwe.

5.5 When to Report Suspected ADRs and ADR reporting tools

An ADR report should be submitted to the MCAZ, as soon as possible after the reaction but in no case later than 15 calendar days of knowledge of the information. To report an ADR, the MCAZ e-ADR reporting platform http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting should be used. Once submission is made on-line, the e-ADR form (Annex 1) is received by the MCAZ. A standard ADR reporting form can also be completed (Annex 2), and submitted to the MCAZ. It is better not to wait until final results and information such as hospital letters are received, because the report may be forgotten. These additional details can be sent to the MCAZ later. Please note that the VigiBase database requires patient initials as a mandatory field, however patient full name is not required for confidentiality reasons. All ADR reports once submitted, are treated in an anonymous format. There are mandatory fields to be completed on an ADR form and the Uppsala Monitoring Centre developed the vigiGrade completeness score which is a measure of the amount of clinically relevant information in a structured format, which would not be reflecting whether the information establishes causality between the medicine and adverse event, Bergval *et al.* 2013.

5.6 Who Should Report

Reporters may be in the public or private health sector. They include physicians, pharmacists, and nurses. Other reporters include public health professionals, staff in medical laboratories and pathology departments, and pharmaceutical companies. Pharmaceutical companies should refer to chapter 10 of this policy handbook. Health and community workers (who are literate) should be encouraged to report, preferably to the clinician who prescribed the treatment, or directly to the MCAZ. Consumers, patients or patient representatives may also report using the e-ADR form or the standard ADR reporting form.

5.7 Follow-Up

All reports of serious events should be followed up if details are incomplete. This may require the involvement of health professionals in a clinical setting who have been trained and appointed for this type of work. Occasionally follow-up information is required to fully assess reports of non-serious events. Follow-up requests should be kept to a minimum as they can discourage further reporting. Examples of follow-up information might be: essential

missing details, information on the final outcome, the result of re-challenge, the results of laboratory tests, and post-mortem results from health facilities where autopsy is undertaken.

5.8 Feedback to Reporters

The pharmacovigilance centre will provide feedback to anyone who reports an ADR. Further feedback information will be provided to the reporter after causality assessment by the MCAZ PVCT Committee. The causality assessment classification for ADRs is classified as per the WHO Causality classification of Adverse Events definitions categories used by MCAZ and PVCT Committee (Annex 16).

5.9 Patient and Consumer Reporting of ADRs, SAEs and AEFIs

Direct and spontaneous patient reporting offers added value for pharmacovigilance in that it can speed up the acquisition of knowledge about adverse effects. Patient reports are more direct and often more detailed and explicit than indirect reports through health professionals.

Unlike reports from clinicians, they often describe how the adverse effects affect people's lives. Spontaneous direct reporting also has important benefits beyond pharmacovigilance: the patient becomes an active participant instead of a largely passive recipient of treatment, and in the process learns how to manage one's medicines and to communicate more effectively with health professionals. Lastly, public health estimates of disease burden in populations do not consider the effects on people's everyday lives, and they should.

For these reasons direct patient and consumer reporting of ADRs, SAEs and/or AEFIs should be encouraged and routinely incorporated in pharmacovigilance activities. The WHO published a guideline which included patient reporting, the WHO Draft Guidelines for Adverse Event Reporting and Learning Systems (WHO, 2005). To report an ADR or an SAE, the MCAZ e-ADR reporting platform http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting or standard ADR reporting form (Annex 2) should be completed and submitted to the MCAZ. An AEFI reporting form (Annex 12) should be completed to report an AEFI. An investigation should be conducted and an AEFI investigation form (Annex 13) completed and submitted for all AEFI cases that;

i. are serious cases (death/ resulted in hospitalization/ disability)
ii. belong to a cluster of AEFI
iii. are a previously unrecognized event associated with an old or newly introduced vaccine involves an increased number or rates of known cause
iv. are a suspected immunization error
v. appear on the list of events defined for AEFI surveillance
vi. cause significant parental or public concern.

Investigations are conducted by healthcare providers.

6. DATA ANALYSIS & MANAGEMENT OF ICSRs (ADRs, SAEs, AEFIs) AND THEIR CAUSALITY ASSESSMENT

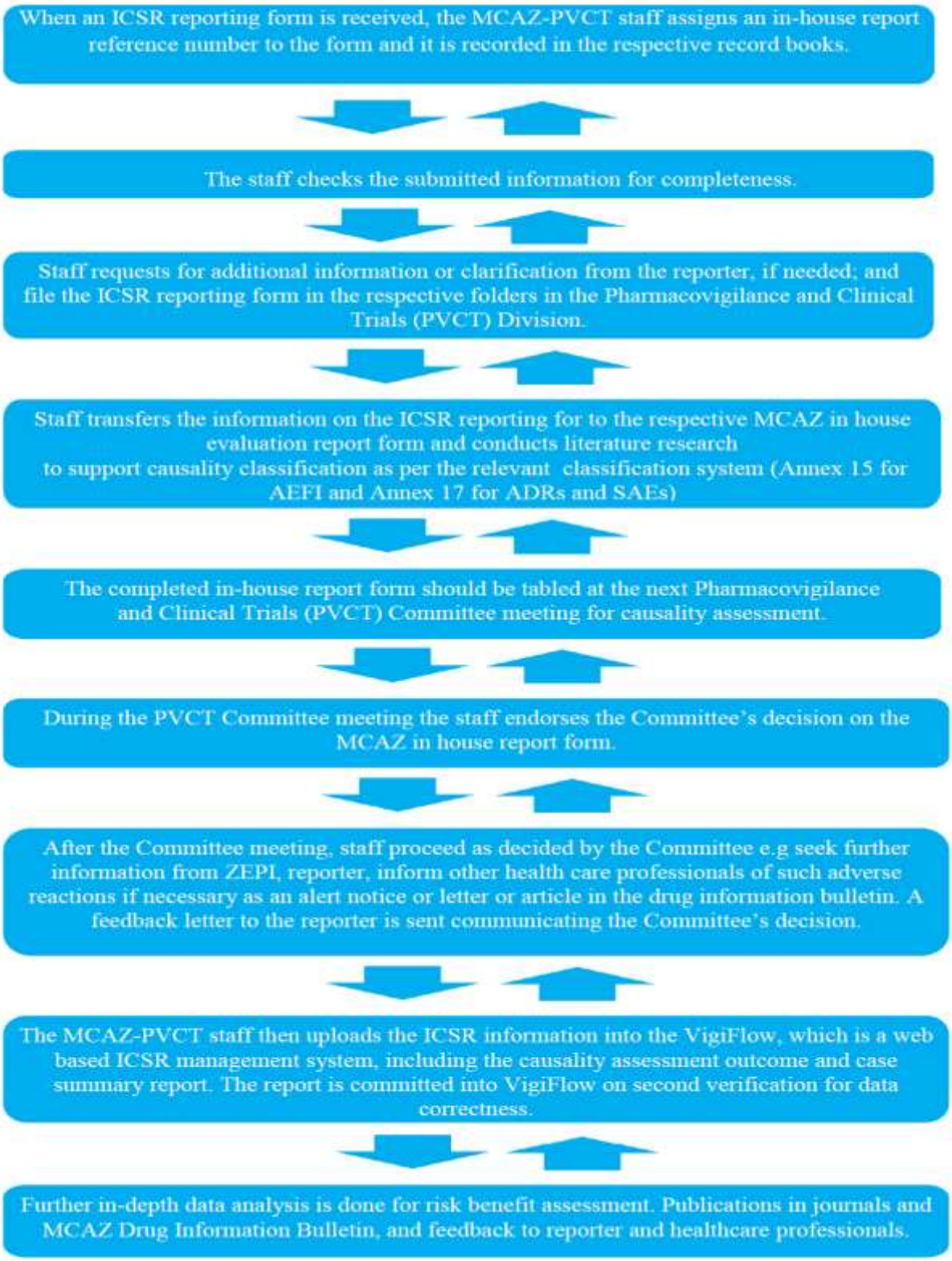
Upon receipt of a completed ADR/SAE/AEFI form an MCAZ officer assigns an in-house report reference number on it and checks the information on the report form for completeness. The officer then requests for additional information or clarification from reporter when necessary and uploads the report into VigiBase database.

The information on the suspected ADR/SAE/AEFI form is transferred to the MCAZ in-house report form and a case summary report is written which includes literature search and a recommendation of provisional causality.

The completed in-house report form is then tabled at the next Pharmacovigilance and Clinical Trials (PVCT) Committee meeting for expert causality assessment. During the PVCT Committee meeting, the Committee decision is endorsed on the MCAZ in house report from. After the Committee meeting, the MCAZ secretariat then proceeds as decided by the Committee e.g. seek further information from EPI-Ministry of Health and Child Care, inform other health care professionals of such adverse reaction if necessary as an alert notice or letter or article in the drug information bulletin. The MCAZ secretariat also writes acknowledgement and feedback letters to the reporter.

Causality classification for AEFIs is per the WHO Aide-memoire on AEFI Causality Assessment, 2013 (Annex 14). SAEs and ADRs causality classification is per the WHO Causality classification of adverse events definitions and categories used by the MCAZ and PVCT Committee meeting (Annex 16).

Figure 1. MCAZ Flowchart for ADR, SAE and AEFI Reports.



6.1 Causality Assessment of Suspected ADRs

There are several causality assessment tools used originally based on the Bradford-Hill criteria such as the WHO Aide-memoire, 2002, WHO Aide-memoire, 2013, the DAIDS causality assessment tool, the Bradford-Hill criteria etc.

6.1.1 The Bradford-Hill Criteria:

These are summarized below, with comments relating to pharmacovigilance.

a. **Strength:** A weak association does not mean that there is not causality but does weaken the case for common causality.
b. **Consistency:** Consistent findings observed by different persons in different places, with different samples, strengthen the likelihood of causality.
c. **Specificity:** Causality is more likely if the effect is observed in a very specific population at a specific geographic location and the disease has no other likely explanation.
d. **Temporality:** The effect has to occur after the cause and, if there is an expected delay between the cause and the effect, the effect must occur after that delay.
e. **Biological gradient:** A positive dose-response relationship strengthens the likelihood of a causal effect. With some interactions a negative dose response relationship may be suggestive.
f. **Plausibility:** A plausible mechanism between cause and effect is an indicator of causality, but not all medicine-effect mechanisms are known.
g. **Coherence:** Evidence from clinical laboratory or clinical pathology increases the likelihood of causality, but the same issue applies as in point 6: such evidence may be unavailable.
h. **Experiment:** Other experimental evidence such as animal studies may be supportive.
i. **Analogy:** The effect of similar factors may be important, such as class effects of medicines.

6.2 Difficult to Categorize Events

6.2.1 Deaths

Relationships to death cannot be coded as probable or certain because there is no opportunity to see the effect of dechallenge or rechallenge. Death is however not considered as an ADR, but rather considered as an outcome. The events preceding death should be outlined in the ADR report. If there is a plausible time relationship and other causes can be excluded, a relationship to death should be coded as possible. If there is no plausible time to onset and other causes are evident, then the relationship should be coded as unlikely. If there is doubt, then they should be coded as unclassified and they can be reassessed as a group after an epidemiological analysis.

The causality classification of AEFIs has has been adapted from *Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance*, as per the WHO Aide-memoire on AEFI Causality Assessment, 2013 (Annex 14). There are four main classes which are; consistent causal association to immunization, indeterminate, inconsistent causal association to immunization (coincidental) and unclassifiable. When there is no strong evidence for other causes, a known causal association with the vaccine/vaccination and the AEFI was within the time period of increased risk the AEFI is classified in the class "consistent causal association to immunisation". An inconsistent causal association to immunization is identified as the causality assessment class when there is an inconsistent causal association to immunization and there is a strong evidence against a causal association. When the review of other qualifying factors suggest the AEFI is not classifiable, the causality assessment class is "unclassifiable". When the conclusion is "unclassifiable", the reviewers should determine the reasons why classification was not possible and all attempts should be made to obtain the necessary supporting evidence for classification. The association is considered "indeterminate" when adequate information on the AEFI is available but it is not possible to assign it to any of the definite AEFI causality assessment classes.

6.2.2 Developing a Case Series

MCAZ suggests that sponsors initially evaluate a signal generated from post-marketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as MCAZ's Adverse Drug Reporting System or AEFI's. As part of the case-level review, the MCAZ suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, MCAZ recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

a. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
b. Absence of symptoms related to the event prior to exposure;
c. Evidence of positive dechallenge or positive rechallenge;
d. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
e. Consistency of the event with the known effects of other products in the class;
f. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and
g. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. MCAZ recommends that sponsors carefully evaluate these cases and not routinely exclude them.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event. MCAZ suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, MCAZ recommends that sponsors report all known contributing factors that led to the event.

6.3 Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, MCAZ recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

a. The clinical and laboratory manifestations and course of the event;
b. Demographic characteristics of patients with events (e.g., age, gender, race);
c. Exposure duration;
d. Time from initiation of product exposure to the adverse event;
e. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
f. Use of concomitant medications;
g. Recreational habits such as smoking, alcohol etc.
h. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
i. The route of administration (e.g., oral vs. parenteral);
i. Lot numbers, if available, for products used in patients with events; and
j. Changes in event reporting rate over calendar time or product life cycle

6.4 Safety Signals That May Warrant Further Investigation

It is not possible to characterize all events definitively because the actual risk to patients cannot be known and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, number of patients exposed to the medicine, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

a. New unlabeled adverse events, especially if serious;

b. An apparent increase in the severity of a labeled event;

c. Occurrence of serious events thought to be extremely rare in the general population;

d. New product-product, product-device, product-food, or product-dietary supplement interactions;

e. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co- morbidities);

f. Confusion about a product's name, labeling, packaging, or use;

g. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);

h. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a Risk MAP goal) and

i. Other concerns identified by the sponsor or MCAZ.

6.5 Signal Detection

6.5.1 Signal Identification-General Approach

A signal is defined as "Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously" (WHO definition).

Usually more than a single report is required to generate a signal, depending on the seriousness and the quality of the information. The publication of a signal usually implies the need for some kind of review or action. Alternatively, several similar events have been identified with a strong relationship to a medicine ("certain" or "probable") and there does not seem to be good evidence anywhere of these events being recognized as a signal. Events coded as "possible" can be used as supporting evidence. A group of unexpected deaths coded as "possible" forms an exception to this general rule and will need to be taken seriously. Occasionally a single event (certain or probable), notable for its severity, seriousness or distinctiveness, can be regarded as a signal. There may be one or two case-reports in the literature, but this is insufficient as validation and the signal needs to be strengthened. Causality assessment varies over time as it is dependent not only on the information in a report but also on our knowledge of the medicine. As this knowledge increases over time, causality assessment of the same report might vary. Causality of previously assessed reports needs to be reviewed when signals are being investigated.

The identification of signals in the national pharmacovigilance centre's database, or another database, of adverse events or suspected adverse reactions requires careful review of individual reports and events. Careful, informed, routine, systematic and standardized clinical review of the centre's reports with the recording and appropriate collation of good data provides the quickest and most satisfying way of identifying previously unsuspected adverse

reactions. Following through the whole process from relationship assessment, to signal identification, to signal strengthening, to communicating the findings is essential.

It is important to stress that new pharmacovigilance systems may have very few reports and may not be able to detect signals. It is therefore important for them to follow closely what is going on in other centres and also to rely on the WHO Pharmaceuticals Newsletter and UMC's Signal document to keep abreast of signals that may be of importance to them. International collaboration is always key to both signal identification and signal strengthening and should be encouraged including use of the WHO VigiBase database.

The data in the report(s) need to be of good quality if a signal of a new ADR is to be considered. There should be sufficient data to fully assess the relationship of the medicine to the event. A well documented report might lead to all degrees of causality: the good quality will simplify the process and ensure that the assessment is more reliable. The strongest signals will have several reports with a certain or probable relationship. According to the WHO, a signal may possibly be identified from one distinctive "certain" report. If there are no "certain" reports, at least three "probable" reports would be necessary for a signal. Causality "certain" is very rare. "Index cases" are fully documented cases with no confounders. Signal detection should follow a recognized methodology, which may vary depending on the type of medicinal product it is intended to cover, and detailed guidance on methods of signal detection may be found in the Report of CIOMS Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) and in the Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System.

The "unlikely" events should be scrutinized on a regular basis because they may contain hidden or unrecognized reactions. A cluster of similar events of significance may suggest an unexpected reaction that was not recognized at the time of clinical assessment. However, they should not be included in the assessment of a signal for which there are reports with certain, probable or possible relationships because differences could mask the characteristics of the signal being investigated.

6.5.1.2 Reviewing Other Experiences for Detection of Signals

Are there other similar reports in the database? Look for related clinical events for the suspected medicine and not simply a single event term. Also, look at related medicines in the same ATC classification grouping. Search the worldwide database of suspected adverse reactions of the WHO Collaborating Centre (UMC). The IC value for a medicine–event combination can be requested for by the National Centre from the UMC. If no reports can be found in VigiBase, ask for information held by other National Centres through the Vigimed e-mail network coordinated by UMC. Search the literature for similar reports, using search tools such as PubMed or Micromedex. Ask the pharmaceutical company if they have received similar reports and ask for details. Were similar events identified in clinical trials? (Search the literature and/or ask the company for reports of clinical trials of the medicine)? Were similar events identified in preclinical studies? (Ask the pharmaceutical company.) Has

this event, or have any similar events, been identified in post marketing cohort event monitoring (ie. prescription event monitoring) studies?

6.5.2 Selection Criteria for Events to Investigate for Signal Detection.

a. There is good data
b. The event is clinically relevant
c. There have been several reports of the event that show a credible and strong relationship with the medicine (certain/probable)
d. What do we know about the medicine itself?
e. What do we know about the way it is used?
f. What do we know about similar medicines (class effects)
g. Is there a reasonable causal relationship between the medicine and reaction in the case reports?
h. If validated, the event is of sufficient importance or interest to:
    - require regulatory action, e.g. labelling amendment;
    - require advice to prescribers;
    - be of scientific importance

6.5.3 Methods of Signal Detection

The main methods of identifying signals are:

a. Clinical assessment of individual events
b. Clinical review of collated events
c. Record linkage
d. Automated signal detection.

Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the identification of medicine-ADR pairs that might warrant further evaluation. Data mining simply identifies medicine-ADR combinations that have been reported more often than expected when compared to the whole database. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate between different medicines and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

Signal detection for AEFIs will be done as per the WHO Causality Assessment of an adverse event following Immunization (AEFI), User Manual for the revised WHO Classification, 2013.

6.5.4 Signal detection in low to medium income countries

The expected achievements of pharmacovigilance systems include to;

i. Identify medicines-related harm to patients exposed to medicines
ii. Identify risk factors and prevent harm to future patients
iii. Spontaneous reporting the easiest and cheapest method for collection of data

It is important to have realistic expectations of possible achievements and to avoid frustration among staff and maintain support from politicians, administrators and funders.

Figure 2. UMC signal detection process

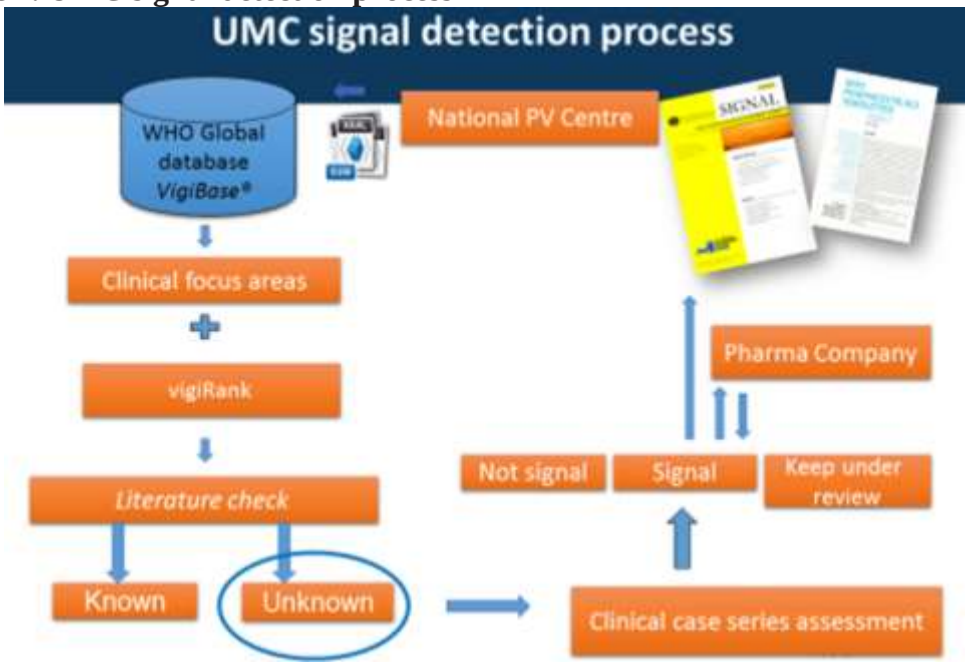


Figure 2. adapted from a UMC presentation

Figure 3. Graph stratifying the number of ADR reports received by the UMC

Figure 3. adapted from a UMC presentation

Signals from the WHO programme

The signals are based on data from developed countries and are primarily relating to medicines new on the market in those countries. They are relatively rare reactions since more common problems are identified earlier in the reporting chain by major national PV systems. Very few signals are relevant to low and middle income countries, as very little data is obtained.

6.6 Analysis of AEFI Data

The analysis of AEFI data is different to the analysis of ADR and SAE data. The Global Manual on surveillance of AEFIs, WHO 2014 details that immunization and vaccine safety surveillance should incorporate inbuilt mechanisms for structured, systematic and continued data collection. Epidemiological analysis of data is required to measure the impact of vaccines used in the country immunization programme and to disseminate findings to advise programme managers, and other stakeholders including manufacturers, WHO 2014.

The MCAZ analyses AEFI data as per the WHO Global Manual on surveillance of AEFI and consider the following:

a. reporting source (reports of AEFI by different sources may provide a wider range of information);
b. completeness of submitted AEFI forms;
c. verification and reassurance of data accuracy;
d. identifying health institutions where AEFI are not reported (determining whether this is due to failure of reporting or whether there are no AEFI to be reported) and checking on “zero reporting” or “nil reporting”;
e. performance of causality assessment to classify the AEFI;
f. estimated AEFI reporting rates (assessing the number of reported AEFI and the rate per 1000, 10 000 or 100 000 doses of vaccine used in a specified time period);
g. estimated rates by type of AEFI and by antigen (assessing the number of causes

specific reported AEFI and the rate for 1000, 10 000 or 100 000 doses of vaccine used in a specified time period);

h. comparison of these observable rates with available or expected known events, whether vaccine reactions or background rates or historic reporting trends.

The table below is extracted from the WHO Global Manual on Surveillance of AEFIs and explains the purpose of AEFI data analysis at different levels of the immunization safety surveillance system, the extent and purposes of analysis at each level.

Table 1. Purpose of AEFI data analysis at different levels

Programme implementation level	What data to analyse	Purpose of data analysis at given level
Local level (immunization provision level)	Number of reports by clinics, hospitals, villages by a given time	These are programme operation/surveillance performance indicators (timeliness, completeness).
	Reported AEFI by place (clinics, hospitals), persons and time	Identification of immunization error-related events will lead to corrective action.
	Reported AEFI by antigen	Will also identify vaccine reactions and coincidence.
Subnational level (regional/ provincial/ district/ town)	Number of reports by local levels	These are programme operation/surveillance performance indicators (timeliness, completeness) at local level.
	Reported AEFI by place (clinics, hospitals), persons and time	Identification of immunization error-related events will lead to corrective action.
	Cluster analysis	Cluster analysis leads to identification of immunization error related events, coincidence and vaccine reactions.
	Reported AEFI by antigen	Will identify vaccine reactions and coincidence.
National level	Number of reports by intermediate levels	These are programme operation/surveillance performance indicators (timeliness, completeness) at intermediate level.
	Reported AEFI by place (clinics, hospitals), persons and time	Cluster analysis leads to identification of immunization error related events, coincidence and vaccine reactions.
	Cluster analysis	Will identify vaccine reactions, including detection of signals.
	Reported AEFI by antigen	Leads to operational and policy decisions being taken in the country.

Table 1. Adapted from the WHO Global Manual on Surveillance of AEFIs, 2014.

The analysis of AEFI data is carried out by following four steps as outlined in the Global Manual on surveillance of AEFI;

Step 1: After verification of cases, all reported AEFI data is line-listed and entered into a data base. Line listing aides in the initial identification of clustering or any unusual or

significant reporting events that need further analysis.

Step 2: AEFI data is tabulated by place, person, time, antigens and type of event. This step further filters the AEFI by different variables and furthers analysis. It is possible to identify common immunization errors at this step.

Step 3: Calculation of AEFI rates, where the number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen at a given time period.

Step 4: Comparison and interpretation of AEFI rates. Expected vaccine reaction rates that are available for each type of AEFI and antigen (from WHO vaccine reaction information sheets) provide a guide to decision-making on corrective action for reported AEFI.

The full document can be downloaded from the WHO website using this link http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

6.7 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 health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use. To report any medication error to the MCAZ, a medication error reporting form (Annex 3) is to be completed ad submitted to the MCAZ. For AEFIs this is categorized as immunization error and it is reported on the AEFI reporting form (Annex 12).

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. Thus minimizing of medication errors, through early detection and clinical audit, is of paramount importance in healthcare by promoting compliance, adherence, recovery and the general well-being of patients.

6.7.1 Sources of Medication Errors

a. Incomplete patient information
b. Unavailable information on medicines (warnings)
c. Miscommunication of medication order
d. Confusion between medicines with similar names
e. Lack of appropriate drug labeling

f. Environmental conditions that distract health care providers
g. Wrong diagnosis (inappropriate therapy)

6.7.2 Most Common Medication Errors

a. Failure to adjust dosage in response to a change in hepatic/renal function
b. History of allergy to the same or related medication
c. Wrong medicine name, dosage form or abbreviation on order
d. Incorrect dosage calculation
e. Atypical or unusual critical dosage consideration

6.7.3 Medication Error Monitoring and Reporting Program Features

a. Evaluate the medication use process in collaboration with other health care professionals.
b. Establish a process for identifying and tracking medication errors.
c. Define categories of medication errors, e.g., prescribing, dispensing, administration, monitoring, compliance errors.
d. Simplify process for documenting errors by developing a medication error reporting and evaluation form.
e. Increase awareness of medication errors through education and the importance of reporting ALL medication errors, regardless of their suspected significance.
f. Establish systems for detecting medication errors in the facility and pharmacy, e.g. P method, random sampling, medication storage survey, etc.
g. Involve health care practitioners, patients, and care givers in the medication error detection and reporting process.
h. Re-emphasize the focus on the punitive aspects to encourage medication error reporting and focus on the improvement of processes and systems.
i. Respect the confidentiality of the patient, facility, and personnel involved with the medication error.

6.7.4 Role of the Pharmacist

6.7.4.1 Assessment

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

6.7.4.2 Prevention Strategies

a. 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.

b. Establish goals and measurable standards.
c. Monitor interventions and make necessary changes.

6.7.4.3 Reporting

a. Communicate the results of the medication error program to healthcare practitioners, patients, and care givers as appropriate and complete the medication error form (Annex 3).
b. Promote reporting of medication errors to a national system for review and analysis, which will result in the development of recommendations to reduce and prevent medication errors and provide bench marking data.

7. PRODUCT DEFECTS

7.1 Product Defect Reporting and Recall Procedures

The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization, including "Section 75 " medicines, and do not place the patient at risk because of inadequate safety, quality or efficacy.

When products are suspected of being potentially harmful to users due to their defective quality, safety or efficacy, they may be subjected to a recall and all related information must be reported to the Pharmacovigilance and Clinical Trial Division at MCAZ.

Complaints must be handled positively and carefully reviewed, and corrective actions must be taken as necessary. This can mean amending a manufacturing process as well as implementing a recall of a defective product from all markets where it has been distributed. This is a very difficult area requiring professional judgement in coming to the correct decision. The company should have procedures to call into operation to decide whether a recall is required and how quickly it should be implemented.

A recall situation may result from customer complaint, detection of GMP failure after release, result from the ongoing stability testing, request by the national authorities, result of an inspection, known counterfeiting or tampering, adverse reaction reporting, or the result from the QC stability programme.

Please note that any person, MAH, health professional, applicant who comes across a product defect is required to complete a product defect form (Annex 4).

The classification and level of recall will depend on the potential hazard of the defective product and the extent of product distribution. These are determined after consultation between the applicant and MCAZ. For the approved recall procedure, please refer to the MCAZ Guidelines for the Notification of a Medicinal Product Problem/Defect and Recall Procedure found on the MCAZ website http://www.mcaz.co.zw/index.php/downloads/file/75-guidelines-for-the-notification-of-medicinal-product-problem-defect-and-recall-procedure. A summary of the recall procedure is also available (Annex 5).

8. SUBSTANDARD/SPURIOUS/FALSELY LABELLED/FALSIFIED/ COUNTERFEIT MEDICAL PRODUCTS (SSFFCs)

Counterfeiting can apply to both branded and generic products; SSFFCs may include those with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging. Although the number of reported cases of SSFFCs – with their serious health repercussions, especially for the poor – continues to rise, the exact magnitude of the problem is unknown. Counterfeiting relates to expensive hormones, steroids and anti-cancer medicines, and pharmaceuticals related to lifestyle; in others, it may relate to inexpensive generic medicines. In developing countries, the most disturbing trend is the common availability of SSFFCs for the treatment of life-threatening conditions such as malaria, tuberculosis and HIV/AIDS. Experience has shown that vulnerable patient groups who pay for medicines out of their own pocket are often the most affected.

Counterfeiting is primarily motivated by its potentially huge profits. The success of counterfeiters is, at least in part, a function of their capacity both to adjust quickly to different contexts and products, and to change their focus of interest swiftly, according to where the most money can be made. Many factors facilitate the production or circulation of SSFFCs, including lack of equitable access to essential medicines; the presence of outlets for unregulated medicines; a lack of appropriate legislation; and weak penal sanctions.

The basic investigational elements of studies aimed at identifying the magnitude of the problem of counterfeiting in a national market are sound laboratory testing and verification of information available from national medicines regulatory authorities. Despite such measures, it is not always possible to trace the source of the problem. Close collaboration with the original manufacturers (which mostly use new technologies to identify their products unambiguously) and enforcement agencies (which use forensic means of analysis) has proved to be effective in tracing and fully identifying SSFFCs in recent years.

8.1 Reporting of Suspected Cases of Substandard and Counterfeit Medicines and Other Related Products

The MCAZ Licensing and Enforcement Division ensures good procurement practices and effective regulation of distribution chains, which closes opportunities for SSFFCs to enter the regular supply system. MCAZ initiates programmes for the prevention and detection of export, import and smuggling of falsely-labelled, spurious, counterfeit or substandard pharmaceutical preparations. Falsified medicines are more than simply substandard; combating falsified medicines is beyond the normal scope of regulatory control, as the manufacturer or distributor is usually difficult to trace. Combating falsified medicines is therefore a joint responsibility of the regulatory authority medical professional organizations, forensic investigation units, customs and other law enforcement agencies.

9. GUIDELINES FOR REPORTING SERIOUS ADVERSE EVENTS (SAEs)/ADVERSE EVENTS (AE)/ADVERSE DRUG REACTIONS (ADRS)/ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) FOR CLINICAL TRIALS IN ZIMBABWE

9.1 Responsibilities of Sponsors, Investigators, Applicants & Clinical Sites

In terms of Sections 23 and 24 of the Medicines and Allied Substances Control Act (Chapter 15:03), the applicant ie. investigator/researcher of a clinical trial is responsible for proper reporting of Serious Adverse Events (SAEs) to the MCAZ. The purpose of reporting SAEs is to ensure participant safety monitoring and to better understand the toxicity and safety of investigational products. Reporting and monitoring of SAEs is required to alert the MCAZ, sponsor, and clinical investigators of real and potential volunteer safety issues including safety information for the investigation product brochure. The MCAZ will carefully review the SAE Report and use this information to monitor the investigational product's toxicity profile and volunteer safety.

Serious adverse events data provide the MCAZ and investigators with an early toxicity profile of an investigational product. The toxicity profile is an early warning system of potentially serious events that may occur with the use of an investigational product. This information might also be used during the application for registration of a new medicine review to determine if a product is safe for marketing. If a product is approved the safety information reported by the clinical sites during the clinical trial phase of product development will have contributed to the "adverse reaction" section of the Product Package Insert.

All researchers are required to report SAE/AE/ADR/AEFI to the MCAZ using the e-ADR reporting platform found on the MCAZ website http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting. In the rare event that a researcher has no internet access, the joint MRCZ-MCAZ Serious Adverse Events (SAE) Form (Annex 6) must be completed and submitted to the MCAZ as soon as possible after the site becomes aware of an event. MCAZ may need to contact the clinical site for additional information regarding the SAE.

For fatal or life-threatening, unexpected events during clinical development, the Principal investigator is required to alert the MCAZ as soon as possible but no later than 7 calendar days after first knowledge by the investigator that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products. Serious, unexpected reactions that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the principal investigator that the case meets the minimum criteria for expedited reporting.

MCAZ will maintain all SAE reports confidential on file and in a regulatory database and provide feedback to the reporter.

9.2 General Information on SAE Reporting of Clinical Trials in Zimbabwe

Please refer to the current Good Clinical Trial Practice Guidelines in Zimbabwe, which available on the MCAZ website www.mcaz.co.zw

10. GUIDELINES FOR REPORTING SUSPECTED ADRs, SAEs AND/OR AEFIs BY THE PHARMACEUTICAL INDUSTRY (MARKETING AUTHORISATION HOLDERS (MAHs))

10.1 Scope

This guideline is intended to assist applicants in the reporting of ICSRs associated with the use of registered medicines ie. medicines that have attained marketing authorization in Zimbabwe, and in the management of safety data which arise during pre and post-marketing clinical trials.

For clinical development safety data, the principal investigator of a study is required to submit an SAE report as described on page 43. For post-approval safety data, expedited reporting of serious and unexpected ADRs is required as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the MAH. Cases of non-serious ADRs, whether expected or not, are also to be reported to the MCAZ.

For the purposes of this guideline, "**Authority**" refers to the Medicines Control Authority of Zimbabwe the terms medicine and drug are used interchangeably. The definition of medicines in the Medicines and Allied Substances Control Act include medicines, vaccines and other biological products, complimentary medicines and investigational medicines for clinical trials including investigational new drugs (INDs).

10.2 Legal Basis

The MCAZ made a mandatory policy in a MCAZ circular dated 21st March 2000, circular 4/2000 Reference B/279/35/9/2000 requiring all MAHs to report suspected ADRs, SAEs and/or AEFIs that occur in Zimbabwe. The MCAZ revised Statutory Instrument (SI) 150 of the Medicines and Allied Substance Control Act (Chapter 15:03) to include a mandatory requirement for applicants and MAHs to report suspected ADRs, SAEs and /or AEFIs that occur in Zimbabwe using the MCAZ e-ADR reporting platform that is E2B compatible. An alternative electronic E2B format that is compatible with the WHO VigiBase database may be used. The file format should be .xml, MAHs may send reports in E2B files via e-mail. Please note that the CIOMS reporting form will no longer be accepted since it complicates the management of ICSRs. It is not a requirement for MAHs to report ICSRs that occur outside Zimbabwe, unless the reports impact the benefit/risk profile of the medicine and changes to the safety data of the medicine are required. For the changes, the MAH is required to submit an application to amend/update the package insert safety information to the MCAZ. ICSRs of special interest may also be submitted to the MCAZ.

10.3 Periodic Safety Update Report (PSUR)

This is a periodic report produced by an applicant intended to provide an update of a worldwide safety experience of a medicinal product to the competent authorities at defined

times post marketing authorization. PSUR to be submitted to the MCAZ as part of the new chemical entity application for registration, Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable. Routine PSURs should **not** be submitted to MCAZ unless the safety quality and effectiveness profile of the product has changed. The changes should be highlighted by the MAH to the MCAZ in writing including the appropriate regulatory action taken already by the country of origin or other countries, or to be taken

10.4 Periodic Benefit Risk Evaluation Reports (PBRERs)

PBRERs to be submitted to the MCAZ as part of the new chemical entity application for registration Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable. PBRERs may however be required as justification for an application for a labeling amendment of Summary of product Characteristics (SmPC) or package insert or a change of indication or a new safety alert or concern for the product or as supporting information for the application for registration of a dossier if necessary as per the CTD format requirements

Routine PBRERs should **not** be submitted to MCAZ unless the safety quality and effectiveness profile of the product has changed. The changes should be highlighted by the MAH to the MCAZ in writing including the appropriate regulatory action taken already by the country of origin or other countries, or to be taken. Such changes in risk/benefit profile may be communicated to the Authority at the time of identification, as an Emerging Safety Issue.

10.5 Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan

For most products, routine pharmacovigilance (i.e., compliance with applicable post market requirements) is sufficient for post-marketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine post marketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information. The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. It is recommended that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

a. The likelihood that the adverse event represents a potential safety risk;
b. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
c. The severity of the event;
d. The nature of the population(s) at risk;
e. The range of patients for which the product is indicated (broad range or

selected populations only); and

f. The method by which the product is dispensed (through pharmacies or performance linked systems only).

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (Risk MAP). Pharmacovigilance plans may be appropriate for products for which:

a. Serious safety risks have been identified pre- or post-approval, or

b. At-risk populations have not been adequately studied. Sponsors may discuss with the Authority the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

a. Submission of specific serious adverse event reports in an expedited manner

b. Routine required reporting (i.e., as 15-day reports);

c. Submission of adverse event report summaries at more frequent, pre-specified intervals

(e.g., quarterly rather than annually);

d. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be

- medicines based: identifying adverse events in patients taking certain products,
- setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or
- event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure).

e. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs

f. Creation of registries or implementation of patient or health care provider surveys and

g. Additional controlled clinical trials.

10.6 Dear Healthcare Professional Letters and alert notices

Pharmaceutical industry may be required to write dear healthcare professional letters (DHCP) and/or alert notices, including update of the patient information leaflet depending on the nature of the medicine safety issue or product defect and/or recall. MAH are required to submit the DHCP letter to the MCAZ for approval prior to distribution.

11. INTEGRATION OF PHARMACOVIGILANCE IN PUBLIC AND PRIVATE HEALTH PROGRAMMES

11.1 Scope

The National Pharmacovigilance Centre was set up in 1994 by the MCAZ in collaboration with the University of Zimbabwe Medical School, Department of Pharmacy Drug and Toxicology Information Service (DaTIS) and the Ministry of Health and Child Care (MoHCC). The pharmacovigilance programme started with the system of spontaneous reporting as per the WHO minimum requirements for a National Pharmacovigilance Centre and then subsequently expanded to integrate pharmacovigilance in public health programmes. Since 2000 to date the EPI - MoHCC joined the spontaneous reporting programme and also conducted targeted spontaneous reporting of H1NI vaccine in 2010 to 2011 in collaboration with the MCAZ. The TSR of H1N1 was sponsored by the WHO and data analyzed using the WHO Paniflow database.

Many of the medicines used by these public health programmes are new and/or have safety concerns associated with them. Pharmacovigilance is effective and sustained if well integrated with regulatory function. Pharmacovigilance centers and public health programmes (PHPs) need to collaborate better to be able to quickly detect ADRs and act accordingly. This promotes confidence in the PHPs and the medicines that are introduced by properly managing with the ADRs. Below is a flow chart which shows how PV can be included in the PHPs. Feedback from patients to health workers at district level promotes increased spontaneous reporting, which increases knowledge. Polices can then be set up in timely fashion to make sure that the PHPs are successful and efficient.

Figure 4. Inclusion of PV in Public Health Programmes (WHO)

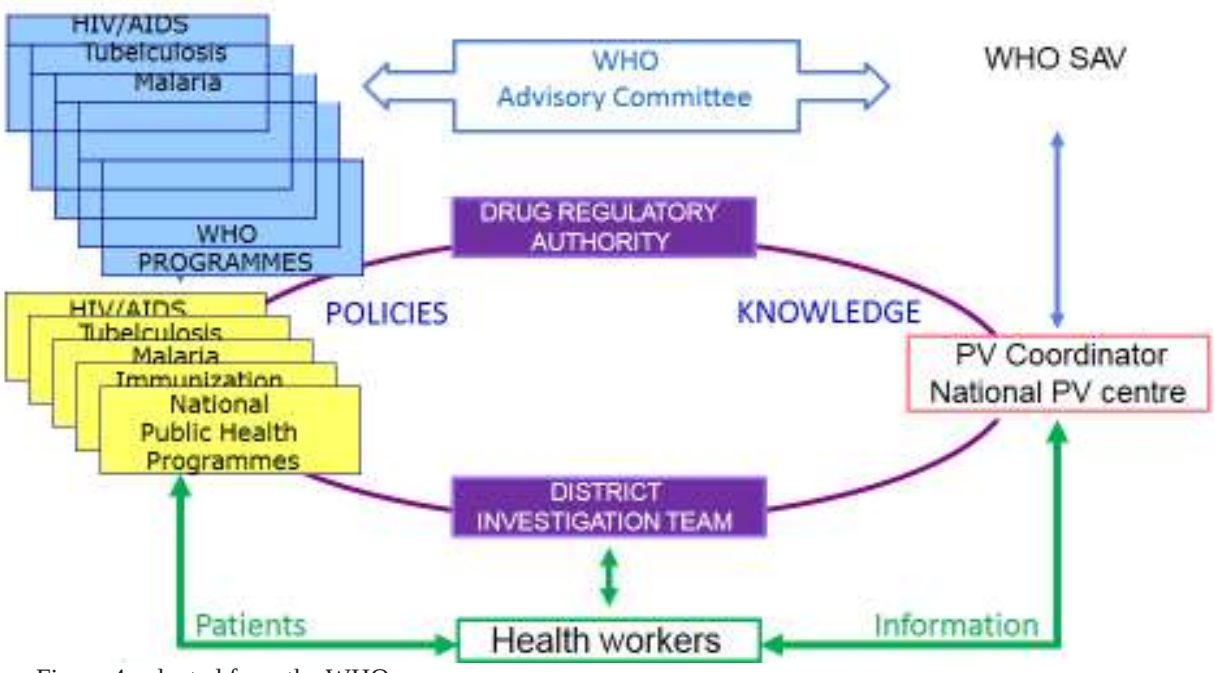


Figure 4. adapted from the WHO

Indicators are specific objective measures that allow the evaluation of the baseline situation and progress in systems and the assessment of services and interventions. Pharmacovigilance indicators are measures of inputs, processes, outputs, outcomes, and impacts of development projects, programmes or policies related to health systems and services. They provide information for measuring how well a pharmacovigilance programme is achieving its objectives.

Figure 5. The nine pharmacovigilance indicators for public health programmes

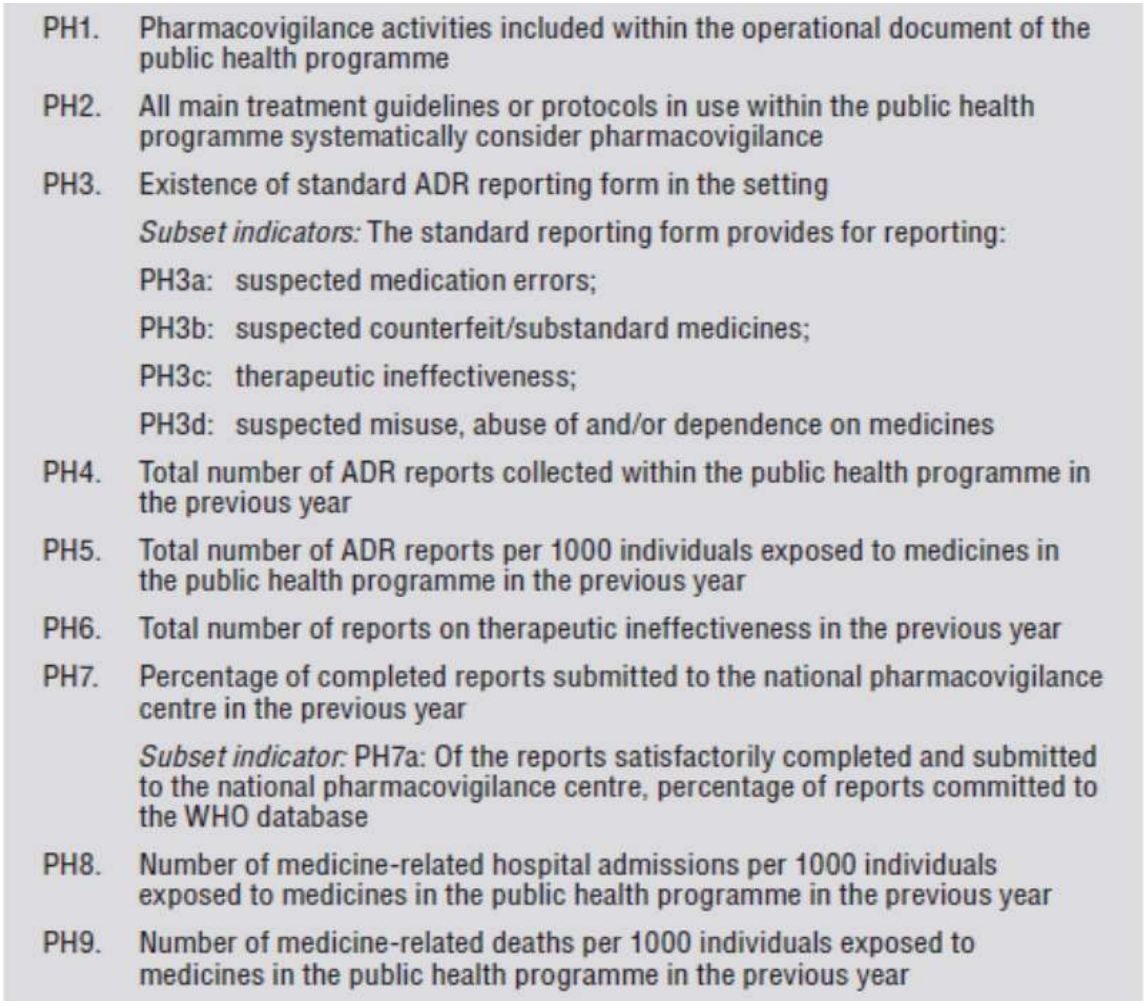


Figure 5. adapted from the WHO pharmacovigilance indicators, a practical manual for the assessment of pharmacovigilance systems, 2015

Integration of pharmacovigilance system with public health programmes, can result in better health outcomes as a consequence of good information on safety, which allows the early identification and prevention of adverse reactions, resulting in the more rational use of medicines, and better adherence within the target population.

11.2 Cohort Event Monitoring of Artemisinin Combination Therapies

The MCAZ as the National Pharmacovigilance Centre, in collaboration with the National Malaria Control Programme (NMCP), MoHCC conducted CEM for Artemisinin Combination Therapies (ACTs) for uncomplicated acute falciparum malaria, subject to confirmatory rapid diagnostic test (RDT) or microscopy testing from 2008 to 2015. The Global Fund Round 5 sponsored the CEM of ACTs program. The MoHCC formulated a new policy and introduced Artemether/Lumefantrine as first line therapy for confirmed malaria. In 2008 there was only one registered product in Zimbabwe for a fixed dose combination (FDC) of Artemether/Lumefantrine, known as Coartem®. The use of Coartem in Zimbabwe was still relatively new, with few countries having practical and long term experience with the use of this product, especially with regards to adverse drug reactions and events. The aim of CEM of ACTs was to monitor any adverse reactions or adverse events associated with Coartem following its widespread use in the Zimbabwean public health programme and to detect any signals of new previously unrecognised and unreported reactions due to ACTs in the general population in Zimbabwe. Eighty-four health facilities (sites) were which are in malaria endemic districts in five provinces, namely Mashonaland West, Mashonaland Central, Manicaland, Mashonaland East and Midlands were selected.

The CEM of ACTs was a success and the MCAZ is in the process of conducting close-out visits which will enable the sites to be further trained on TSR of all essential medicines including ARVs and Anti-TB medications. This will promote reporting of ADRs from the programme sites. The problems that marred the CEM of ACTs were noted to be that, it was very expensive, required adequate staff and follow-up tools such as cell phones and internet which were not readily available in Zimbabwe at the time. However, the MCAZ gained confidence to conduct active pharmacovigilance and has since increased its capacity to handle future CEM programmes with greater success.

A questionnaire-based survey was conducted to capture the experiences of countries that had implemented CEM for active post-marketing surveillance of antimalarial medicines in sub-Saharan Africa. The aims of this study were to describe the experiences of National Pharmacovigilance Centres (NCs) that have used CEM to monitor artemisinin-based combination therapy (ACT) for uncomplicated malaria in the African setting, to raise awareness of some of the challenges encountered during implementation and to highlight aspects of the method that require further consideration. A journal article published in the Drug Safety Journal, titled ‘Experiences and Lessons From Implementing Cohort Event Monitoring Programmes for Antimalarials in Four African Countries: Results of a Questionnaire-Based Survey’ outlines the study and its findings. It was concluded that the reported experiences in the survey indicated that CEM helped to build pharmacovigilance capacity within the countries’ pharmacovigilance centres and monitoring sites, and that healthcare professionals are generally willing to be involved in implementing the CEM method.

11.3 Targeted Spontaneous Reporting of Anti-retrovirals and Anti-tuberculosis

Following an invitation in October 2012 by the Secretary for Health and Child Care to strengthen pharmacovigilance of antiretroviral and antituberculosis, the MCAZ is currently conducting a program of Targeted Spontaneous Reporting (TSR) of Anti-retrovirals and Anti-tuberculosis medicines in collaboration with the MoHCC, AIDs and TB Unit, and Directorate of Pharmacy Services.

The pilot phase was conducted from October 2012 to September 2013 in seven provinces of Zimbabwe and indicated that the method was feasible and successful and resulted in scale up to the main phase from October 2013 to 2015. The results of the pilot phase of TSR of antiretrovirals and anti-tuberculosis medicines were presented at the 6th PVSF WHO-USAID meeting held in November 2013 in Accra, Ghana and at the First African Society of Pharmacovigilance held in December 2013 in Rabat, Morocco. The TSR of antiretrovirals and anti-tuberculosis was sponsored by the UNICEF, Health Trust Fund and Global Fund Round 8. Results of the Pilot phase of TSR of anti-retrovirals and anti-tuberculosis were also published in the MCAZ Drug Information bulletin and Drug Safety journal. The two active methods of pharmacovigilance, CEM and TSR, have assisted greatly in the integration of pharmacovigilance in public health programmes as per the WHO guidelines.

Objectives:

i. To use the TSR system in pharmacovigilance of essential medicines mainly anti-retrovirals, anti-tuberculosis, anti-asthmatics, anti-diabetes, anti-hypertensives anti-malarials and vaccines.
ii. To strengthen pharmacovigilance activities in Zimbabwe.
iii. Estimate prevalence of adverse drug reactions associated with use of essential medicines in Zimbabwe.
iv. To characterize known and unknown adverse reactions from essential medicines mainly anti-retrovirals, anti-tuberculosis, anti-asthmatics, anti-diabetes, anti-hypertensives and anti-malarials.
v. To assess the feasibility and impact of TSR on pharmacovigilance system in Zimbabwe
vi. To identify potential regional (sentinel) pharmacovigilance centres to work with the MCAZ National Pharmacovigilance Centre.
vii. To integrate pharmacovigilance into public health programs

Methods

The MCAZ, in collaboration with the Ministry of Health and Child Care (MoHCC) through the Directorate of Pharmacy Services (DPS) and AIDS and TB Departments are responsible for coordinating the program, training of sites, and collection of reports and data analysis.

Selection of sites

All public health care centres in Zimbabwe will be introduced to and trained on pharmacovigilance activities (Targeted Spontaneous Reporting of Essential Medicines). This scale up phase will involve intensive training of all provinces until all public health care centres in the country have been trained. Sites that were involved in the pilot phase (TSR of anti-TB and ARVs) will also be re-trained, and re-trained in the TSR main phase.

Target Population

Patients in the public and private health institutions receiving medical care using essential medicines including Anti – TBs and ARVs.

Data management and analysis

The MCAZ Pharmacovigilance and Clinical Trials (PVCT) Committee will analyse the data for causality assessment. The data will be entered into the VigiBase database (WHO recommended database), through the VigiFlow platform, analyzed and then published.

Monitoring and Evaluation

Quarterly monitoring and evaluation supportive visits to the sites will be carried out to provinces for feedback and collection of completed ADR forms. This will help in identifying the training needs of the staff at the sites, challenges being faced, and give an opportunity for training and re-training exercises to be done. The number of reports received and the quality of the reports will be monitored using the WHO-UMC VigiGrade Completeness score.

Results dissemination

The results will also be presented to the MoHCC - DPS, AIDS and TB Division including all MoHCC essential medicines programs in all the provinces countrywide, Pharmacovigilance and Clinical Trials Committee, National HIV/TB forum, MoHCC, project sites, and healthcare professional societies. A scientific article will also be published in a peer reviewed Journal.

11.4 Set up of pharmacovigilance regional or sentinel sites

Sentinel surveillance is the collection and analysis of data by designated institutions selected for their geographic location, medical specialty, and ability to report high quality data. Active surveillance can also be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient sub-groups that would not be available in a spontaneous reporting system. Further, information on the use of a medicine, such as abuse, can be targeted at selected sentinel sites. Generally, sentinel surveillance is very useful for answering specific questions, but because sentinel sites may not represent the general population or the general

incidence of disease, it may have some limitations in generalizing for national disease patterns and trends. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.

Centralised

De-Centralised

11.4.1 Regional or sentinels sites of pharmacovigilance are also being identified and set up countrywide for sustainable public health pharmacovigilance programs including use of Hospital Medicine Therapeutics Committees (HMTC) being established countrywide by the MoHCC since 2012. Zimbabwe's successful participation in the pharmacovigilance medicine safety initiatives in Africa was acknowledged when Zimbabwe hosted the 5th World Health Organization/USAID African Pharmacovigilance Consultants Meeting in Harare from 21st – 24th August 2012. The meeting was cosponsored by WHO and USAID and attended by Pharmacovigilance consultants from WHO, USAID and 15 African countries. The meeting recommended that for pharmacovigilance activities to continue to be successful in African countries, there was need for the countries through their national pharmacovigilance centres to improve the following:

a. **Collaboration with public health programmes**. There is increasing recognition that vertical programmes also need horizontal health systems for issues that are common to all disease programmes, including medicines safety. Disease control initiatives involving the administration of medicines to large communities need to be implemented with good knowledge of safety profile of the medicines and how these medicines could interact with each other. Pharmacovigilance should be a priority for every country with a public health disease control programme.
b. **Coordination and partnerships at country level.** The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the field of pharmacovigilance. Sustained commitment to such collaboration is vital for countries to meet the continually increasing demands and expectations of the public.
c. **Capacity building:** The third and possibly most important challenge was that new medicines are being introduced in a very rapid fashion into settings that have very

little capacity to monitor the safety and safe use of these medicines. Not only is there need to build capacity in pharmacovigilance in these settings, but there is also need to explore ways in which capacity could be shared in the region.

d. **Submission of Individual Case Safety Reports (ICSRs) or ADRs to the WHO International Drug Monitoring Programme** Of note of concern was that African countries only contributed about 2% to this data of 8 million ICSRs reports and that there was need for all African countries to improve their pharmacovigilance systems and frequency of reporting (ICSRs) to the WHO Monitoring programme.

e. **Collaboration with private health sector:** Private health sector clinics, hospitals including specialists and healthcare professionals are welcome to express interest to MCAZ, and participate as pharmacovigilance sentinel sites. Please note that terms of reference for PV regional sentinel sites apply to both the public and private health sectors.

12. PHARMACOVIGILANCE TRAINING AND PHARMACOVIGILANCE TOOLKIT

The safety of patients and the safe use of medicines are high priorities in the modern world. They are critical for the best health policy development and delivery of the best healthcare. They affect not only the welfare of patients but also the effective prevention and control of all kinds of diseases and the reduction of suffering and costs associated with them.

The Pharmacovigilance (PV) Toolkit is a package of simple PV tools and a description of supporting processes for the conduct of pharmacovigilance. It is targeted primarily at PV professionals in low and middle income countries, but is relevant everywhere PV is practiced. It provides the framework and support needed for the effective conduct of pharmacovigilance at local, regional, national and international levels. The Toolkit contents are endorsed by the WHO Advisory Committee on the Safety of Medicinal Products after the original text has been written and reviewed by global experts. The Toolkit is reviewed periodically to ensure that it is abreast with developments in PV.

The PV toolkit can be found on the following link: http://pvtoolkit.org

The pharmacovigilance toolkit aims to provide countries with a complete guide, tools and assistance to undertake comprehensive pharmacovigilance according to WHO guidelines and recommendations and in line with contemporary best practice. The toolkit include guidelines on methods, resources, crisis management, technical assistance, training courses providers and communication in pharmacovigilance. It also provides a means of monitoring and evaluating activities using a novel pharmacovigilance indicator that all countries can use to measure performance (WHO-UMC Pharmacovigilance Toolkit, 2014). There are disease specific toolkits and also a Vaccine PV toolkit. These toolkits are all found on the PV link shown above.

12.1 Disease-specific Toolkits

Disease specific toolkits were also developed in addition to the main PV Toolkit. These were designed for certain diseases and subgroups of people. The Malaria, HIV, and TB PV Toolkits were developed. These disease-specific toolkits should be used in combination with the main PV Toolkit.

12.2 Technical / Financial assistance and Training course providers

In pharmacovigilance, there are various stakeholders with specific and different interests requiring pharmacovigilance training. There is a growing need for pharmacovigilance capacity building, particularly by professional training through a broad range of high-quality pharmacovigilance courses with different focuses and different levels of detailing. For this

purpose, experts working in various fields of medicine safety around the world have co-operated to create a comprehensive, detailed and balanced curriculum of pharmacovigilance. Some are appointed members in PV committees associated with the World Health Organization (WHO) or work at its collaborating centres. Others are members of the Executive Committee of the International Society of Pharmacovigilance (ISoP) or its Education and Training Project (ETP) group, or work in institutions dedicated to pharmacovigilance (Ju¨rgen Beckmann et al, 2014).

In addition, the PV Toolkit provides information on organizations offering technical/financial assistance and training course providers. The list provided below is restricted to those organizations whose activities are aimed primarily to providing technical assistance to governments, organizations and centres in resource-limited settings and excludes those whose activities are aimed solely at the pharmaceutical industry. They are divided into Collaborating Centres, Financing Entities, Technical Agencies, Academic/Research Institutions and Consultants though the distinctions may be arbitrary in that some financing entities may directly or indirectly also provide direct technical assistance (Pharmacovigilance Toolkit, Version, 2.0; 2012).

12.2.1 WHO collaborating centres

Uppsala Monitoring Centre (UMC), WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, www.who-umc.org

WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, University of Medical School, Accra, Ghana, www.pvafrica.org

WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway
www.whocc.no

The WHO Collaborating Centre for Pharmacovigilance, Rabat, Morocco
www.capm.ma/sources_site_capm/pv_site_capm/pharmacovigilance_site_capm.htm

12.2.2 Financing entities

The Global Fund Against AIDS, Tuberculosis and Malaria, www.theglobalfund.org

The Bill & Melinda Gates Foundation, www.gatesfoundation.org

The World Bank, www.worldbank.org

The European Commission, http://ec.europa.eu/index_en.htm

The United States Agency for International Development (USAID), www.usaid.gov

The Global Alliance for Vaccines and Immunization, www.gavialliance.org

UNITAID, www.unitaid.eu

The Roll Back Malaria Partnership, www.rollbackmalaria.org

12.2.3 Technical agencies

Management Sciences for Health, Arlington, Virginia, USA, www.msh.org

University of Washington, Department of Epidemiology, USA
http://depts.washington.edu/epidem/fac/facBio.shtml?Stergachis_Andreas

Clinton Health Access Initiative, www.clintonfoundation.org

Medicines for Malaria Venture www.mmv.org

The RaPID Pharmacovigilance Initiative, www.rapidpharmacovigilance.org

12.2.4 Pharmacovigilance training course providers

WHO Headquarters www.who.int/

WHO-CC for International Drug Monitoring (UMC), www.who-umc.org

WHO-CC for Advocacy & Training in Pharmacovigilance / UMC-Africa (UMC-A)
www.pvafrica.org

WHO-CC for Pharmacovigilance
www.capm.ma/sources_site_capm/pv_site_capm/pharmacovigilance_site_capm.htm

Drug Safety Research Unit (DSRU), www.dsru.org/

International Society of Pharmacovigilance (ISoP), www.isoponline.org

International Society for Pharmacoepidemiology (ISPE), www.pharmacoepi.org

Drug Information Association (DIA), www.diahome.org/DIAHome/Home.aspx

European Medicines Agency (EMA), www.ema.europa.eu

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), www.ich.org

London School of Hygiene and Tropical Medicine (LSHTM), www.lshtm.ac.uk/

Swiss Tropical and Public Health Institute (Swiss TPH), www.swisstph.ch/

Spanish Medicines Agency, www.aemps.gob.es/vigilancia/medicamentosUsoHumano/home.htm

13. EFFECTIVE COMMUNICATION IN PHARMACOVIGILANCE

13.1 The ERICE Declaration on Effective Communication in Pharmacovigilance

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, medicines regulators, patients, lawyers, consumers and International health organisations from 30 countries of the world

Monitoring, evaluation and communicating medicines 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, medicines regulators, governments and international organisations – 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 medicines 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 medicines 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 medicines safety and 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 a) - e) set forth the basic requirements for this to happen, and were agreed upon by all participants from 30 countries in Erice:

a. Medicines safety information must save 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 medicines, including interpretation of safety information, is essential for the public at large as well as for the patients and health care providers. Such education requires special commitment and resources. Medicines 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 recognised and overcome.
d. Every country needs a system with independent expertise to ensure that safety information on all available medicines is adequately collected, impartially evaluated, and also made accessible to all. Adequate nonpartisan 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 medicines 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 recognised and efficiently dealt with, and that information and solutions are effectively communicated.

Health studies and reports are done to improve the quality, effectiveness and safety of healthcare in a country. Reports generated through pharmacovigilance plan/studies, provide evidence based information for healthcare practitioners, policy makers and ultimately to patients, with the ultimate goal of providing quality, safe and efficacious medicines and care to patients. Findings from these studies/reports need to be communicated and disseminated effectively to influence optimal and timely practice and healthcare policies. Clear communication and active dissemination of evidence based information to all relevant audiences in easy-to-understand formats are critical to increasing awareness, consideration, adoption and use of evidence based information. Strategies for information dissemination include media coverage, press release, research summary document, flyers, posters, brochures, research briefs, policy briefs, study newsletters, community agency publications and websites, local events, seminars, conferences, community meetings and letter of thanks to study patients, amongst others.

The safety of patients worldwide is served by dedicated professionals doing their work well, but that work will never reach its considerable potential without excellent supporting communications. Excellent communications require a degree of expertise, creativity and skill which not all officials and scientists have as a matter of course. In every organization there is likely to be someone with a communications gift: look for them and use them if you can; otherwise put communications on your regular agenda as a high priority and give the activity of communicating as much attention as the content of what you wish to communicate. Failure to pay attention to the complexity and demands of effective communication lies at the heart of many of the most serious failures throughout health-care and regulation.

13.2 Risk Management and Communication

This is one of the components of the Indicator-Based Pharmacovigilance Assessment Tool (IPAT); Manual for Conducting Assessments in Developing Countries, Strengthening Pharmaceutical Systems (SPS) Program 2009. The Risk Management and Communication component has ten indicators which are listed below and the purpose, rationale and evidence for each is also outlined.

13.2.1 Risk mitigation plans currently in place that are targeted at high-risk medicines

Purpose: To identify whether risk management plans (either formal ones or in the form of restricted prescription rights) exist or are planned for high-risk products.

Rationale and evidence: The U.S. Institute of Medicine estimates that at least 1.5 million preventable adverse drug events occur within the health system each year. The majority of ADRs can be prevented when clear plans exist for avoiding serious known risks of medicine. Some medicines are considered as high-alert or high-risk agents because they bear heightened
risk of causing significant patient harm when used in error. This indicator tries to identify whether any efforts are made from the national level or from the hospital management level(or HMTCs) to mitigate the impact of high-risk medicines.

13.2.2 Prequalification schemes (e.g., WHO prequalification program and Pharmaceutical Inspection Co-operation Scheme) used in medicine procurement decisions

Purpose: To identify whether opportunities provided by internationally recognized authorities, such as the WHO through the prequalification program and the Pharmaceutical Inspection Cooperation Scheme (PIC/S), are used to inform procurement of quality and safe products.

Rationale and evidence: When countries lack the capacity for manufacturing site inspection and for determining the quality of products they intend to procure, they can rely on prequalification certification issued by internationally recognized authorities such as the WHO through the prequalification program and the PIC/S.

13.2.3 Number of medicine safety information requests received and addressed in the last year

Purpose: To identify the number of medicine information requests received and addressed by the pharmacovigilance centre in the last year.

Rationale and evidence: User satisfaction increases and confidence in the pharmacovigilance centre improves when ADR or medicine safety information requests from clients are processed and responded to in a timely manner. This indicator gives a general idea about the use of the available service and the centre's responsiveness. A number of 100 requests per million population per year has been recommended as a threshold for a minimally functional centre.

13.2.4 Percentage of planned issues of the medicine safety bulletin (or any other health-related newsletter that routinely features ADR or medicine safety issues) published in the last year

Purpose: To identify whether regular issues of the bulletin are produced as originally planned.

Rationale and evidence: Many medicine information and pharmacovigilance centers may be able to initiate a medicines bulletin, but most experience challenges in the longer run in meeting their publication schedules and at times completely cease publishing due to various

constraints. This indicator helps track whether the bulletin is appearing as planned. For a bulletin or newsletter to be considered minimally functional, this tool recommends that at least 70 percent of planned issues must be published.

13.2.5 Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, or from regional or international sources) and acted on locally in the last year.

Purpose: To identify whether medicine safety issues of local relevance that are identified from outside sources, such as through global safety literature scanning, stimulate any form of local attention and plans for further evaluation.

Rationale and evidence: When a medicine safety issue of local relevance is identified through outside sources, such information provides an alert that should be further studied or acted on to ensure that related experiences from other places are used for improving local safety. Ideally, all global safety alerts of local relevance should be acted on (regulatory decision, communicated to health care workers, etc.); however, this tool recommends that at least 70 percent of such alerts should be communicated by a minimally functional system.

13.2.6 Number of "Dear health care professional" letters or other safety alerts developed and distributed in the last year

Purpose: To identify whether and how many regulatory alert letters were sent out in the last year (Distribution can be confirmed through review of documents).

Rationale and evidence: When new medicine safety issues arise either from spontaneous reports or from global safety literature scanning, relevant information and alert letters should immediately be sent to health care professionals to alert them of the safety concerns. Ideally, such alerts should be sent for all essential medicines in the country's essential medicines list. This tool recommends a threshold of 70 percent for a minimally functional system.

13.2.7 Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to health care workers and the public

Purpose: To identify how fast serious ADR signals and significant safety issues are communicated to health care workers and to the public

Rationale and evidence: New signals of serious ADR or significant safety issues should be communicated to health care workers and the public as soon as the signals are generated. Safety signals and significant safety issues can be generated either locally or through scanning the global literature for safety reports. Once these reports are obtained, locally relevant ones that are significant to in-country clinical practice and public health should be immediately communicated to health workers and the public. This indicator helps determine how fast such reports are communicated. The tool recommends that such communications should happen within three weeks of the publication of that alert in global literature.

13.2.8 Percentage of the sampled Drug and Therapeutics Committees (DTC) that have carried out pharmacovigilance activities or addressed medicine safety issues in the last year

Purpose: To identify how much of DTC (or HMTC) activities address safety of medicines

Rationale and evidence: Drug and Therapeutic Committees are critical for implementing efforts to improve medicine safety within health facilities. Interventions designed to improve medicine safety should include the participation of DTCs in the area. DTCs should have medicine safety as part of their terms of reference, and all DTCs ideally should carry out pharmacovigilance-related activities. The tool recommends that at least 70 percent of DTCs should address pharmacovigilance.

13.2.9 Number of public or community education activities relating to medicine safety carried out in the last year

Purpose: To determine the number of medicine safety–related public and community education activities carried out within the last year

Rationale and evidence: Public health education on medicine safety is important to ensure patients and caregivers are well informed on safety and effectiveness of the medicines they use. At least one formal community education activity on medicine safety should be carried out every year. Examples of community education activities include community medicines safety campaigns, radio talk shows, public health outreach campaigns, and other outreach programs.

13.2.10 Percentage of medicines sampled in the last year that passed product quality tests

Purpose: To determine the extent of problems in product quality

Rationale and evidence: When poor-quality products are identified, remedial actions should be taken to ensure that they are no longer in circulation. This indicator determines the extent of product quality problems among the medicines circulating in the country. When tracked longitudinally, the indicator also helps quantify whether the problem has increased or decreased over time.

14. REPORTING OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIs)

Immunization is a successful and cost-effective public health intervention that led to global eradication of diseases like smallpox and poliomyelitis in large areas of the world. It is estimated that immunization averts an estimated 2 to 3 million deaths from diphtheria, tetanus, pertussis (whooping cough), and measles every year in all age groups. Zimbabwe attained Universal Child Immunization in 1990 with considerable reduction in morbidity and mortality from vaccine preventable diseases and longer inter-epidemic periods of measles up to 2008.As Zimbabwe continues to adopt WHO recommended vaccination strategies in its population, it is becoming imperative that surveillance of AEFI be increased. The vaccine products and equipment used in immunization undergo intensive World Health Organization prequalification exercises to determine quality and approve their uses in countries. These precautionary measures do not necessarily eliminate the risk of adverse events that may arise from the use of products for immunization. Previous experiences have shown that determining causality of an event to a vaccine is a challenge that requires engagement of expert opinion and thorough investigation of the event. Events that occur after vaccination are called Adverse Events Following Immunization (AEFI); defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine, WHO 2013. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

The safety of immunization programmes involves a wide spectrum of activities that include regulation, vaccine safety and quality, safe injections, waste disposals, and AEFI surveillance. Effective vaccines (i.e. vaccines inducing protective immunity) may produce some undesirable side effects which are mostly mild and clear up quickly. The majority of events thought to be related to the administration of a vaccine are actually not due to the vaccine itself - many are simply coincidental events or programmatic errors. It is not possible to predict every individual who might have a mild or serious reaction to a vaccine, although there are a few contraindications to some vaccines. Adherence to contraindications minimizes the risk of serious adverse events. During mass immunization campaigns there usually is a general increase in adverse events following immunization. This can be attributed to two factors; the large number of vaccinations performed in a short period of time (from a few days to a few weeks) causes a temporary concentration of adverse events following immunization, and the pressure during the campaigns on vaccination teams means they may fail to observe safe injection practices. Public misconceptions may arise due to occurrence of AEFIs, and these may cause collective fear of vaccination. It is against this background that standardization and surveillance of adverse events following immunization is critical to enhance effective management of AEFIs. This document is a guide for health workers in the management of Adverse Events Following Immunization (AEFIs), can be adapted to suit

each level of health care, and is meant to cover issues of vaccine safety and quality, as well as communication of these events for management.

According to the WHO, case detection is the first important step in AEFI surveillance. The primary reporter (i.e. the one who first reports an AEFI) may be a field health worker, clinic or hospital staff, a volunteer, parent or any other person who detects the AEFI. The WHO recommends that suspicion alone is sufficient for reporting; the primary reporter is not expected to assess causality. In investigating suspected AEFIs, it is important that rapid detection and evaluation of a possible link to vaccines is carried out to ensure the continued safety of vaccines. The WHO Global Manual on Surveillance of AEFIs highlight that in the case of a suspected AEFI, it is preferable to submit a report to a suitable technical authority on time rather than waiting for all aspects of an investigation to be completed; and this is particularly true for serious reports.

To report a suspected AEFI, an AEFI reporting form is to be completed. Five forms are to be fully completed, dated, stamped and signed. One copy of the forms should be filed at the clinic and four submitted to the District level for onward submission of three of the copies to the Provincial level. The Provincial level would then forward two of the three copies to the Zimbabwe Expanded Programme on Immunization Unit, and from there one copy would be forwarded to the MCAZ. For serious AEFI a case investigation form is required to be completed, together with an AEFI reporting form, and submitted to the EPI-MoHCC and the MCAZ.

All events that are actively notified to the health care system by the parents/guardians or patients themselves or identified by a health care provider that are submitted to the MCAZ are assessed for causality according to the Causality Assessment of an AEFI, User Manual for the revised WHO classification, Aide-memoire 2013.

Zimbabwe documented 80 AEFI cases in 2010, 14 in 2011, 76 cases in 2012, 39 cases in 2013, 48 cases in 2014, 249 cases in 2015 and 11 cases by the 2nd quarter of 2016; most of which were known reactions. Documentation of AEFI cases is an essential part of AEFI management when they occur in children to augment other safety precautions that will have been taken, and do causality assessment and risk assessment.

Any AEFI that is of concern to parents or health-care workers should be reported. In particular, health workers must report:

a. serious AEFIs
b. signals and events associated with a newly introduced vaccine
c. AEFI that may have been caused by an immunization error

d. significant events of unexplained cause occurring within 30 days after vaccination
e. events causing significant parental or community concern.

14.1 Immunization Schedule For Children Under Five Years

Table 2: National Immunization Schedule In Zimbabwe For Children Under Five Years, as of May 2016

Age of Administration	Name of Vaccine	Route of administration
At birth	BCG	Intradermal deltoid muscle right arm
6 weeks	OPV 1	Oral
	Pentavalent 1	Intramuscular antero-lateral aspect of the right mid-thigh
	PCV 1	Intramuscular antero-lateral aspect of the left mid- thigh
	Rotavirus 1	Oral
10 weeks	OPV 2	Oral
	Pentavalent 2	Intramuscular antero-lateral aspect of the right mid-thigh
	PCV 2	Intramuscular antero-lateral aspect of the left mid-thigh
	Rotavirus 2	Oral
14 weeks	OPV 3	Oral
	Pentavalent 3	Intramuscular antero-lateral aspect of the right mid-thigh
	PCV 3	Intramuscular antero-lateral aspect of the left mid-thigh
	IPV	Intramuscular antero-lateral aspect of the left mid-thigh 2cm from the PCV 3 Site
9 months	MR 1	Subcutaneous on left upper arm
18 months	DPT Booster	Intramuscular antero-lateral aspect of the right mid-thigh
	OPV Booster	Oral
	MR 2	Subcutaneous on left upper arm

This is the only national immunization schedule to be used in Zimbabwe, for both private and public sectors. Please refer to future revised schedule, if any, after publication of these guidelines. Children should receive first doses at these stated ages **or** at first contact after reaching that age. Maximum age limits are: BCG 11 months, Rotavirus 32 weeks and Pentavalent 23 months (these antigens **should not** be given after these age limits).

Zimbabwe will be part of the global polio endgame countries that will work toward switching from tOPV to bOPV then IPV as stipulated in the Zimbabwe SWITCH plan timelines from 1st May 2016 to 2020.

14.2 VITAMIN A SUPPLEMENTATION

Vitamin A supplementation has been integrated in the routine immunization since 2005. Any contact with a health worker is an opportunity to screen mothers and children for eligibility to receive Vitamin A supplementation. The optimal interval between doses for children is every 6 months until 59 months, in Zimbabwe.

Table 3: Vitamin A supplementation schedule

Target for Vitamin A	Immunization Contact	Route	Dose
Infants 6 – 11 months	Routine immunizations/Campaigns	Oral	100 000 IU
Children 12 – 59 months	Routine immunizations/Campaigns	Oral	200 000 IU

14.3 Basics of AEFIs

14.3.1 Definition

An Adverse Event Following Immunization (AEFI) is any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. (WHO: Causality Assessment of an Adverse Event Following Immunization, 2013)

14.3.2 Types of AEFIs

In 2012, the Council for International Organizations of Medical Sciences (CIOMS) and WHO revised the classification regarding cause-specific categorization of AEFI. There are five cause-specific type AEFI namely; vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, immunization anxiety-related reaction and coincidental event.

14.3.2.1 Vaccine product-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine such as the adjuvant, preservative or stabilizer.

A vaccine product-related reaction, is an individual's reaction to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. Most often the exact mechanism of a vaccine product-related reaction is poorly understood. The reaction may be due to an idiosyncratic immune mediate reaction (e.g. anaphylaxis) or to

replication of the vaccine-associated microbial agent (e.g. vaccine-associated poliomyelitis following OPV which contains attenuated live virus). However, it is important to note that, among certain high-risk individuals, there is a higher probability of these rare vaccine product-related reactions which do not occur in the majority of vaccines (Global Manual on Surveillance of AEFIs -WHO, 2014).

14.3.2.2 Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.

A vaccine quality defect-related reaction, is a due to a defect in a vaccine (or its administration device) that occurred during the manufacturing process. Such a defect may have an impact on an individual's response and thus increase the risk of adverse vaccine reactions. Insufficient inactivation of wild-type vaccine agent (e.g. wild polio virus) during the manufacturing process or contamination introduced during the manufacturing process could cause the vaccine quality defect-related reactions. In the early years of immunization programmes, some major vaccine quality defect-related reaction incidents were reported. However, since the introduction of good manufacturing practice (GMP) manufacturing defects are now very rare. Since vaccine manufacturers have started following GMP, and NRAs have been strengthened, the potential risk of such quality defects is now rare (Global Manual on Surveillance of AEFIs – WHO, 2014).

14.3.2.3 Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature, is preventable.

When errors in vaccine handling such as exposure of the vaccines and or diluents, where applicable, to excess heat or cold; use of a vaccine post expiration date, or errors in vaccine prescribing, vaccine administration or non-adherence to recommendations for use occur, immunization error-related reactions result (Global Manual on Surveillance of AEFIs – WHO, 2014).

14.3.2.4 Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization. These reactions are commoner, resulting from fear of, or pain due to, injection rather than from the vaccine itself. In some cases the cause of the AEFI remains unknown, however clusters of fainting after immunization are well recognized as anxiety-related reactions during immunization programmes targeting adolescent girls (Global Manual on Surveillance of AEFIs – WHO, 2014).

14.3.2.5 Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists. These require specific domain knowledge for comprehensive investigation and correct interpretation as they may be mistaken for vaccine reactions and could lead to inappropriate suspension of a vaccine programme.

14.4 Objectives of AEFI Surveillance

i. To ensure patient safety
ii. To detect, investigate and report AEFIs

iii. To analyse AEFI reports and take corrective action

iv. To minimize AEFIs in routine immunization and mass campaigns

14.5 Roles and Responsibilities at Various Levels

Roles and responsibilities are as described below and summarized in the flowchart for AEFI management (annex 17). The flowchart also shows the reporting timelines that should be followed.

14.5.1 Community

i. Identification of AEFIs

ii. Reporting to nearest health worker/health centre

14.5.2 Service Delivery Level (hospitals/clinics - public and private)

i. Identification and/or detection of AEFIs

ii. Clinical management of AEFIs

iii. Reassure the care giver

iv. Completion of AEFI reporting forms (Annex 12) and case investigation forms (Annex 13)

v. Notify district of any cases of AEFIs (NB. Use fastest means of communication in case of serious or fatal AEFIs; notification to be done within 24 hours)

vi. All fatal cases to be reported to the police for a post mortem

vii. Refer serious cases to district hospital with well completed AEFI reporting and investigation forms

viii. Keep the respective vaccine vial (clearly labeled) under cold chain in cases of severe reaction until investigations are complete

ix. In case of clustering of AEFIs (more than one case) from one batch number of vaccines, stop using that batch and report immediately

x. Maintain line list of AEFIs

xi. Refer all questions to the DMO

xii. Write report and follow up

xiii. Ensure that all fields are completed

14.5.3 District Level

i. Ensure all staff are trained on AEFI surveillance

ii. Provide AEFI SOPs to all facilities and ensure adherence

iii. Generate the AEFI report ID number and record it on the submitted AEFI reporting forms

iv. Investigation of - all serious AEFI cases (death/ resulted in hospitalization/ disability)
- belongs to a cluster of AEFI
- is a previously unrecognized event associated with an old or newly introduced vaccine
- involves an increased number or rates of known cause
- is a suspected immunization error;
- appears on the list of events defined for AEFI surveillance; and
- causes significant parental or public concern.

v. Classify all the AEFIs

vi. Correct programme errors through on job training

vii. Facilitate management of cases

viii. Complete AEFI investigation report

ix. Notify province of any cases of AEFIs (NB. Use fastest means of communication in case of serious or fatal AEFIs)

x. Maintain district line list

xi. Ensure post mortems are done for deaths and reports are submitted timeously to next level, including the AEFI reporting and investigation forms

xii. Refer all questions to the DMO

14.5.4 Provincial Level

i. Contact National level focal person for severe and fatal AEFIs

ii. Maintain provincial line list of AEFIs

iii. Investigate or support investigation of serious AEFIs, and forward completed AEFI reporting and investigation forms to the national level

iv. Conduct regular supportive visits to districts

v. Ensure training of staff and provide resources for system

vi. Ensure all reports are submitted to national level in duplicate

vii. Reconcile provincial and national surveillance databases on a quarterly basis

viii. Refer all questions to the PMD

14.5.5 National Level

i. Receive and review AEFI case reports from sub-national levels
ii. Conduct investigations when necessary
iii. Submit all AEFI reporting and investigation forms to the Medicines Control Authority of Zimbabwe (MCAZ), within 48 hours of notification
iv. Give regular feedback to lower level and MCAZ
v. Ensure SOPs are compliant to requirements at all times
vi. Provide training to all focal persons
vii. Provide national guidelines on all vaccine management and surveillance issues
viii. Refer all questions to the Public Relations Officer

14.5.6 Medicines Control Authority of Zimbabwe

i. On receipt of a completed AEFI reporting and investigation form, assign an in house report reference number.
ii. Check information on the report form for completeness and clarity.
iii. Request for any additional information or clarification from EPI where necessary and file the report form in the current AEFIs reports file.
iv. Transfer the information from the AEFI form to the MCAZ in-house report form, and draft the causality assessment and case definition as per the WHO Aide-memoire on Causality assessment of an AEFI, 2013.
v. The completed in-house report form should be tabled at the next Pharmacovigilance and Clinical Trials (PVCT) Committee meeting for causality assessment. The PVCT Committee is the National AEFI Committee.
vi. During the PVCT Committee meeting endorse on the MCAZ in house report form the Committee decision.
vii. After the Committee meeting proceed as decided by the Committee e.g. seek further information from EPI, inform other health care professionals of such AEFIs if necessary as an alert notice, letter or article in the drug information bulletin.
viii. Code report and compute details into the Adverse Drug Reaction (ADR) VigiBase database as per the SOP.

ix. Complete a letter communicating the causality assessment decision made by the Committee; and send to EPI together with additional report forms, and a feedback letter to the reporter.

x. Conduct further in-depth analysis and risk benefit assessment for serious AEFI and/or cluster AEFI including literature review. Provide feedback to EPI and reporter including publication of results in reputable journal.

14.6 Steps for AEFI Reporting

i. Receive the report, conduct a quick assessment and inform the next level

ii. Take full socio-medical history

iii. Review available records which the patient might have brought and check any history of previous medication given

iv. Find out if the child had similar episodes prior to immunization or any history of allergies to food and/or medicines eg. Egg, red meat etc., injury or any rituals done

v. In case of an abscess refer the child to the next level for probable laboratory tests, incision and drainage

vi. Find out from care giver if anyone in the community had the same problem after being vaccinated

vii. Notify the next level and refer patient to next level when necessary

viii. Compile an incident report of what transpired and submit to the next level with copy of the completed AEFI reporting forms, and AEFI case investigation forms for serious AEFIs.

ix. After results are out dispel myths and misconceptions.

x. In case of a suspected AEFI death offer bereavement counseling and inform the police

xi. Request for post mortem and parents to consent

xii. Refer all questions to the DMO/PMD/PRO.

xiii. Have a fully equipped emergency tray

xiv. Check the cold chain equipment and temperature records

xv. Keep the used vials under cold chain for investigation

14.7 Procedures of Determining and Recording an AEFI

An AEFI reporting form should be completed to report an AEFI (annex 12). For a serious AEFI an AEFI reporting form and case investigation form (annex 13) is required to be completed.

14.7.1 History Taking

History taking should include the following:

i. Vaccination history
ii. Chronic illnesses
iii. Acute infections
iv. Medications given before and after vaccination; including herbal medicines
v. Allergies to food eg. eggs, red meat etc., medicines
vi. Feeding practices
vii. Growth and development of child, including malnutrition
viii. Previous reactions to medicines
ix. Exposure to HIV

14.7.2 Examination

i. Resuscitate the child and conduct a head to toe examination
ii. Note any abnormalities
iii. Take and record the child's temperature
iv. Confirm type of AEFI e.g. abscess and document findings
v. Counsel and reassure the care giver
vi. Explain procedure to be followed and manage child appropriately

14.7.3 Completion of AEFI Forms

i. Fill in five (5) AEFI reporting forms
ii. Ensure complete documentation
iii. Sign the forms
iv. Date stamp all the AEFI reporting forms
v. File 1 copy at clinic

vi. Submit 4 copies to District Level for onward submission of 3 of the copies to the Provincial Level. The Provincial Level would then forward two of the three copies to the Zimbabwe Expanded Programme on Immunization Unit, and from there one copy would be forwarded to the MCAZ.

vii. A completed AEFI form and case investigation form for serious AEFI are required by EPI and MCAZ to enable causality assessment and risk assessment

14.7.4 Communication

i. In case of fatal or severe AEFI use the fastest means of communication to inform the next level ie. phone. Fatal cases to be relayed to next level within 24 hours

ii. and The communication should follow the normal channel: District, Provincial EPI Head office

iii. Submit a comprehensive report and attach the AEFI reporting forms

14.8 Investigation of AEFIs

Once an AEFI report has been received by the District level, an assessment should be made to determine whether or not an investigation is needed. The reported AEFI must be investigated if it:

i. appears to be a serious event (death/ resulted in hospitalization/ disability) of known
or unknown cause;

ii. belongs to a cluster of AEFI;

iii. is a previously unrecognized event associated with an old or newly introduced vaccine

iv. involves an increased number or rates of known cause;

v. is a suspected immunization error;

vi. appears on the list of events defined for AEFI surveillance; and

vii. causes significant parental or public concern.

The ultimate goal of a case investigation is to find the cause of an AEFI and to implement follow-up actions. Investigation should identify any immunization error-related or vaccine product-related reactions because these are preventable. If coincidental events are recognized, proving them will be important to maintain public confidence in the immunization programme. It is important to investigate suspected adverse events promptly and completely. The District level is responsible for carrying out the investigation.

The investigation can be a simple assessment or a more rigorous scientific evaluation of the reported AEFI in order to recognize its possible cause(s). The extent of the investigation depends on the nature of the reported AEFI. The WHO's Aide-mémoire on AEFI investigation, 2013 (Annex 15) should be used as resource material in the investigation of AEFIs. The aide-mémoire proposes a systematic, standardized process to investigate reported serious AEFIs and ascertain the underlying cause.

14.8.1 Investigation procedures

a. Investigation

The investigation team should fill the AEFI case investigation form and submit the form to the next level, with the AEFI reporting form attached. The following should be checked:

i. Cold chain maintenance
ii. Immunization technique
iii. Vaccine given
iv. Documentation practices
v. Emergency tray
vi. Sharps disposal

b. Composition of Investigation Team

i. Programme Manager
ii. Clinician (Pediatrician/Nurse/Epidemiologist/Pathologist/Physician)
iii. Health Promotion Officer
iv. Pharmacist
v. Surveillance Officer
vi. Logistician
vii. Laboratory and forensic expert
viii. Health Information Officer

Surveillance and investigation of AEFI is important in order to take corrective action and preserve public confidence in EPI.

c. How to investigate an AEFI

An AEFI investigation follows standard principles of epidemiologic investigation.

Figure 6. How to investigate an AEFI

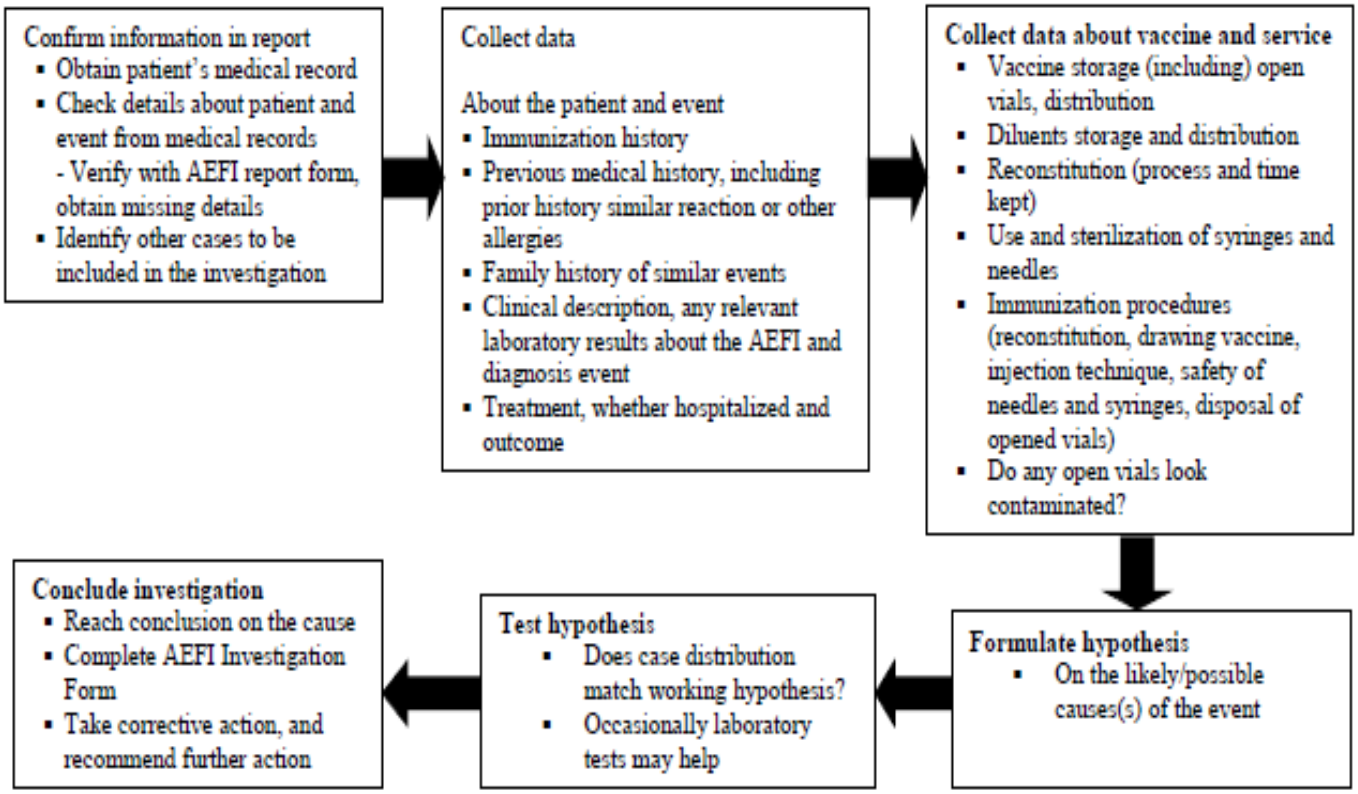


Figure 6. adapted from the WHO Global Manual on Surveillance of AEFIs, 2014.

It is important to investigate suspected adverse events promptly and completely. The investigator will primarily need to focus on the reported reaction as well as gather information from the patient/parent, health workers and supervisors, and community members.

i. Investigation of AEFI Clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. According to the WHO Global Manual on Surveillance of AEFI, 2014 when investigating cluster AEFIs the investigator should look for AEFIs occurring in similar age groups and populations with genetic predisposition or disease. Cluster investigation begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition.

Cluster identification (i.e. cases with common characteristics) is done by gathering details (who, when and where) of vaccines administered (WHO, 2014). This can be achieved by collecting and recording:

i. detailed data on each patient;
ii. programme-related data (storage and handling, etc.); and
iii. immunization practices and the relevant health workers' practices.

Common exposures among the cases can be identified by reviewing:

i. all data on vaccine(s) used (name, lot number, etc.);
ii. data on other people in the area (also non-exposed); and
iii. any potentially coincident factors in the community.

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. The identification of the causes of an AEFI cluster may be investigated as the process flow under Figure 7.

Figure 7. Investigation of AEFI cluster

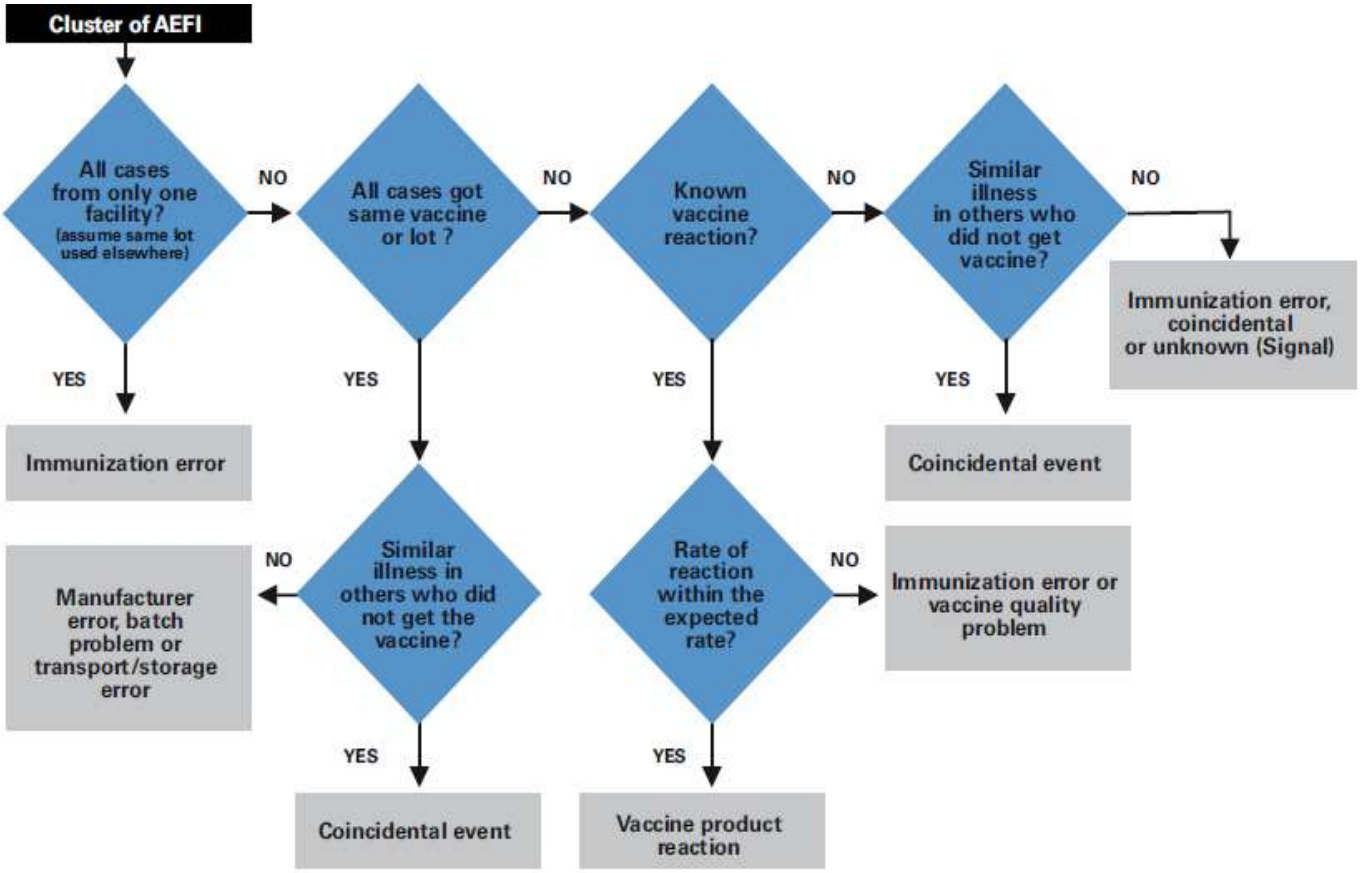


Figure 7. adapted from the WHO Global Manual on Surveillance of AEFIs, 2014.

ii. Investigation of Deaths

A field investigation of a death following immunization has to be conducted without delay as the death can cause significant community concern, and all administrative levels, including the national immunization programme, should be notified of the death (WHO, 2014).

The WHO recommends that death investigation should be carried out by a team comprising clinical, laboratory and forensic experts, and that the team should be supported by the programme managers, as listed under 7(b) above. All relevant information on the event should be available to the investigation team.

An autopsy is preferred and is recommended following all deaths suspected to be caused by vaccine or immunization; however, the decision to conduct the autopsy should be taken within the context of religious, cultural and the legal framework of the country. At the time

of autopsy, the autopsy surgeon should be provided documents outlining detailed preclinical and clinical history, including laboratory and radiological findings.

14.9 AEFI Causality Assessment

Causality assessment, in the context of AEFI surveillance, a systematic review of data about AEFI case(s) in order to determine the likelihood of a causal association between the event and the vaccine(s) received (Global Manual on Surveillance of AEFI, WHO 2014). Causality assessment does not necessarily establish whether or not a definite relationship exists, but generally ascertains a degree of association between the reported adverse events and the vaccine/vaccination. The WHO recommends that the national (central) expert committee for causality assessment and for high-level technical support and decision-making may use the WHO Aide-mémoire on causality assessment as resource material, and is encouraged to use in its investigations the comprehensive case definitions developed by the Brighton Collaboration. To classify AEFI causality, the MCAZ-PVCT Committee, which is the National AEFI Committee, follows these recommendations. To classify causality, the MCAZ-PVCT Committee uses the WHO Aide-memoire on AEFI Causality, 2013.

14.9.1 Before AEFI Causality Assessment

i. The AEFI case investigation should have been completed. Premature assessments with incomplete investigation could mislead the classification of the event. When an investigation is incomplete, follow-up efforts to obtain additional information and documents should be made.

ii. There must be a "diagnosis" using standard or widely accepted criteria for the adverse event, clinical sign, abnormal laboratory finding, symptom and/or disease in question. In other words, it should be clearly understood which vaccine is being associated with what specific event that was reported.

14.9.2 Causality Assessment Method

The WHO publication, Causality assessment of an AEFI – User manual for the revised WHO classification was developed by WHO as a method for assisting national committees for AEFI case review and causality assessment. It was patterned on an algorithm developed in the USA by the Clinical Immunization Safety Assessment network and with new AEFI definitions proposed by the Council for International Organizations of Medical Sciences (CIOMS).

The revised WHO causality algorithm focuses on two critical questions: "Is there evidence in literature that this vaccine(s) may cause the reported event even if administered correctly?" and "Did the event occur within an appropriate time window after vaccine administration?", WHO 2013.

There are four steps in causality assessment, which are;

Step 1. Eligibility: to determine if the AEFI case satisfies the minimum criteria for causality assessment. It is to be ensured that the AEFI case investigation is completed and that all

details of the case are available. One or more vaccines administered before the event are identified and a valid diagnosis selected which is thought to be casually related to the vaccination. An appropriate definition to assess diagnostic certainty is to be used (Brighton Collaboration definition, standard literature, national definition or other approved definition). If an AEFI is reported and appears to not meet the eligibility criteria because of suspected inadequate information, it is important to make attempts to collect the additional information required in order to ensure that the case can be properly assessed for eligibility, WHO 2014.

Step 2. Checklist: to systematically review the relevant and available information to address possible causal aspects of the AEFI. The checklist is used as a guide to assemble information on patient-immunization-AEFI relationships.

Step 3. Algorithm: to obtain direction as to the causality with the information gathered in the checklist. A stepwise approach using the algorithm helps determine if the AEFI could be consistent, or inconsistent, with an association to immunization, or is indeterminate or unclassifiable.

Step 4. Classification: to categorize the AEFI's association to the vaccine/vaccination on the basis of the direction determined in the algorithm. The final classification is based on there being available adequate information for the case and the classes are classified as;

a. **A: Consistent causal association to immunization**

A1 – Vaccine product-related reaction

A2 – Vaccine quality defect-related reaction

A3 – Immunization error-related reaction

A4 – Immunization anxiety-related reaction

b. **B: Indeterminate**

B1 – Temporary relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)

B2 – Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

c. **C: Inconsistent causal association to immunization**

Coincidental

d. **Unclassifiable**

14.10 Communication

Communication with parents, the community, health staff and the media need to be carried out under many circumstances, from launching new vaccines, putting in place mass immunization campaigns, to issuing reminders to maintain vaccinations up to date. When a vaccine safety investigation is underway resulting from one of the reasons outlined in earlier chapters of this manual, communications involve keeping the public informed about the investigation, results and action already taken or going to be taken regarding the AEFI. At the same time it is crucial to highlight the benefits of immunization even while communicating about an investigation.

Trust is a key component in the exchange of information at every level. Any overconfidence about risk estimates that are later shown to be incorrect contributes to a breakdown of trust among people involved. Admit uncertainty of AEFI, investigate fully, and keep the community informed. Avoid making a premature statement about the cause of the event before the investigation is complete. If the cause is identified as immunization related error, it is vital not to lay personal blame on anyone, but to focus on system- related problems that resulted in the immunization error(s) and steps being taken to correct the problem.

In communicating with the community, it is useful to develop links with community leaders and the peripheral health workers so that information can be rapidly disseminated. Maintaining lines of communication with the community is important throughout the investigation. Upon completion of the investigation, the cause of the event(s) needs to be communicated to the community. This communication must include information about the steps being taken to remedy the situation and to prevent a recurrence, if such steps are needed.

In this age of instant communication, as outlined in the WHO Euro manual, "the ease with which information can be disseminated now means that negative comments about vaccines can go "viral" on the internet without balanced professional input. As a result, the media have found rich pickings in vaccine safety issues". Nevertheless, employing strong communication principles and strategies is not a substitute for evidence-based risk analysis. But having a communications plan for rapid implementation may prevent vaccine safety scares from become crises.

14.10.1 Communication with stakeholders

There are many parties to whom communications should be tailored in order to meet their particular needs. These include:

iv. Parents and the community
v. Health staff
vi. Particular stakeholders such as the ministry of health/ NRA /NCL, politicians, professionals/academia, international agencies: WHO, UNICEF, and manufacturers.
vii. The media

In addition, there are principles of communication that apply to most if not all. These include the need to:

i. Listen empathetically to concerns.
ii. Reassure and support but do not make false promises.
iii. Communicate frequently
iv. Build up and maintain relationship among the stakeholders.
v. Inform about possible common adverse events and how to handle them.

vi. Prepare factsheets on adverse events and other key information for all audiences.
vii. Continuously communicate during the investigation period to assure understanding both the situation and the risk-benefit of vaccination. Do not lay blame, especially not on the health worker(s), but focus on the correction and quality of the EPI system.

While health staff should have some training or at least experience in communication skills by the nature of their work, at the same time communication with them by public health authorities and investigators should be sensitive to their needs. Thus:

i. Communication should be among all levels of health authorities involved.
ii. Reassure the staff of their knowledge, ability, skills and performances.
iii. Do not blame the health worker(s) but focus on the correction and quality of the EPI system.
iv. Keep them updated on investigation process, progress, and findings.

Vaccine safety information needs to be shared with other stakeholders in order to ensure dissemination of correct information and, by doing so, ensure the smooth functioning of national immunization programme in the country. This may be done at two stages: sharing preliminary information at initial stage and sharing the final data/report after completion of investigation/causality assessment.

14.10.2 Communicating with the media

The media (newspaper, radio, television and the internet) play an important role in public perception. Understanding what the media want from a story will assist communication with them. In certain situations, media coverage can lead to public concern about immunization. In these situations, it is important to coordinate with professional organizations, health professionals and workers before responding to or addressing the media. The coordination should include preparation on dealing with public concern on this issue, in order to minimize any potential harm to the immunization programme. It is also useful to have other groups and individuals that merit public respect and authority to publicly endorse and strengthen key immunization messages.

Communicating with the media requires particular skills that require training. Reporters are highly trained professionals and their perspective must be properly understood. The media are interested in stories that will attract attention. While the success of a vaccination programme can attract attention, so can a programme that has not gone as planned. Dramatizing and personalizing events can both highlight success as well as create a sense of panic about an AEFI with a particular vaccine product – regardless of whether they are either unrelated to immunization (coincidental) or a localized immunization error. One other important fact is the media want early responses to their questions: therefore waiting for the conclusion of an investigation is rarely possible. Information may need to be disseminated early and often, and it is vital to be honest about what is known and what is not known, and to avoid being evasive and unresponsive.

At the same time, the media can be leveraged positively for the benefit of immunization. Health topics are popular among the public and, therefore, the media like to report about them. The media can be helpful allies in communicating public health messages. They can be helpful allies in reminding the public of the risk benefits of immunization. Building a personal relationship with key health reporters will help them to understand the public health perspective.

Effective communication with the media includes advance preparation. This is part of a communication plan and is particularly important before a new vaccine is introduced or before and during an immunization campaign. A communication plan can also provide ongoing communication support to routine immunization programmes. A good media plan consists of the following:

Table 4: Media plan for communication

A database of journalists	A list of print and electronic media journalists covering health (local, national, international) with contact information. Always use a database where updating can be done immediately. Update regularly any changes in the media list.
Information packages	An information package may contain the following documents both in hard copy and e-copies: Frequently Asked Questions (FAQs) on immunization in general, for specific disease, and AEFI Fact Sheet or a Technical Brief on a specific vaccine preventable disease: burden of the disease and background rates of AEFI, expected AEFI rates Recent updates – Statistics, progress made in country, WPR, globally Contact addresses of spokespersons (experts) in the Ministry. This information package needs regular updating.
The draft media release	Must specifically answer the 6 W's for journalists: Who is affected/is responsible? What has happened? What is being done? Where has it happened? When did it happen? Why did it happen? Will it happen again?

Information specific to media characteristics	Local media: Read and believed by more people in the community than national media. National media: a wide reach and influences national agendas. International media: Can influence national agendas.
A spokesperson system:	Identify in advance an appropriate spokesperson (or several spokespersons in the different agencies). Share contact details of spokesperson(s) with all concerned focal points at different levels of programme implementation. Ensure spokesperson(s) has experience or some training in dealing with media.

Other tips to keep in mind

Media interest is usually greatest initially when relatively little is known. In this environment, rumours can flourish and the potential for harm is huge. A media conference, convened early even if there is only very limited information to give, can provide a uniform message to all at the same time, thus avoiding any conflicting messages. This will also prevent the circulation of rumours and build a relationship with the reporters. At the end of the press conference, advise that a further conference will be held within a day or so, at which time full details of the event and the investigation will be provided. A media or press conference requires expert planning and expert communications input to ensure that messages are clear, unambiguous and that all expert spokespersons are well prepared.

Professional organizations and other stakeholder parties may have greater credibility than the government, particularly in a crisis situation. Providing them an opportunity for their unified support for immunization and the approach being taken to handle/investigate the problem can help considerably.

14.10.3 Preparing key messages

Messages need to be as simple as possible. Use simple words and short sentences. It is helpful to tell a story, if possible. Create a 'word picture' (a graphic or vivid description) to get the message across. The key messages should be kept to a minimum and should include some of the facts. The benefit of immunization in preventing certain diseases is well proven. Introduction of vaccines has saved millions of lives.

i. It is risky not to immunize (risk of disease and complications).
ii. Vaccines may/do cause reactions, but these are rarely serious.
iii. Immunization safety is of paramount importance – maintaining confidence in immunization programs is only possible this way.

iv. Any suspicion of a problem is investigated (an advantage of well-established immunization safety surveillance). This investigation is an example of such action being taken.

It is rarely necessary to suspend an immunization programme during an investigation unless it is obvious that there is a problem with the vaccine that warrants such drastic steps. The vast majority of situations prove to be coincidental or due to a very localized problem (depending on type of event), and the immunization programme must continue to keep the population safe from disease.

Preparing a press statement

i. All the information to be conveyed in a media conference should be prepared in advance and included in a press statement.

An effective press statement/ release must specifically answer the six questions ("W's") stated above and include a one page account (400-500 words) written in short sentences outlining:

i. A complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI, or a coincidental event). No technical jargon.
ii. An outline of actions taken or planned (such as the AEFI investigation).
iii. A description of the possible cause of the event.
iv. An assurance that corrective action will be taken, and what steps have already been taken.
v. Reference to any relevant publication or web site for further information.
vi. Sender's name and spokesperson's details.
vii. Quotes from key officials may be used after seeking their permission. (The quotes must be positive and carry the key messages.)
viii. Repetition of key positive message.

Follow-up actions with communications

Keeping promises: If it has been promised that updates about the investigation will be disseminated, make sure that this is kept by the promised date. If the findings have been delayed, ensure the delay is communicated.

Providing answers to unanswered questions: if a question could not be answered for any reason, get back to the requestors with the answers as soon as possible.

Keeping the public informed about subsequent developments: If any decision or action is taken at the highest levels following AEFI investigations or during the investigations and the public must know about it, keep them informed though a press release to the media or other locally appropriate means.

14.10.4 Crisis management

A crisis is a situation in which a real or potential loss of confidence in the vaccine or in the immunization programme is triggered by information about an AEFI. Crises can often be

avoided through foresight, care and training. If managed properly, the investigation and management of a vaccine safety situation will boost public confidence and acceptance and ultimately strengthen the immunization programme.

How to manage a crisis?

Anticipate: do not wait until a crisis occurs. Prepare for the unavoidable. Develop a good relationship with the media. Good public awareness and understanding of the immunization programme is necessary.

Train staff at all levels to respond adequately: develop confidence responding to the public and the media (particularly to local media) properly and correctly.

Confirm all facts and prepare (see steps for a press conference or press release) before making any public comments.

Prepare a plan to react to a crisis when it occurs. This has to be done in advance, identifying responsible persons to handle the crisis and preparing all supporting documents and information.

Summary

Communication with parents, community, staff, other stakeholders and the media is necessary and important.

During communication make sure to build confidence on immunization programme. Be aware of risk-benefits of immunization and the progress and findings of the investigation.

Communication needs assurance from one in authority, with knowledge and expertise in the subject.

It is recommended to prepare a communication plan in advance, as this will minimize negative impact of AEFI-related matters.

15. PHARMACOVIGILANCE INDICATORS

"Pharmacovigilance practitioners in low and middle-income countries (LMIC) currently enjoy the luxury of having 2 indicators for assessing performance – the WHO PV Indicators as well as the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) and Management Sciences for Health (MSH) developed Indicator-based Pharmacovigilance Assessment Tool (IPAT). Whilst the two are largely similar, both aiming to achieve nearly-identical aims, the existence and promotion of both appear duplicative and may be an issue for policy makers as well as practitioners." - *Communique issued at the end of the 7th African Pharmacovigilance Consultants Network (PVSF) meeting in Accra, Ghana, 24-25 November 2015*

The need to harmonise these indicators with the aim of having one Pharmacovigilance Indicator for LMICs in the medium term was agreed by all stakeholders including both WHO and SIAPS/MSH, and this issue was a central theme of the 7th PVSF meeting held in Accra, Ghana from 24-25 November 2015 with participation from WHO, the Uppsala Monitoring Centre, MSH/SIAPS as well as several African countries, including Zimbabwe, and hosted by the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, University of Ghana.

The guiding philosophy and principles of the national pharmacovigilance policy include the requirements for a national pharmacovigilance centre as per the WHO Pharmacovigilance Indicators Handbook 2015 (http://pvtoolkit.org/pv-wp/wp-content/uploads/2016/11/WHO-PV-Indicators-Manual.pdf), and Indicator-Based Pharmacovigilance Assessment Tool (IPAT); Manual for Conducting Assessments in Developing Countries, Strengthening Pharmaceutical Systems (SPS) Program 2009.

There are 27 core WHO pharmacovigilance indicators, which are 10 structural, 9 process and 8 outcome or impact indicators.

Figure 8. The ten core structural indicators (CSTs)

CST1. Existence of a pharmacovigilance centre, department or unit with a standard accommodation

CST2. Existence of a statutory provision (national policy, legislation) for pharmacovigilance

CST3. Existence of a medicines regulatory authority or agency

CST4. Existence of any regular financial provision (e.g. statutory budget) for the pharmacovigilance centre

CST5. The pharmacovigilance centre has human resources to carry out its functions properly

CST6. Existence of a standard ADR reporting form in the setting

Subset indicators: The standard reporting form provides for reporting:

CST6a: suspected medication errors;

CST6b: suspected counterfeit/substandard medicines;

CST6c: therapeutic ineffectiveness;

CST6d: suspected misuse, abuse of and/or dependence on medicines;

CST6e: ADRs by members of the general public

CST7. A process is in place for collection, recording and analysis of ADR reports

CST8. Incorporation of pharmacovigilance into the national curriculum of the various health-care professions (includes *subset indicators*:

CST8a: for medical doctors;

CST8b: for dentists;

CST8c: for pharmacists;

CST8d: for nurses or midwives;

CST8e: for others – *to be specified*)

CST9. Existence of a newsletter, information bulletin or website for dissemination of pharmacovigilance information

CST10. Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety.

Figure 8. adapted from the WHO pharmacovigilance indicators, a practical manual for the assessment of pharmacovigilance systems, 2015

Figure 9. The nine core process indicators

CP1.	Total number of ADR reports received in the previous calendar year (also expressed as number of ADRs per 100 000 persons in the population)
CP2.	Current total number of reports in the national, regional or local database
CP3.	Percentage of total annual reports acknowledged and/or issued feedback
CP4.	Percentage of total reports subjected to causality assessment in the previous calendar year
CP5.	Percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance centre in the previous calendar year
	Subset indicator CP5a: of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database
CP6.	Percentage of total reports attributed to therapeutic ineffectiveness received in the previous calendar year
CP7.	Percentage of reports on medication errors reported in the previous year
CP8.	Percentage of registered pharmaceutical companies having a functional pharmacovigilance system
CP9.	Number of active surveillance activities initiated, ongoing or completed during the past five calendar years

Figure 9. adapted from the WHO pharmacovigilance indicators, a practical manual for the assessment of pharmacovigilance systems, 2015

Figure 10. The eight core outcome or impact indicators

CO1.	Number of signals detected in the past 5 years by the pharmacovigilance centre
CO2.	Number of regulatory actions taken in the preceding year as a consequence of national pharmacovigilance activities includes
	CO2a: number of product label changes (variation);
	CO2b: number of safety warnings on medicines to: (i) health professionals, (ii) general public;
	CO2c: number of withdrawals of medicines;
	CO2d: number of other restrictions on use of medicines
CO3.	Number of medicine-related hospital admissions per 1000 admissions
CO4.	Number of medicine-related deaths per 1000 persons served by the hospital per year
CO5.	Number of medicine-related deaths per 100 000 persons in the population
CO6.	Average cost (US$) of treatment of medicine-related illness
CO7.	Average duration (days) of medicine-related extension of hospital stay
CO8.	Average cost (US$) of medicine-related hospitalization

Figure 10. adapted from the WHO pharmacovigilance indicators, a practical manual for the assessment of pharmacovigilance systems, 2015

16. GLOSSARY

The definitions given below apply to the terms used in this policy. They may have different meanings in other contexts

Adverse Event: Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

Adverse event following immunization (AEFI): Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding symptom or disease.

Adverse Drug Reaction (ADR): A response to a medicine which is noxious and unintended, which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Applicant: The person by, or on whose behalf, an application for registration is made.

Causal Relationship: A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance; a medicine causing an adverse reaction.

Causality Assessment: The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction.

Cohort Event Monitoring (CEM): 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.

Counterfeit Medicine: Medicines that are deliberately and fraudulently mislabeled with respect to identity and/or source.

Data Mining: A general term for computerized extraction of potentially interesting patterns from large data sets, often based on statistical algorithms.

Dechallenge: The withdrawal of a medicine from a patient; the point at which the continuation, reduction or disappearance of adverse effects may be observed.

Diary (patient): A dated record of health events recorded by the patient.

Event Dictionary: A standard listing of terms which describe health events for use in event monitoring.

Excipients: All materials included to make a pharmaceutical formulation (e.g. a tablet) except the active drug substance(s).

Health Practitioner: Any person in respect of whose profession or calling a register is kept in terms of the Health Professions Act.

Incident: A health event which is believed to be incidental to the taking of a particular medicine.

Index Case: One of the first good descriptions of a specific adverse reaction to a medicine.

Individual Case Safety Report (ICSR): A report that contains information describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patient.

Information Component (IC): A measure of the disproportionality in the reporting of a medicine–ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the medicine and the ADR. Positive IC values indicate higher reporting than expected.

Marketing Authorization Holders (MAHs): The holder (an applicant, principal, individual, institute, manufacturer, company, importer, distributor, development partner/donor agency) of a marketing authorization to market a medicinal product. For the purpose of this policy document, the MAH's will have full responsibility and liability for their product on the market and full responsibility for ensuring that appropriate action can be taken when necessary as per the Medicines and Allied Substances Control Act (MASCA) Chapter 15:03 and regulations. Medicines and vaccines distributed in Zimbabwe under section 75 provision of MASCA Chapter 15:03 including donated medicines, vaccines, and complementary medicines are subject to complying with pharmacovigilance requirements in Zimbabwe.

Medical Dictionary for Regulatory Activities (MedDRA): Medical terminology developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with an emphasis on ease of use for data entry, retrieval, analysis and display.

Medication Error: An error which occurs during the prescribing, dispensing and/or use of a medication.

Medicine: Any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in the diagnosis, treatment, mitigation or prevention of disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or restoring, correcting or modifying any physical, mental or organic function in man or in animals.

Medicines Control Authority of Zimbabwe (MCAZ): A statutory body established by an act of Parliament, The Medicines and Allied Substances Control Act (MASCA) [Chapter 15.03]. MCAZ is responsible for protecting public and animal health by ensuring that accessible medicines and allied substances and medical devices are safe, effective and of good quality through enforcement of adherence to standards by manufacturers and distributors.

National Pharmacovigilance Centre (NPVC): It is a centre of expertise for the art and science of monitoring and analysis of ADRs, and in use of the information analysed for the

benefit of patients. The centre may function within the regulatory authority, a hospital, an academic institution or as an independent facility such as a trust or foundation.

Periodic Safety Update Report (PSUR): A periodic report produced by an applicant intended to provide an update of a worldwide safety experience of a medicinal product to the competent authorities at defined times post marketing authorization applicable. PSUR to be submitted to the MCAZ as part of the new chemical entity application for registration Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable.

Periodic Benefit Risk Evaluation Reports (PBRERs): PBRERs are to be submitted to the MCAZ as part of the new chemical entity application for registration Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem.

Post-Marketing Surveillance (PMS): The practice of monitoring safety and effectiveness of pharmaceutical products or other consumable medical products after it has been released on the market with the objectives to decrease mortality and morbidity associated with adverse events and improving understanding of effectiveness in real-world situations.

Rechallenge: To try a therapeutic pharmaceutical drug, suspected allergen, or medical treatment on a patient a second or subsequent time, to see if the suspected effects of the treatment occur again. This is typically performed to confirm allergic or adverse reactions to allergens or medications, but may also be used to confirm beneficial treatments or to retry a probable beneficial treatment which did not appear to be effective previously.

Reporter: Any person, patient or healthcare professional or institute who describes a suspected adverse effect on an ADR or ICSR form for submission to the National Pharmacovigilance Centre or any other relevant organisation for further consideration.

Section 75 Medicines: refers to exemptions which may apply to certain medicines, in line as stated in Section 75 of Medicines and Allied Substances Control Act [Chapter 15:03]. Such medicines require authorization for importation from the MCAZ.

Serious Adverse Event: A serious adverse event or reaction is any untoward medical occurrence that at any dose results in death requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is life-threatening.

Side Effect: Any unintended effect of a medicine occurring at normal dosage which is related to the pharmacological properties of the medicine.

Signal: Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

Spontaneous Reporting: Unsolicited communication by healthcare professionals or consumers 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 organized data collection scheme.

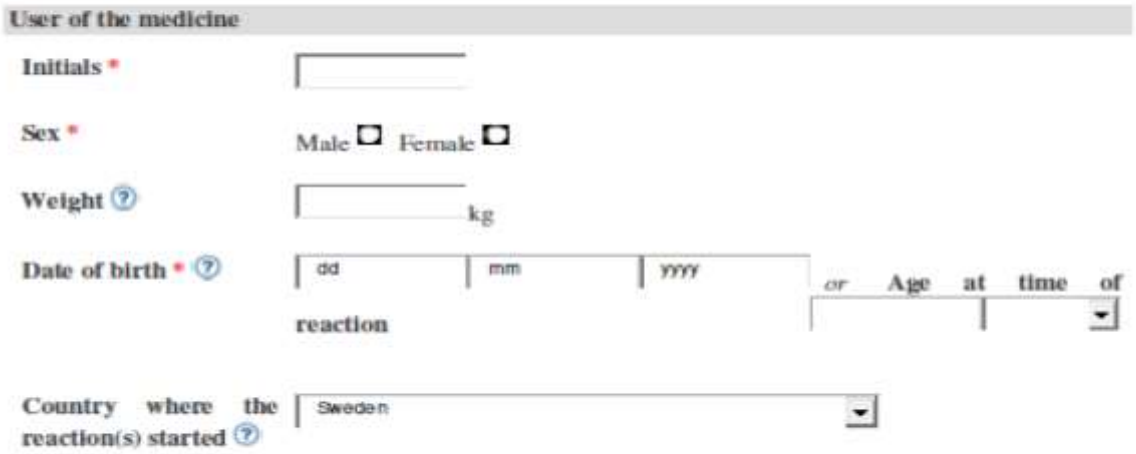
Targeted Spontaneous Reporting (TSR): A method that monitors and records all or a specific set of safety concerns in a defined population of treated patients, e.g. drug-resistant TB patients on treatment.

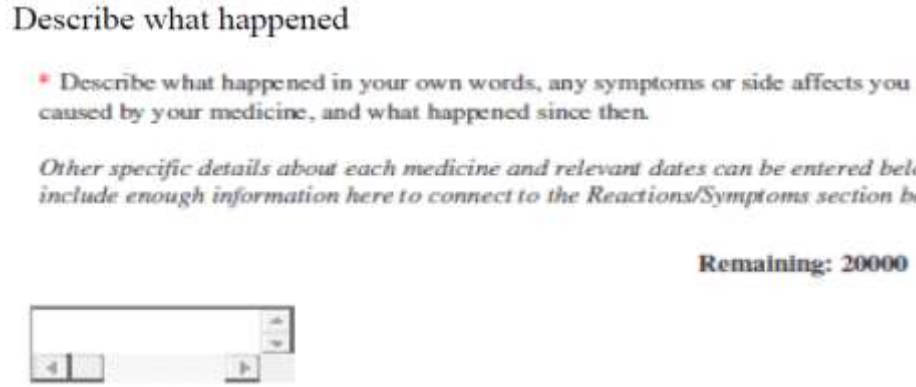
Unexpected Adverse Reaction: An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the medicine.

WHO Adverse Reactions Terminology (WHO-ART): The WHO terminology for coding clinical information in relation to medicinal product therapy.

Annex 1: e-ADR reporting form

The MCAZ e-Reporitng platform is found on the weblink; http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting. The fields to fill are as shown below;





Reaction / Symptoms

Enter a short description (headache or diarrhoea for instance) for each reaction that you suffered and the relevant details. Click on the "Add another reaction/symptom" button for each new reaction you need to describe.

1 **Reaction/Symptom** * **Remaining: 200**

Outcome of the Reaction

- ☐ Recovered/Resolved
- ☐ Recovering/Resolving
- ☐ Not recovered/Not resolved
- ☐ Reaction ended, but with after effects
- ☐ Fatal
- ☐ Unknown

Add another reaction / Symptom

Did the reaction lead to any of the following

Tick those that apply or leave blank

- ☐ Caused/prolonged hospitalization
- ☐ Disabling/Incapacitating
- ☐ Congenital anomaly/birth defect
- ☐ Life threatening
- ☐ Results in death
- ☐ Other medically important condition

Medicines

Enter the name and details for each medicine you were taking before the reaction occurred. Click on "Add another medicine" for each new medicine you need to describe. Please also describe any herbal preparations, recreational drugs or other alternative medicines you were taking.

1 **Name on medicine** * **Medicine producer**

Probably causing the reaction

Strength **Dosage**

Route **Place where medicine was obtained**

Start date **End date** **Duration**

dd mm yyyy dd mm yyyy or

Reason for taking the medicine

What else did you do? **Remaining: 90** **Action taken with medicine**

Has the medicine caused a similar reaction before? Yes No Unknown Clear

Add information on all medicines, one by one. Please do not forget about "over the counter" medicines, herbal preparations, recreational drugs or other alternative medicines.

Additional Information

Please give a short description of your medical history. This is important since some reactions only appear with a combination of previous or ongoing disease, special diets, recreational drugs, smoking habits, alcohol intake or allergies. You can also enter other comments you feel are important.

Current and previous illnesses

Remaining: 10000

Additional comments

Remaining: 500

Next page

Annex 2: ADR Reporting Form.

MCAZ Medicines Control Authority of Zimbabwe

PVF 01

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

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

Rev 6_November 2016

Page **1** of **1**

Annex 3: Medication Error Reporting Form

MCAZ Medicines Control Authority of Zimbabwe

PVF 45

PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

MEDICATION ERROR FORM

Date of event: **Time of event:**	**Type of Facility:** Govt / Private **Hospital** **Clinic** **Pharmacy** **Others**	**Location of event:** **Ward** **Casualty** **Clinic** **Pharmacy** **Theatre** **Others**
Please describe the error: description/sequence of events and medical/nursing care or management done: Immediate action or intervention done: Corrective action taken on the error:		**In which process did the error occur?** Prescribing Dispensing Administration Others (specify):
Did the error reach the patient? **Yes** **No** Was the incorrect medication, dose or dosage form administered to or taken by the patient? **Yes** **No**	**PLEASE TICK THE APPROPRIATE **ERROR OUTCOME CATEGORY (SELECT ONE)** **NO ERROR** **A** Potential error, circumstances/events have potential to cause incident **ERROR, NO HARM** **B** Actual error **C** Additional monitoring required – caused no harm	**ERROR, HARM** **D** Treatment intervention required – caused temporary harm **E** Treatment intervention required – caused temporary harm **ERROR, DEATH** **I** Death
Describe the direct result on the patient (eg death, type of harm, additional patient monitoring)		
INDICATE THE POSSIBLE ERROR CAUSES(S) AND CONTRIBUTING FACTORS		
Inexperienced personnel Wrong dose administered Medication administration record not accurately documented Failure to adhere to work procedure	Peak hour Illegible prescription Patient information/record unavailable/inaccurate Error due to use of product with similar packaging	Wrong medication given Medication not given Family error
Which category made the error? Doctor Pharmacy Nurse Pharmacist Assist. Clinical Officer Others (specify):	**Other category involved in the error?** Doctor Pharmacy Nurse Pharmacist Assist. Clinical Officer Others (specify):	**Which category detected the error or recognized the potential error?** Doctor Pharmacy Nurse Pharmacist Assist. Clinical Officer Others (specify):
IF AVAILABLE, PLEASE PROVIDE PATIENT'S PARTICULARS – NO PATIENT IDENTIFIERS ARE NEEDED **Age** years/months **Gender** Male Female **Indication for therapy:**		
PRODUCT DESCRIPTION	**Intended product**	**Product administered in error**
Medication brand		
Generic name		
Dose, frequency, duration, route		
Manufacturer		
Dosage form		
Strength		
Type and size of container		

Reported by	
Name:	Address:
Designation:	Email address:
Contact number:	Signature: Date:

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Annex 4: Product Defect Form

Medicines Control Authority of Zimbabwe

PVF 05

PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

REPORT ON MEDICINAL (PHARMACEUTICAL) PRODUCT DEFECT OR PROBLEM

To be completed by Pharmacists, Pharmacy Technicians, Medical Practitioners, Nurses, Veterinary Surgeons and other Distributors of Medicines.

1. Product Name (Brand and Generic)			
2. Description of the Device/Medicine	3. Intended Use	4. Size/Type of Container	5. Registration No.
6. Batch Number		7. Expiry Date	
8. Name and Address of Manufacturer			
9. Name and Title of Reporter			
10. Your Practice Location and Address of Hospital, Clinic, Retail Surgery etc.			
11. Phone Number		12. Date Problem Occurred or Observed	
13. If requested will the actual product involved be available for examination by MCAZ. **YES** **NO**			
14. Signature of Reporter		15. Date	
16. Defects/Problem Noted or Suspected (see a-j below)			

NATURE OF DEFECT OR PROBLEM

a) Presence of foreign material
b) Unusual odour
c) Colour changes
d) Fungal growth
e) Suspected contamination
f) Parenteral solution – leaks, particulate matter, discoloration etc.
g) Wrong label, wrong packaging, wrong strength
h) Lack of therapeutic response
i) Leakages
j) Other (specify)

Return To:
The Director-General
Medicines Control Authority of Zimbabwe
106 Baines Avenue
P O Box 10559
Harare
Tel: +263-4-736981/2/3/4/5, 708255 or 792165
Email: mcaz@mcaz.co.zw

For Office Use Only
Report Number:
Date Received:

Rev 2_March 2015

Page **1** of **1**

Annex 5: MCAZ Guidelines for the Notification of a Medicinal Product Problem/Defect and Recall Procedure

When medicines, vaccines or medical device products are suspected of being potentially harmful to users due to their defective quality, safety or efficacy, they may be subjected to a recall and all related information must be reported to the MCAZ.

The MCAZ Guidelines for the Notification of a Medicinal Product Problem/Defect and Recall Procedure are intended to ensure that in the event of a necessary recall, the recall operations are effectively and efficiently carried out by the manufacturer, importer, distributor or certificate holder of pharmaceutical product (hereafter known as the applicant) in order to safeguard public health. The guidelines are found on the MCAZ website: http://www.mcaz.co.zw/index.php/downloads/file/75-guidelines-for-the-notification-of-medicinal-product-problem-defect-and-recall-procedure

1. DEFINITIONS

- Recall

A process for withdrawing or removing a medicine, vaccine and/or medical device product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/ or concerns that the product is or may be counterfeit. The recall might be initiated by the manufacturer, wholesale dealer applicant or the MCAZ.

- Withdrawal or Cancellation of Registration and/or Withdrawal of a listed product- The total removal of a medicinal product from the market that could be due to an irreversible quality, safety or efficacy concern due to published research findings or non-compliance to current GMP. The withdrawal or cancellation maybe voluntarily initiated by the applicant or manufacturer or by the MCAZ.

2. CLASSIFICATION OF RECALLS

Recalls are classified according to the following system:

2.1 Class I recall

Occur when products are potentially life-threatening or could cause a serious risk to health.

Examples of Class I Defects

- Wrong Product (label and contents are different products)
- Correct product but wrong strength, with serous medical consequences
- Microbial contamination of sterile injection or ophthalmic product
- Chemical contamination with serious medical consequences

- Mix up of some products with more than one container involved
- Wrong active ingredient in a multi-component product with serious medical consequences
- Lack of effectiveness for a life threating condition.

2.2 Class II recall

Occur when product defects could cause illness or mistreatment, but are not Class I.

Examples of Class II Defects

- Mislabeling e.g. wrong or missing text or figures
- Missing or incorrect information- leaflets or inserts
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- Chemical/ physical contamination (significant impurities, cross contamination, particulates)
- Mix up of products in containers
- Non-compliance with specification (e.g. assay, stability, fill/ weight or dissolution)
- Insecure closure with serious medical consequences (e.g. cytotoxics, child resistant containers, potent products)
- Lack of efficacy/effectiveness for medical condition that is not life threatening.

2.3 Class III recall

Occur when product defects may not pose a significant hazard to health ie low risk to health but recall may be initiated for other reasons, due to quality, safety or efficacy concerns.

Examples of Class III Defects

- Faulty packaging e.g. wrong or missing batch number or expiry date
- Faulty closure
- Contamination- microbial spoilage, dirt or detritus, particulate matter

Class I or Class II recalls are considered to be urgent safety-related recalls. They must be reported to the MCAZ for further evaluation and investigation. Class III recalls are

considered to be minimum risk to public health but should however still be reported to the MCAZ.

Note: Each recall is a unique exercise and there may be occasions when the scope of a recall can be narrowed to particular customer groups. The classification is determined by the MCAZ. Expert advice might be sought where the nature of the hazard or its significant is not clear. Decision made by other stringent regulatory authorities internationally will also be considered.

The Guidelines do not apply to the recall of a medicine, vaccine or medical device related to regulatory issues such as cancellation of registration due to non-payment of retention fees, approved change of applicant, manufacturer, labeling, package insert or other registered particulars. Regulatory issues in which there is lack of compliance to cGMP may lead to a recall and/or a cancellation of registration.

3 LEVELS OF RECALL

As with classification, the level (or depth) of a recall is to be assigned in agreement with the MCAZ. In determining the recall level, the principal factors to be considered are the significance of the hazard (if any), the channels by which the medicine, vaccine or medical device pharmaceutical products have been distributed, and the level to which distribution has taken place. Again, expert opinion may be necessary to determine the significance of the hazard or risk.

There are three levels of recall: wholesale, retail and consumer.

3.1 Wholesale level

Includes all parties involved in wholesale distribution and may include wholesalers and retail pharmacies.

3.2 Retail level

Includes:

- All public and private hospital pharmacies;
- Retail pharmacies;
- Clinical investigators and the institutions in which clinical investigations are performed;
- Medical, dental and other health care practitioners;
- Nursing homes and other related institutions;
- Other retail outlets e.g. medicine shops, supermarkets and health food stores;

3.3 Consumer level

Includes patients and other consumers.

4. POST-RECALL

After the timeframe directed by MCAZ to complete the recall, or at other agreed times, the applicant is to provide the MCAZ with an interim report during recall process for the monitoring of progress within 7 days after initiation of recall. The interim report should contain the following information:

- the number of organizations or persons to whom the defective product has been supplied;
- the date and means of notifying them of the recall;
- the number of responses received from them;
- the names of the non-responders;
- the quantity of stock returned;
- the quantity of stock that has been off shelves pending return to applicant;
- the estimated time frame for the completion of the recall.

A final report (refer Final Report Form PVF 49) containing the following information should be submitted to MCAZ within 14 days after commencing of the recall:

- the circumstances leading to the recall;
- the consequent action taken by the applicant or manufacturer;
- the extent of distribution of the relevant batches in Zimbabwe and external; -
- the result of the recall
    - the quantity of stock returned, corrected, outstanding;
    - the quantity of stock used by the consignees and;
    - the quantity of stock not located;
    - date of recall completion;
- confirmation (using Recall Reply Form PVF48) where practicable, the retailers have returned all the recalled products to the applicant or manufacture and the customers have received the recall letter;
- the method of destruction or disposal of the recalled products; and

The applicant or manufacture should report to MCAZ with relevant explanation and obtain its approval if the final report cannot be submitted within 14 days after commencing of the recall. After completion of the recall, a report on investigation results on the problem and the action proposed to be implemented in future to prevent a recurrence of the problem should be submitted to MCAZ in a timely manner, not more than 30 days after the recall.

NB. These reports establish the effectiveness of the recall and unless satisfactory reports are received, further recall action may have to be considered.

Annex 6: SAE Reporting Form

MEDICAL RESEARCH COUNCIL OF ZIMBABWE - MEDICINES CONTROL AUTHORITY OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE and MEDICINES CONTROL AUTHORITY OF ZIMBABWE

SERIOUS ADVERSE EVENT REPORTING FORM

Instructions :Complete entire form. Do not leave any blank spaces
Reporting period: SAEs should be reported within 3 days of site being aware. AE should be reported 7 days of site being aware.
Please use a separate adverse event reporting form for separate reportable adverse events

MRCZ Protocol #:		***Institution***	
MCAZ Protocol #			
Principal Investigator:		***Phone:***	
		Email:	
Report prepared by:	***Designation in the study:***	***Date Form completed***	

Study Title:			
Study Sponsor:			
Date of Adverse Event:	**Participant ID:**	**Hosp. Num.:**	**Type of Report:**
Date of Site Awareness:	**Date of Birth:**	**Sex:**	*Initial* ☐ *Follow-up* ☐ *Resolution* ☐
		1. Male ☐ *2.Female* ☐	*Study week:-* *Visit number:-*

B ***1. What type of adverse event is this?***	1. AE ☐	2. SAE ☐	3. Death ☐

2a. If SAE, is it:
- ☐ 1. Fatal
- ☐ 2. Life-threatening (an actual risk of death at the time of the event).
- ☐ 3. Caused or prolonged hospitalization (non-elective).
- ☐ 4. Resulted in persistent or significant disability or incapacity.
- ☐ 5. Any other important medical event.

2b. Toxicity Grade: Grade 1 ☐ Grade 2 ☐ Grade 3. ☐ Grade 4 ☐ Grade 5 ☐

3a. Any previous Adverse Event's report on this participant?: Yes ☐ No ☐	**If yes, how many?**	
3b. Total Number of SAEs to date for the whole study:		

4. Location of the current Adverse Event:
1. Home ☐ 2. Clinic/Hospital ☐ 3. Work ☐ 4. Study site ☐ 5. Other, specify:

5. Research involves a: 1. Drug ☐ 2. Device ☐ 3. Procedure ☐ 4. Vaccine ☐ 5. Other ☐	**6. Name of Drug, Device or Procedure:**

Version 2.0 dated February 2014 MRCZ/MCAZ SAE Form Page 1

7. Is the drug/device investigational: ☐ Yes ☐ No

C

8a. List all study / intervention drugs being taken at the time of onset of the SAE, or within 30 days prior to onset, and describe their relationship to the SAE:

Drug/ Device/Vaccine	Dose	Route	Schedule	Date commenced	Taking drug at onset of SAE	Relationship of SAE to drug					
						Definitely related	Probably related	Possibly related	Probably not related	Not related	Pending
					Yes ☐ No ☐	☐	☐	☐	☐	☐	☐
					Yes ☐ No ☐	☐	☐	☐	☐	☐	☐
					Yes ☐ No ☐	☐	☐	☐	☐	☐	☐

9. Was the patient taking any other drug at the time of onset of the AE? ..... Yes ☐ No ☐

10. If yes, then list all concomitant medication being taken at least one month before the onset of the SAE and describe the relationship to the SAE:

Concomitant medication	Date commenced	Relationship of SAE to medication					
		Definitely related	Probably related	Possibly related	Probably not related	Not related	Pending
		☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐

11. Has the Adverse Event been reported to:	(a) MCAZ	(b) MRCZ	(c) Sponsor	(d) IRB
	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
If YES, Date of reports:				

12. Describe the SAE with diagnosis, immediate cause or precipitating events, symptoms, any investigations, management, results and outcome (with dates where possible). Include relevant medical history. Additional narrative, photocopies of results of abnormal investigations and a hospital discharge letter may be attached:

Summary of relevant past medical history of participant	
(a) Diagnosis :	
(b) Immediate Cause:	
(c) Symptoms:	
(d) Investigations-Laboratory and any other significant investigations conducted:	

Lab test	Abnormal Result	Site Normal Range	Collection date	Lab value previous or subsequent to this event	Collection date

(e) Results:	
(f) Management (Include management of study treatment, continued, temporarily held, reduced dose, permanent discontinuation, off Product):	
(g) Outcome:	

NB If the outcome is death, please complete & attach the death form.

D

D1. Was this Adverse Event originally addressed in the protocol and consent form? ☐ Yes ☐ No ☐ N/A
D2. Was this Adverse Event originally addressed in Investigators Brochure? ☐ Yes ☐ No ☐ N/A
D3. Are changes required to the protocol as a result of this SAE? ☐ Yes ☐ No ☐ N/A
D4. Are changes required to the consent form as a result of this SAE? ☐ Yes ☐ No ☐ N/A

If changes are **required**, please attach a copy of the revised protocol/consent form *with changes highlighted with a bright coloured highlighter.*

If changes are **not required**, please explain as to why changes to the protocol /consent form are not necessary based on the event.

From the data obtained or from currently available information, do you see any need to reassess the risks and benefits to the subjects in this research. ☐ Yes ☐ No

P.I. Signature _____ Date _____

Annex 7

	Title	Reference	Website
Hyperlink 1	MCAZ Drug Information Bulletin 2015	MCAZ Drug Information Bulletin 2015	www.mcaz.co.zw

Annex 8

	Title	Reference	Website
Hyperlink 2	Strengthening National Surveillance of Adverse Events Following Immunization	MCAZ Drug Information Bulletin Volume: 2 No:1 June 2013	www.mcaz.co.zw

Annex 9

	Title	Reference	Website
Hyperlink 3	Safety Monitoring of H1N1 Vaccine (August 2010 to December 2011)	MCAZ Drug Information Bulletin Volume: 2 No:1 June 2013	www.mcaz.co.zw

Annex 10

	Title	Reference	Website
Hyperlink 4	Cohort Event Monitoring Of Artemisinin Combination Therapies (ACTs) In Zimbabwe	MCAZ Drug Information Bulletin Volume: 1 December 2012	www.mcaz.co.zw

Annex 11

	Title	Reference	Website
Hyperlink 5	Targeted Spontaneous Reporting (TSR) Program of Antiretrovirals (ARVs) and Antituberculosis (Anti-TBs) and all essential medicines in Zimbabwe	MCAZ Drug Information Bulletin Volume: 2 No:1 June 2013	www.mcaz.co.zw

Annex12: Adverse Events Following Immunization (AEFI) Reporting Form.

AEFI Report ID Number (ZW-PR-DS-FAC-000-YR): ZW-_ _ _-_ _ _-_ _ _-_ _ _-_ _ _ _

ZIMBABWE REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Patient first name*: **Surname *Next of Kin:* **Patient's physical address*: Telephone: Sex: ☐M ☐ F **Date of birth (DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *OR Age at onset :* ☐☐ *Years* ☐☐ *Months* ☐☐☐ *Days*	**Reporter's Name*: Designation, Department & address: District/ Province: Reporting Institution Telephone & e-mail: *Today's date (DD/MM/YYYY)*: _ / __ / __ __

Health facility (or vaccination centre) name:

Vaccine						*Diluent*		
**Name*	**Date of vaccination*	**Time of vaccination*	Dose (1st, 2nd, etc.)	**Batch/ Lot number*	Expiry date	**Batch/ Lot number*	Expiry date	Time of reconstitution

**Adverse event (s):* ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever≥38°C ☐ Other (specify)..... Date & Time AEFI started (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ ☐☐ Hr ☐☐Min Was the patient hospitalized? ☐Yes ☐No Date patient notified event to health system (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	Describe AEFI (Signs and symptoms):

Treatment provided: yes/ no
**Serious: Yes/ No;* *If yes,* ☐ *Death* ☐ *Life threatening* ☐ *Disability* ☐ *Hospitalization* ☐ *Congenital anomaly*

**Outcome:*
☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown
☐ Died If died, date of death (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ Autopsy done: ☐Yes ☐No ☐Unknown

Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases). *Use additional sheet if needed :*

First decision making level to complete (District level):

Investigation needed: ☐ Yes ☐ No	If yes, date investigation planned (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

National level to complete:

Date report received at national level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	AEFI worldwide unique ID :
Comments:	

**Compulsory field*

Annex 13: AEFI Case Investigation Form

AEFI INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A — Basic details

Province: **District:** **AEFI Report ID:**

Name of vaccination site:

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐Other (specify) _____
Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Name of Investigating Health Worker:

Date AEFI reported: __ __ / __ __ / __ __ __ __
Date investigation started: __ __ / __ __ / __ __ __ __
Date investigation completed: __ __ / __ __ / __ __ __ __

Designation / Position:
Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐M ☐F
(use a separate form for each case in a cluster)
Patient's physical address *(Street name, house number, ward/village, phone number etc.)*:

Date of birth (DD/MM/YYYY):	***OR** Age at onset:*	***OR** Age group:*
___ / ___ / ____	___ *years* ___ *months* ___ *days*	☐ < 1 year ☐ 1–5 years ☐ > 5 years

Complete below table if vaccination information missing on the AEFI reporting form

Vaccine						*Diluent*		
**Name*	**Date of vaccination*	**Time of vaccination*	Dose (1st, 2nd, etc.)	**Batch/ Lot number*	Expiry date	**Batch/ Lot number*	Expiry date	Time of reconstitution

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom *(hr/min)*: __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐Unknown

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *(hr/m)*: __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B — Relevant patient information prior to immunization

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event	Yes / No / Unkn	
Adverse event after previous vaccination(s)	Yes / No / Unkn	
History of allergy to vaccine, drug or food	Yes / No / Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause	Yes / No / Unkn	
Was patient on medication at time of vaccination?	Yes / No /	

(If yes, name the drug, indication, doses & treatment dates)	Unkn	
Did patient consult faith healers before/after vaccination? *specify	Yes/ No / Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unkn	

For adult women
- Currently pregnant? Yes (weeks) _____ / No / Unknown
- Currently breastfeeding? Yes / No

For infants
The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

Section C Details of first examination** of serious AEFI case

Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy** ☐ **Other**_____ *If from verbal autopsy, please mention source* _____

Name of the person who first examined/treated the patient:_____

Other sources who provided information (specify): _____

Signs and symptoms in chronological order from the time of vaccination:

Name and contact information of person completing these clinical details:	Designation:	Date/time

Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day

Number vaccinated for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

a) When was the patient vaccinated? (✓ the ☐ below and respond to ALL questions)

☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown

In case of multidose vials, was the vaccine given ☐ within the first few doses of the vial administered? ☐ within the last doses of the vial administered? ☐ unknown?	
b) Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes / No
c) Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes / No / Unable to assess
d) Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes / No / Unable to assess
e) Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes / No / Unable to assess
f) Based on your investigation, do you feel that there was an error in vaccine handling (e.g. cold chain failure during transport, storage and/or immunization session etc.)?	Yes / No / Unable to assess
g) Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes / No / Unable to assess
h) Number vaccinated from the concerned vaccine vial/ampoule	
i) Number vaccinated with the concerned vaccine in the same session	
j) Number vaccinated with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k) Is this case a part of a cluster?	Yes / No / Unkn
i. If yes, how many other cases have been detected in the cluster?	
a. Did all the cases in the cluster receive vaccine from the same vial?	Yes / No / Unkn
b. If no, number of vials used in the cluster (enter details separately)	

It is compulsory for you to provide explanations for 'yes' answers separately

Section E Immunization practices at the place(s) where concerned vaccine was used

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn
If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____	
Specific key findings/additional observations and comments:	

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			

Section F Cold chain and transport

(Complete this section by asking and/or observing practice)

Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn

• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation from the refrigerator to the vaccination centre:	
• Was cold chain properly maintained during transportation?	Yes / No / Unkn
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Were conditioned coolant-packs used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality?
Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those affected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

Other comments:

Section H Other relevant findings/observations/comments

Annex 14: WHO Aide-memoire on AEFI Causality Assessment, 2013

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ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON CAUSALITY ASSESSMENT

Purpose: This aide-mémoire serves as a guide to a systematic, standardized process of assessing whether serious adverse events following immunization (AEFI[1]) are causally linked to vaccines/immunization or not.

Definition: AEFI causality assessment determines if a causal relationship exists between a vaccine (and/or vaccination) and an adverse event.

Rationale: Safety requirements for vaccines are stricter than those for drugs since vaccines are biological products that are more prone to lot variation and instability, they are used in healthy populations and the target groups are vulnerable. Vaccines therefore require a causality assessment process that responds in a timely manner and with scientific rigour to AEFI.

WHO SHOULD ASSESS AEFI CAUSALITY?

Ideally an AEFI review committee should be in place backed by written terms of reference. It should consist of independent experts who have no conflicts of interest. As far as possible, the experts should cover a broad range of expertise: infectious diseases, epidemiology, microbiology, pathology, immunology, neurology, forensics and vaccine programming. The committee should be supported by a secretariat (usually the national regulatory authority [NRA] and the immunization programme) that can provide supporting evidence and investigation findings to enable causality to be determined.

WHAT ARE PREREQUISITES FOR AEFI CAUSALITY ASSESSMENT?

- AEFI case investigation should be completed. Premature assessments may mislead classification.
- All relevant information should be available, including documents of investigation, laboratory and postmortem findings (if applicable).
- Valid diagnosis (unfavourable or unintended sign, abnormal laboratory finding, symptom or disease) for the AEFI must be defined, be well-founded and correspond accurately to the event being assessed.
- Information that could bias results (patient name, hospital name, etc.) should be anonymized.

POSSIBLE CAUSES OF AEFI

- **Related to vaccine or vaccination**
  - Vaccine product-related
  - Vaccine quality defect-related
  - Immunization error-related
  - Immunization anxiety-related
- **Coincidental adverse event**

AT WHAT LEVELS IS AEFI CAUSALITY ASSESSED?

AEFI causality assessment could be performed:

- **At population level** (is there a causal association between usage of a vaccine and a particular AEFI in the population?)
- **For an individual** (is the adverse event in the individual patient causally linked to the vaccine/vaccination?)

CONSIDERATIONS FOR ASSESSING CAUSALITY OF A SOLITARY AEFI:

- **Temporal relationship:** is it certain that the vaccination preceded the adverse event?
- **Alternate explanations:** is the event coincidental, i.e. is it due to something other than the vaccine product, immunization error or immunization anxiety?
- **Proof of association:** is there clinical or laboratory proof that the vaccine caused the event?
- **Prior evidence:** has a similar AEFI been previously reported in studies/literature or other sources?
- **Population-based evidence:** does the rate of event occurrence exceed the expected rate of the event in the population? (Refer to WHO information sheets on observed rates of known vaccine reactions.)
- **Biological plausibility:** can the association be explained by the natural history, biological mechanisms of the disease, laboratory evidence or animal studies? However this is not an important consideration.

WHICH AEFI TO SELECT FOR CAUSALITY ASSESSMENT?

All reported AEFI require verification of diagnosis, coding, review, information collation and storage. Causality assessment needs to be done for:

- **Serious AEFI** (i.e. events that are life-threatening or lead to death, hospitalization, significant disability or congenital anomaly)
- **Clusters of AEFI** (the cause for each case in the cluster should be determined separately). Line-listing of data may identify patterns that could constitute a signal
- Occurrence of **events above the expected rate** or of **unusual severity**

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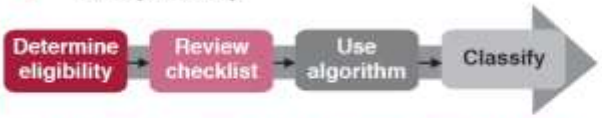
ADVERSE EVENT FOLLOWING IMMUNIZATION

- **Signals** resulting from single or cluster cases
- Other AEFI as decided by the review committee or an investigation team such as **immunization errors**, significant **events of unexplained cause** occurring within 30 days after a vaccination (not listed in the product label), or events causing **significant parental or community concern.**

WHAT ARE THE STEPS[2] OF A CAUSALITY ASSESSMENT?

- Determine the eligibility of the case
- Review the checklist to ensure that all possible causes are considered
- Use algorithm to determine trend of causality
- Classify causality.



HOW ARE CASES CLASSIFIED AT THE END OF THE ASSESSEMENT?

I. Case with adequate information

A. Consistent with causal association to immunization

A1. Vaccine product-related

A2. Vaccine quality defect-related

A3. Immunization error-related

A4. Immunization anxiety-related

B. Indeterminate

B1 Consistent temporal relationship but insufficient definitive evidence for vaccine causing the event

B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent with causal association to immunization (coincidental)

Underlying or emerging condition(s) or condition(s) caused by exposure to something other than vaccine

II. Case without adequate information

It is categorized as "unclassifiable" since it requires additional information to determine causality (the available information on such cases should be archived in a repository or an electronic database and classified when additional information becomes available)

WHAT ARE THE ACTIONS AFTER CAUSALITY ASSESSMENT?

They include providing feedback, training, modifying systems, refining tools, research, etc. to avoid and/or minimize recurrences. Based on outcomes of assessment, the following need to be considered:

A. Consistent with causal association to immunization

A1 Vaccine product-related reaction: Follow protocols adopted by each country.

A Vaccine quality defect-related reaction: Inform the NRA, manufacturer and relevant stakeholders. Take decision on existing vaccine stock.

A3 Immunization error-related reaction: Training and capacity-building are critical to avoid recurrences.

A4 Immunization anxiety-related reaction: Vaccinating in an ambient and safe environment.

B. Indeterminate

B1 The temporal relationship is consistent but there is insufficient evidence for vaccine causing the event: A national database of such AEFI cases could help to identify signals.

B2 Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization: If additional information becomes available, the classification can move into more definitive categories; if not, they are to be archived.

C. Inconsistent with causal association to immunization (coincidental)

Confirm diagnosis; information on why the case is classified as coincidental to be provided to the patients, relatives, care provider and community.

KEY RESOURCES FOR CAUSALITY ASSESSMENT

Causality assessment of an AEFI - User manual for the revised WHO classification
http://www.who.int/vaccine_safety/publications/gvs_aefi/en/

WHO vaccine reaction rates information sheets
http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

Brighton Collaboration
https://brightoncollaboration.org/public.html

[1] AEFI definition: any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf

[2] For detailed description of the steps, please refer to the Causality assessment of an AEFI - User manual for the revised WHO classification shown in key resources

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ADVERSE EVENT FOLLOWING IMMUNIZATION

STEP 1 (ELIGIBILITY)

Name of the patient	Name of one or more vaccines administered before this event	What is the Valid Diagnosis? (The case diagnosis of the AEFI)	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine/vaccination caused _____ ?(The event for review in step 2)

STEP 2 (EVENT CHECKLIST) [✓ check all boxes that apply]

I. Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
Does clinical examination, or laboratory tests on the patient, confirm another cause?	☐	☐	☐	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐	☐	☐	☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐	☐	☐	☐	
Immunization error					
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☐	☐	☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐	☐	☐	☐	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	☐	☐	☐	☐	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐	☐	☐	☐	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐	☐	☐	☐	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐	☐	☐	☐	
Immunization anxiety					
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	☐	☐	☐	☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?					
Did the event occur within an appropriate time window after vaccine administration?	☐	☐	☐	☐	
III. Is there strong evidence against a causal association?					
Is there strong evidence against a causal association?	☐	☐	☐	☐	
IV. Other qualifying factors for classification					
Could the event occur independently of vaccination (background rate)?	☐	☐	☐	☐	
Could the event be a manifestation of another health condition?	☐	☐	☐	☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐	☐	☐	☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐	☐	☐	☐	
Was there acute illness prior to the event?	☐	☐	☐	☐	
Did the event occur in the past independently of vaccination?	☐	☐	☐	☐	
Was the patient taking any medication prior to vaccination?	☐	☐	☐	☐	
Is there a biological plausibility that the vaccine could cause the event?	☐	☐	☐	☐	

Y: Yes. N: No. UK: Unknown. NA: Not applicable.

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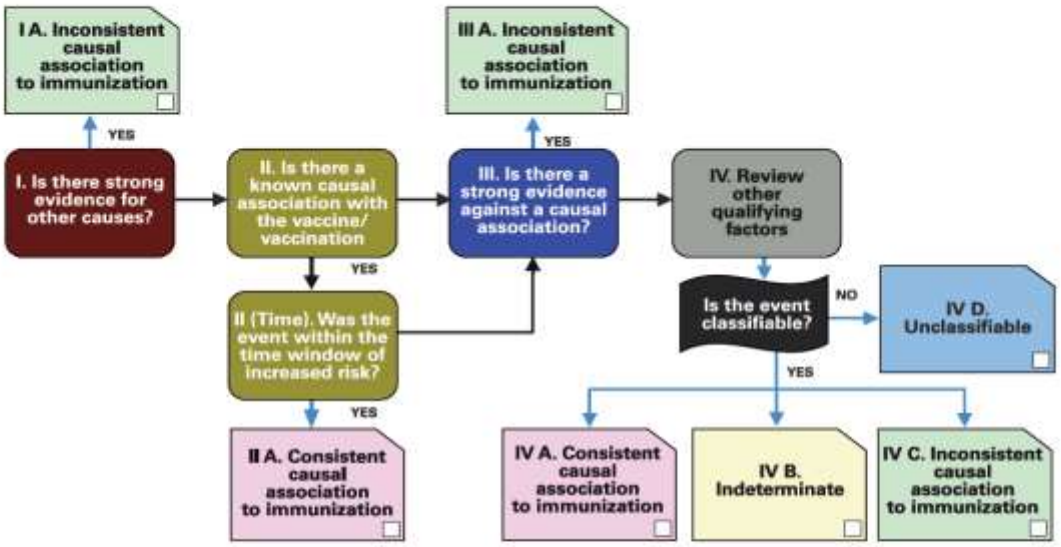
ADVERSE EVENT FOLLOWING IMMUNIZATION

STEP 3: (ALGORITHM) REVIEW ALL STEPS AND ✓ ALL THE APPROPRIATE BOXES



Notes for Step 3:

STEP 4: (CLASSIFICATION) ✓ ALL BOXES THAT APPLY

Adequate information available

A. Consistent causal association to immunization

- ☐ A1. Vaccine product-related reaction (As per published literature)
- ☐ A2. Vaccine quality defect-related reaction
- ☐ A3. Immunization error-related reaction
- ☐ A4. Immunization anxiety-related reaction

B. Indeterminate

- ☐ *B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
- ☐ B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent causal association to immunization

- ☐ C. Coincidental
  Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

Adequate information not available

Unclassifiable

- ☐ Specify the additional information required for classification

*B1: Potential signal and maybe considered for investigation

Summarize the classification logic

With available evidence, we could conclude that the classification is _____ because:

FEEDBACK AND CORRECTIVE ACTION RECOMMENDED:

Annex 15 Aide-mémoire on AEFI Investigation, 2013

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ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON AEFI INVESTIGATION

Purpose: This aide-mémoire proposes a systematic, standardized process to investigate reported serious adverse events following immunization (AEFI) and ascertain the underlying cause of the AEFI by:

- confirming a diagnosis and timing
- identifying details of vaccine(s) administered
- documenting the outcome of the reported adverse event
- determining whether the reported event is solitary or part of a cluster
- reviewing the operational aspects of the programme

DETECTION AND REPORTING

Vaccine recipients themselves and/or parents of vaccine recipients who identify AEFI should notify the same to the health care provider. All notified AEFI cases should be documented and reported in a simple standard reporting form by the health care provider.

WHICH OF THE REPORTED AEFI SHOULD BE INVESTIGATED IN MORE DETAIL?

A detailed AEFI investigation to assess causality is necessary if:

- it is serious[i]
- it is part of a cluster[ii]
- it is part of a suspected signal[iii]
- it is a suspected immunization error[iv]
- it appears on the list of events defined for AEFI investigation or
- it causes significant parental or public concern

WHO SHOULD INVESTIGATE AEFI?

Detailed AEFI field investigation can be done based on the program's operational structure and the expertise available. A basic preliminary investigation by local programme managers may be sufficient if the cause of the reported AEFI is very clear; otherwise, investigation should be done by next/higher administrative level, by a trained/skilled person/ team, depending on the nature of event, its seriousness and impact to the programme.

WHEN TO INVESTIGATE AEFI

If a detailed investigation is warranted, it should be initiated as soon as possible, ideally within 24 to 48 hours of the case being first reported.

CHECKLIST FOR AEFI INVESTIGATION

1. PRELIMINARY STEPS

- ☐ Develop national guidelines with case definitions for reportable AEFIs, reporting forms, investigation procedures, roles and responsibilities
- ☐ Develop resource documents and training material on reporting, management and investigation of AEFIs
- ☐ Designate and train staff to conduct an AEFI investigation using the investigation form and guidelines
- ☐ Train staff on how to collect and store specimens
- ☐ Have a functioning National AEFI Review Committee with suitable representation
- ☐ Establish procedure, criteria and designate focal persons for notifying and communicating with WHO and UNICEF (if UN- supplied vaccine) or other relevant party depending on procurement mechanism
- ☐ Identify a spokesperson for public communications

2. RECEIVING A REPORT

- ☐ Provide rapid attention to all reports received and immediate response to serious events
- ☐ Verify the information in the report, confirm the diagnosis, classify and assess the AEFI using established case definitions. Decide whether it needs further detailed investigation.
- ☐ If investigation is warranted, travel to the location of the AEFI, or delegate responsibility to another trained person

3. INVESTIGATE AND COLLECT DATA

- ☐ Obtain information from patient or relatives directly/ use available records
- ☐ Obtain information from immunization service providers and medical care service providers (hospital staff)/ use available records
- ☐ Ask about the vaccine(s) administered and other drugs potentially received
- ☐ Establish a more specific case definition if needed
- ☐ Ask about other vaccinees who may have received the same or other vaccines
- ☐ Observe the service in action
- ☐ Ask about cases in unvaccinated persons
- ☐ Formulate a hypothesis as to what may have caused the AEFI (see table below)
- ☐ Collect specimens (if indicated by investigation, but not as a routine):
  - ✓ from the patient
  - ✓ the vaccine and diluent if applicable
  - ✓ the syringes and needles

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ADVERSE EVENT FOLLOWING IMMUNIZATION

- ☐ Dispatch specimens to appropriate testing facility (laboratory, regulatory authority, etc.)

4. ANALYSE THE DATA

- ☐ Review epidemiological, clinical, and laboratory findings
- ☐ Share findings with national AEFI committee for expert advice
- ☐ Summarize and report findings

5. TAKE ACTION

The local response after an AEFI investigation should be based on findings (data/information) and local practices.. The highest priority is to treat patient. Suspending vaccination at the locality of the event temporarily pending investigation outcome may be necessary but is uncommon. Broader suspension of vaccination is only very rarely necessary. When taking action, it is important to

- ☐ Provide feedback to health staff
- ☐ Communicate findings and action to the parents and public – during all stages of the investigation
- ☐ Correct problem (based on the cause) by improving training, supervision and/or distribution of vaccines/injection equipment
- ☐ Replace vaccines if indicated

INVESTIGATING DEATHS AFTER IMMUNIZATION

After informing higher authorities, field investigation should be conducted by a team of clinical, laboratory and forensic experts supported by programme managers. A decision on autopsy should be taken within the local sociocultural, religious, political context. Autopsies should be done with adequate information of the circumstances of the event using standard autopsy protocols. Appropriate specimens should be collected for testing.

If an autopsy is not possible, a verbal autopsy can be carried out using established guidelines and protocols.

OUTCOME OF AEFI INVESTIGATION

On concluding the investigation, the documents and evidence collected should be compiled, a report prepared and submitted to a group of experts to determine/evaluate causality.

POSSIBLE CAUSES OF AEFI
Related to vaccine or vaccination
Vaccine product-related
Vaccine quality defect-related
Immunization error-related
Immunization anxiety-related
Coincidental adverse event

KEY RESOURCES FOR AEFI INVESTIGATION

- WHO standard AEFI reporting form http://www.who.int/vaccine_safety/REPORTING_FORM_FOR_ADVERSE_EVENTS_FOLLOWING_IMMUNIZATION.pdf?ua=1
- WHO standard AEFI investigation form http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2Dec14.pdf?ua=1
- Global manual on surveillance of AEFI http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/
- User manual for the revised WHO AEFI causality assessment classification http://www.who.int/vaccine_safety/publications/gvs_aefi/en/
- Brighton Collaboration standard case definitions https://brightoncollaboration.org/public.html
- Verbal autopsy standards: ascertaining and attributing causes of death http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index1.html

* An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

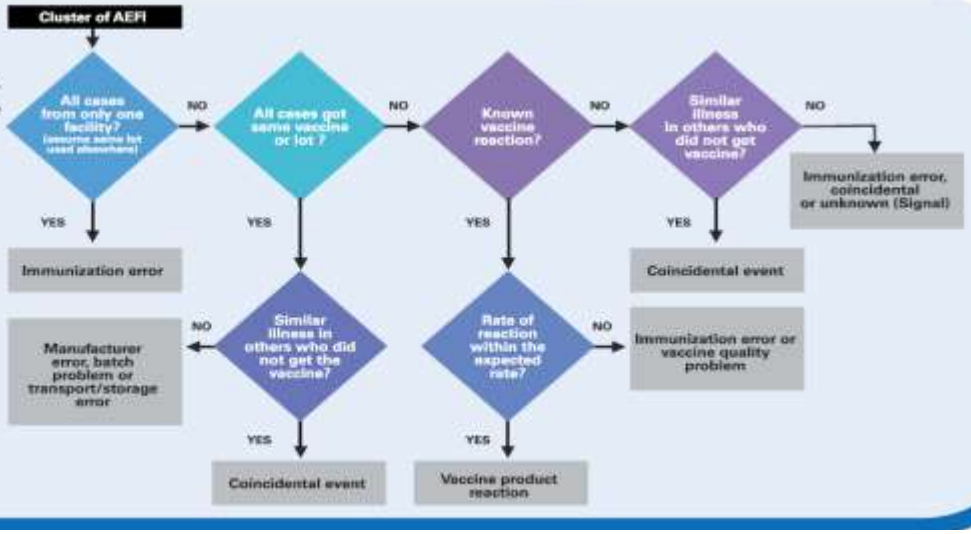
* Serious AEFI include death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or is life-threatening

* A cluster of AEFIs is two or more cases of the same adverse event related in time, place or vaccine administered

* Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.

INVESTIGATING AEFI CLUSTERS

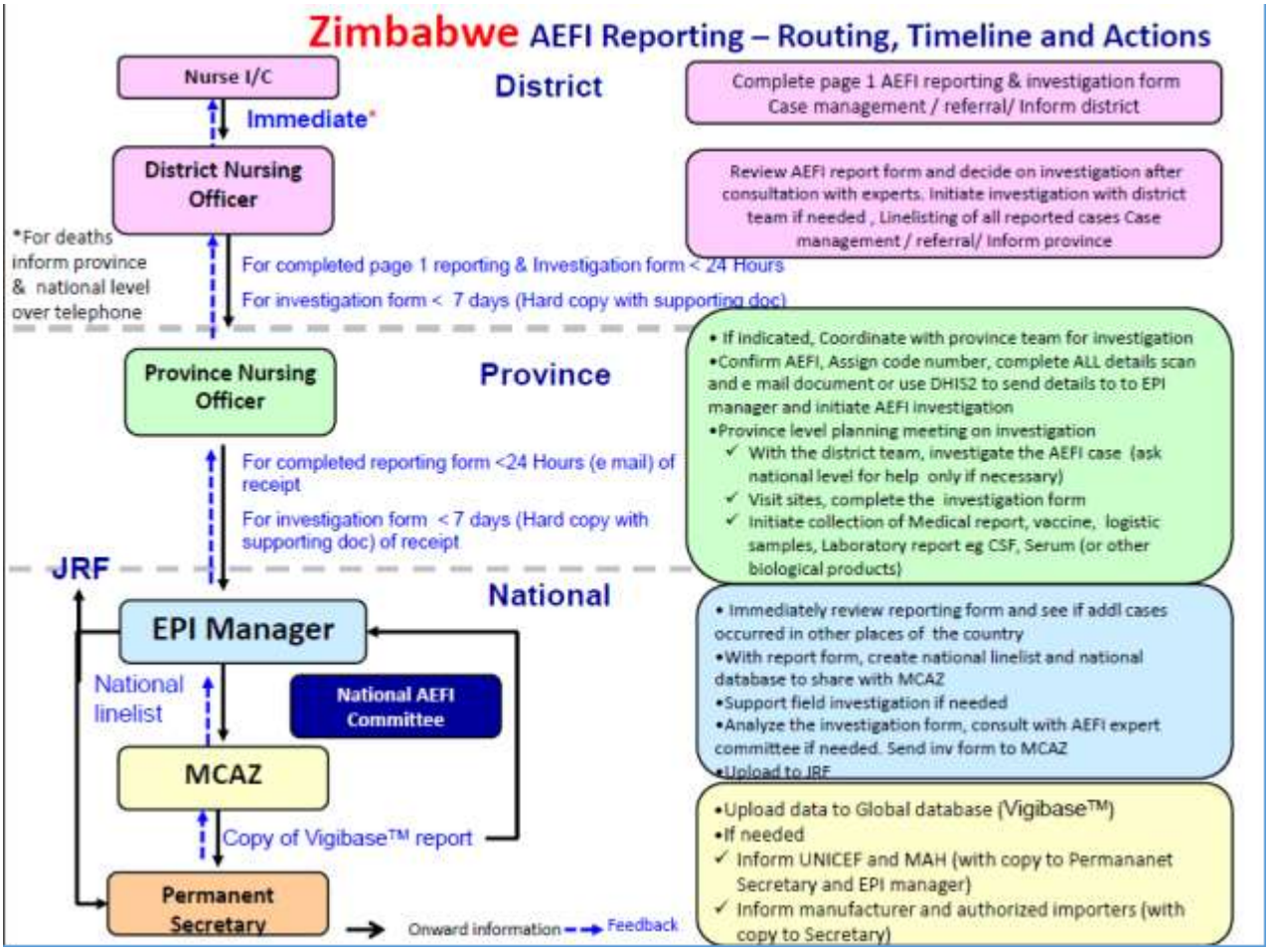
Suggested steps for identifying the most likely cause of a cluster of AEFI



Annex 16: WHO Causality Classification of Adverse Events (AE) Definition Categories Used by the MCAZ and the PVCT Committee

WHO Causality classification of Adverse Events (AE) definitions categories used by MCAZ and ADR &MR Committee	DAIDS Investigator causality classification of (AE) definition categories commonly used for clinical trials
CERTAIN -event or laboratory test abnormality, with plausible time relationship to drug intake. -cannot be explained by disease or other drugs. -response to withdrawal clinically plausible. -event definitive pharmacollogically or phenomenologically. -rechallenge if necessary.	**DEFINITELY RELATED** . The exposure to the study agent and adverse event are related in time, and a direct association can be demonstrated (e.g. the adverse experience has been identified as a known toxicity of the study agent product, and the study agent is clearly responsible for the event.
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.	**PROBABLY RELATED** The administration the study agent/procedures & adverse event are considered reasonably related in time and the event is more likely explained by the study agent than other causes.
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 lacking or unclear.	**POSSIBLY RELATED** The adverse event and the administration of the study agent/procedures are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent/procedures
UNLIKEL Y -event or laboratory test abnormality, with a time to drug intake which -makes relationship improbable. -disease or other drugs provide plausible explanations.	**PROBABLY NOT RELATED** A potential relationship between the study agent/ procedures and the adverse event could exist (i.e. the possibility cannot be excluded) but the adverse event is most likely explained by causes other than the study agent/procedures
CONDITIONAL/UNCLASSIFIED -event or laboratory test abnormality. -more data for proper assessment needed. -or additional data under examination.	**NOT RELATED** The adverse event is clearly explained by another cause not related to the study agent/procedures.
UNASSESSIBLE/UNCLASSIFIED -a report suggesting an adverse reaction. - cannot be judged because of insufficient or contradictory information. -report cannot be supplements or verified.	**PENDING** *****May be used as a temporary assessment only for death *Used only if data necessary to determine the relationship to study agent/procedures is being collected *A final assessment of relationship should be within 3 business days after reporting the death *If no final assessment is made within 3 business days by site, event will be assesses as possibly related to study agent/procedures *Any additional information received at a later time including an autopsy (post-mortem) report should be submitted as follow up report

Annex 17 Flowchart for AEFI management



VigiBase is the WHO Drug Safety database for the WHO International Drug Monitoring Programme, which is also the Zimbabwe National Pharmacovigilance drug safety database.

Joint Reporting Form (JRF): The WHO and UNICEF jointly collect information through a standard questionnaire, the JRF, which is sent to member states. The information collected in the JRF include estimates of national immunization coverage, reported cases of vaccine-preventable diseases, immunization schedules, as well as indicators of immunization system performances,WHO 2016.

Annex 18 Table of Useful Guidelines

Number	Name of Document/Guideline	Source of document/ URL link
1	7th Essential medicines List and Standard Treatment Guidelines for Zimbabwe. 2015.	NMTPAC, AIDS and TB Unit MOHCC
2	Guidelines for Antiretroviral Therapy in Zimbabwe. 2013.	NMTPAC, AIDS and TB Unit MOHCC
3	Guidelines for Good Wholesaling practice of Pharmaceuticals	MCAZ. http://www.mcaz.co.zw/index.php/downloads/category/9guidelines?download=9:goodwholesaling-practice-guidelines
4	A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Enhancing the safety of the TB patient. 2012.	WHO. http://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf
5	Safety of Medicines. A guide to detecting and Reporting Adverse Drug Reactions. Why health professionals need to take action. 2002.	WHO. http://whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf
6	Safety monitoring of medicinal products. Guidelines for setting up and running a pharmacovigilance centre.2000.	WHO.
7	The safety of Medicines in public health programmes: Pharmacovigilance an essential tool. 2006.	WHO. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Phar macovigilance_B.pdf
8	The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products	WHO. http://whqlibdoc.who.int/hq/2002/a75646.pdf
9	Pocketbook of Hospital Care for Children. Guidelines for the Management of Common Illnesses With Limited Resources. 2005.	WHO http://whqlibdoc.who.int/publications/2005/9241546700.pdf
10	Guidance for Industry. E2E Pharmacovigilance Planning. 2005	FDA http://www.fda.gov/cber/guidelines.htm

11	Causality assessment of an adverse event following immnunisation (AEFI): User manual for the revised WHO classification	WHO. http://www.who.int/vaccine_safety/publications/gvs_aefi/en/
12	Adverse Event Following Immunization (AEFI) case definition document	Brighton Collaboration . https://brightoncollaboration.org/pu blic/what-we-do/settingstandards/case-definitions/availabledefinitions/ extras/0/link/Case Defi nition Format Template.pdf
13	British National Formulary (BNF)	Royal Pharmaceutical Society of Great Britain
14	British National Formulary for children	Royal Pharmaceutical Society of Great Britain
15	ICH E2A Guideline – Clinical Safety Data Management: Definitions And Standards For Expedited Reporting	ICH. http://www.ich.org/fileadmin/Publi c Web Site/IC H Products/Guideli nes/Efficacy/E2A/Step4/E2A Guid eline.pdf
16	ICH E2B Guideline - Clinical Safety Data Management : Data Elements For Transmission Of Individual Case Safety Reports	ICH. http://www.ich.org/fileadmin/Publi c Web Site/ICH Products/Guidelines/Efficacy/E2B/S tep4/E2B R2 Guideline.pdf
17	ICH E2C(R2) Guideline - Periodic Benefit - risk Evaluation Report (PBRER)	EMA. http://www.ema.europa.eu/docs/en GB/document library/Regulatory a nd procedural guideline /2012/12/ WC500136402.pdf
18	ICH E2D Guideline – Post Approval Safety Data Management	EMA. http://eudravigilance.ema.europa.eu /human/docs/ICH%20E2D.pdf
19	ICH E2E Guidelines - Pharmacovigilance Planning	ICH. http://www.ich.org/fileadmin/Publi c Web Site/ICH Products/Guideli nes/Efficacy/E2E/Step4/E2E Guideline.pdf
20	Safety Monitoring of Medicinal Products: Reporting system for the general public	WHO. http://www.who.int/medicines/areas /quality safety/safety efficacy/Con sumerReporting.pdf
21	An Operational Plan for the Nationwide Transition to Option B+ in Zimbabwe, September 2013-November 2014. Ministry of Health and	PMTCT-AIDs & TB Unit, MoHCC guidelines

	Child Care.	
22	Global Manual on Surveillance of AEFIs	WHO: http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

Annex 19 Experiences and Lessons from Implementing Cohort Event Monitoring Programmes for Antimalarials in Four African Countries: Results of a Questionnaire-Based Survey

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ORIGINAL RESEARCH ARTICLE

Experiences and Lessons From Implementing Cohort Event Monitoring Programmes for Antimalarials in Four African Countries: Results of a Questionnaire-Based Survey

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Abstract

Introduction Cohort event monitoring (CEM) is an intensive method of post-marketing surveillance for medicines safety. The method is based on prescription event monitoring, which began in the 1970s, and has since been adapted by WHO for monitoring the safety of medicines used in Public Health Programmes. CEM aims to capture all adverse events that occur in a defined group of patients after starting treatment with a specific medicine during the course of routine clinical practice.

Objective The aims of this study were to describe the experiences of National Pharmacovigilance Centres (NCs) that have used CEM to monitor artemisinin-based combination therapy (ACT) for uncomplicated malaria in the African setting, to raise awareness of some of the challenges encountered during implementation and to highlight aspects of the method that require further consideration.

Method A questionnaire-based survey was conducted to capture the experiences of NCs that have implemented CEM for active post-marketing surveillance of antimalarial medicines in sub-Saharan Africa. Six NCs were identified as having implemented CEM programmes and were invited to participate in the survey; five NCs indicated willingness to participate and were sent the questionnaire to complete.

Results Four NCs responded to the survey—Ghana, Kenya, Nigeria and Zimbabwe—providing information on the implementation of a total of six CEM programmes.

Key Points

Cohort event monitoring (CEM) provides an opportunity to raise awareness of pharmacovigilance among healthcare providers and encourage a perception that pharmacovigilance falls within the scope of clinical practice.

Detailed planning for every step in the implementation of CEM is necessary to avoid costly study prolongation.

CEM data collection and management should integrate with existing patient management and pharmacovigilance systems wherever possible, to minimise workload.

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Their experiences indicate that CEM has helped to build pharmacovigilance capacity within the participating NCs and at the monitoring sites, and that healthcare providers (HCPs) are generally willing to participate in implementing the CEM method. All of the programmes took longer than expected to complete: contributing factors included a prolonged enrolment period and unexpectedly slow data entry. All of the programmes exceeded their budget by 11.1–63.2 %. Data management was identified as a challenge for all participating NCs.

Conclusions The reported experiences of four NCs that have undertaken CEM studies on ACTs indicate that CEM has helped to build pharmacovigilance capacity within NCs and monitoring sites and that HCPs are willing to participate in CEM programmes; however, the method was found to be labour intensive and data management was identified as a challenge. Reducing the workload associated with CEM, particularly in relation to data management, and integrating the method into the routine work of HCPs and NCs should be considered for future implementation.

1 Introduction

The introduction of artemisinin-containing anti-malarial therapies in early 2000 for the treatment of uncomplicated malaria in endemic countries highlighted a need for studies that would yield more complete safety data in the post-authorisation period, especially under large-scale use where their safety had not been fully assessed. To meet this need, a modified version of prescription event monitoring [1–3] was proposed in 1998 [4] and was subsequently developed by the World Health Organization (WHO) as cohort event monitoring (CEM), a method of intensive post-marketing surveillance for medicines used in public health programmes. Although initially developed for monitoring artemisinin-based combination therapies (ACTs), the method has since been adapted for use in HIV/AIDS treatment programmes and is now being considered for use in tuberculosis control programmes [5–7]. CEM is intended for monitoring the safety of a new chemical entity in the early post-marketing phase, but is also suitable for monitoring older medicines with new indications [5].

CEM is a prospective, observational (non-interventional), cohort study that is undertaken early in the post-marketing phase of a new drug. The method is designed to capture all adverse events[1] that occur in a defined group of patients (the cohort) who are exposed to a specific, newly marketed medicine during the course of routine clinical practice [5]. CEM differs from its predecessor (prescription event monitoring) in that the cohort is enrolled by the healthcare provider instead of relying on prescription details supplied by pharmacies (a practice not common in resource-constrained settings).

Patients are enrolled in the cohort as they start treatment on the monitored medicine (treatment initiation); demographic information and medical information on the patient's disease status, pregnancy status, past medical history, medication use and presenting symptoms is captured at this initial encounter. Any new medical events (change in clinical condition, new symptoms or diagnoses, or significant changes in laboratory parameters) that have occurred during a defined comparator period prior to starting the monitored medicine are also recorded at treatment initiation. Patients are then followed up after a defined interval (treatment review) to record any new adverse events that began after starting treatment with the monitored medicine, regardless of whether or not the drug was suspected to have caused the event. The information is sent to the National Pharmacovigilance Centre (NC), where each reported event is assessed for causality to determine the likelihood that the event was caused by the monitored medicine, based on the WHO Uppsala Monitoring Centre (WHO-UMC) causality assessment system [8].

By capturing all clinical events, regardless of suspicion of causality, CEM has the potential to identify previously unrecognised and unsuspected adverse drug reactions (ADRs). The cohort data provides a denominator for calculation of incidence rates and, because background health information is collected at treatment initiation, it may also be possible to identify risk factors for some ADRs.

The CEM method has been used to monitor the safety of antimalarial medicines in Ghana, Kenya, Nigeria, Tanzania and Zimbabwe [9]. Practical handbooks have been published by the WHO on how to conduct CEM in public health programmes for malaria, HIV/AIDS and tuberculosis [5–7]. Several CEM programmes have published their results from monitoring selected ACTs [10–13], and one

[1] An adverse event is described as "Any untoward medical occurrence temporally associated (i.e. associated in time) with use of a medicinal product, but not necessarily causally related" (WHO). Adverse events may include: (1) any new condition or diagnosis recorded in patient's medical record (favourable or unfavourable); (2) reason for referral to a specialist or admission to hospital; (3) unexpected deterioration or improvement in concurrent/pre-existing condition; (4) suspected drug reaction; (5) clinically important alteration in laboratory values; (6) lack of expected therapeutic effect; (7) pregnancy-related conditions; (8) events in infants exposed in utero; (9) accidents; (10) death—including cause of death, if known.

CEM programme has recently published preliminary results from monitoring antiretrovirals [14]. Related publications identify challenges for implementing pharmacovigilance in resource-constrained settings [15] and propose strategies to complement spontaneous reporting for monitoring the safety of medicines in public health programmes [7]. This is the first paper to document country experiences of CEM implementation. In this paper, we report on the experiences of four NCs that have each implemented one or more CEM programmes for ACTs in the African setting, following the method outlined in the WHO publication 'A Practical Handbook on the Pharmacovigilance of Antimalarial Medicines' (the CEM handbook) [5]; we aim to raise awareness of some of the challenges encountered during the planning and implementation process and to highlight aspects of the method that require further development. The results of individual CEM programmes are beyond the scope of this paper.

2 Methods

A questionnaire-based survey was conducted to capture the experiences of African countries that have implemented the CEM method for active post-marketing surveillance of antimalarial medicines. The NCs of six African countries that had implemented a CEM programme were contacted to indicate their interest in sharing their experiences; five NCs agreed to participate. A questionnaire was developed in English and sent to the five NCs for feedback on the content and wording of the questions to ensure there was no ambiguity and that they could provide the required information. A final version of the questionnaire (see electronic supplementary material) was then sent out for completion by the NCs. In the event that a country had implemented more than one CEM programme, the NC was requested to fill in a separate questionnaire for each CEM programme. The questionnaire was circulated in October 2013 and responses were received between January and May 2014.

The questionnaire was divided into three sections. The first section concerned characteristics of the country, including information about the structure of the health system and pharmacovigilance in the country. The second section focused on the preparation phase, including the rationale for undertaking a CEM study, ethical approval, stakeholders and funding, development of programme tools, site selection, training and sensitisation. The third section focused on the actual implementation of the CEM study, including human resources, patient enrolment and follow-up, data management and monitoring and evaluation. Two final questions asked the respondents to consider the challenges and lessons learnt from undertaking the CEM study.

The responses from the completed questionnaires were entered into an Excel spreadsheet that was organised into the same sections as the questionnaire. Reponses from each country were compared and themes identified. These themes formed the basis for presentation of the results and subsequent discussions.

3 Results

Survey responses were received from the NCs of four countries—Ghana, Kenya, Nigeria and Zimbabwe; a fifth country had agreed to participate but did not send a completed questionnaire.

3.1 Profile of Participating Countries

Population data for each of the countries that responded and information on each of the NCs are presented in Table 1. All of the four participating NCs are located within the national medicines regulatory authority, as shown in Table 1, which also shows the year that each of the countries joined the WHO Programme for International Drug Monitoring and indicates the size and activity of each of the participating NCs.

3.2 Cohort Event Monitoring (CEM) Programme(s) and Stakeholders

The four NCs undertook a total of six CEM programmes. All six programmes monitored ACTs, particularly artemether-lumefantrine (AL) and artesunate-amodiaquine (AA). Table 2 provides an overview of each of the CEM programmes.

The NCs in all four countries coordinated implementation of CEM in collaboration with other stakeholders such as the national malaria control programme, selected healthcare institutions/sentinel monitoring sites across the country, national and international non-governmental organisations (NGOs), the WHO and marketing authorisation holders.

3.3 Development and Pre-Testing of CEM Data Collection Tools

The data collection forms used in the CEM programmes were based on a template provided in the CEM handbook [5]. Each programme adapted the template to suit their specific needs. Four of the six CEM programmes pre-tested the data collection tools by enrolling a small number of patients at each monitoring site using the forms. Nigeria did not pre-test the tools used during the pilot programme; however, because the forms used during the pilot

Table 1 Characteristics of countries participating in the survey on cohort event monitoring (CEM) programme implementation

	Ghana	Kenya	Nigeria	Zimbabwe
Population (million)	26	41	168	14
Urban population (%)	50	25	50	45
Agency responsible for pharmacovigilance	Food and Drugs Authority Ghana	PPB	NAFDAC	MCAZ
Year joined WHO Programme[a]	2001	2010	2004	1998
No. of pharmacovigilance staff at NC	6	8	26	10
No. of ICSRs committed to VigiBase[b] in 2013	227	2324	4050	356

ICSRs Individual Case Safety Reports, *MCAZ* Medicines Control Authority of Zimbabwe, *NAFDAC* National Agency for Food and Drug Administration and Control, *PPB* Pharmacy and Poisons Board, *WHO* World Health Organization

[a] The WHO Programme for International Drug Monitoring

[b] The Global ICSR Database of the WHO Programme for International Drug Monitoring

programme were used during the scale-up (with slight modifications), the pilot served as a pre-test for the scale-up programme.

3.4 Training

All participating NCs trained the CEM site teams on the principles of pharmacovigilance and the CEM method prior to commencement of the programme. The training was either conducted centrally, where master trainers were trained and equipped to train other members of the CEM team, or through training meetings and/or on-site training for site personnel. High staff turnover at some monitoring sites and NCs necessitated frequent training for new members.

3.5 Cohort Size and Monitoring Sites

Details of the number of patients enrolled into the cohort in each CEM programme, the number, type and urban/rural distribution of monitoring sites and the human resources requirements are provided in Table 2. The criteria for site selection included regional representation, interest and willingness of the institutional contact person to participate in pharmacovigilance and CEM, active participation of the site in pharmacovigilance (measured by the number and quality of ADR reports sent to the NC), malaria burden in the locality and accessibility of the site. In addition to the public sector health facilities, two programmes engaged private sector community pharmacies for patient monitoring.

3.6 Use of Incentives

All programmes reported using incentives to encourage healthcare providers (HCPs) to participate in the programme. The reasons given for using incentives were to motivate the HCPs to collect quality data, to compensate for their time, for logistics and transport support and to ensure their commitment to the programme. The nature and quantity of incentives was determined independently by each country based on their operating environment and local context. Details of the incentives provided to HCPs are shown in Table 3.

Most respondents considered that it would not be possible to undertake CEM without providing incentives for HCPs. The reasons stated were that CEM is demanding and time consuming and since many HCPs were already overworked, it is unlikely that they would take on additional work (especially work they consider to be outside their primary responsibility) without an incentive. Only one NC considered that it would be possible to undertake CEM without incentives because of the "availability of professionals who would be willing to participate" but warned that the "response rate might be low".

Five of the CEM programmes also provided incentives for patients. The nature and quantity of the patient incentives are detailed in Table 3. Opinions on the feasibility of conducting CEM without incentives for patients were equally split between the six programmes. In Zimbabwe, where no incentive was given to patients, it was reported that patients saw the monitoring as part of their treatment and were appreciative of the treatment, especially at a time when the country was going through a financially challenging period. The NC in Ghana offered reimbursement of transportation costs by way of incentive, but reported that "over 98 % of follow-up was by telephone call" and "most patients did not take [the incentive] even when they came back to report ADR". The NCs in Kenya and Nigeria, on the other hand, both considered that the programme would be unsuccessful without the use of incentives for patients.

Table 2 Overview of the cohort event monitoring (CEM) programmes

	Ghana (WHO)	Ghana (AMFm)	Kenya	Nigeria (pilot)	Nigeria (scale-up)	Zimbabwe
Agency responsible for CEM Programme	Food and Drugs Authority Ghana	Food and Drugs Authority Ghana	PPB	NAFDAC	NAFDAC	MCAZ
Programme name	WHO CEM	AMFm CEM	CEM for AL	Pilot CEM on patients treated for malaria with ACTs	Scale-up CEM on patients treated for malaria with ACTs	Cohort Event Monitoring of artemisinin combination therapies
Monitored medicines	All antimalaria medicines	AA, AL	AL	AL, AA[a]	AL, AA[a]	AL
Rationale for CEM study	Assess safety and quality of anti-malaria medicines as a result of a high number of ADR reports received for anti-malarials	Assess safety and quality of AMFm anti-malarials due to change in malaria treatment policy	Change in treatment policy to use of new antimalaria medicines, widespread use of the new medicine, safety of monitored medicine not known	Change in malaria treatment policy to ACTs. Inadequate information on safety of ACTs among populations in Nigeria	Change in malaria treatment policy to use of ACTs. Inadequate information on safety of ACTs among populations in Nigeria. Inadequate information on safety profile of ACTs obtained from the pilot	To understand safety and effectiveness of AL combination therapy introduced for the treatment of uncomplicated malaria in Zimbabwe following WHO guideline in 2006
Cohort size, target/actual	10,000/7320	10,000/5949	3000/3238	3000/3010	10,000/10,260	10,000/6800
Monitoring sites, total no. (% urban distribution)	5 (100)	4 (100)	8 (60)	6 (100)	18 (100)	84 (30)
Type of sites	Public sector tertiary and secondary level hospitals	Public sector tertiary and secondary level hospitals	Public sector secondary and primary level hospitals	Public sector tertiary, secondary and primary level hospitals	Same as pilot with the inclusion of private sector community pharmacies	Public sector secondary and primary level hospitals and private sector community pharmacies
Staff required for monitoring, total no. and type of staff	50 Doctors, pharmacists, nurses, dispensing technologists	51 Doctors, pharmacists, nurses, pharmacy assistants	63 Doctors, nurses, pharmacists, clinical assistants, clerical staff and lab personnel	41 Doctors, nurses, pharmacists, clinical assistants, Lab technician, clerical assistants	103 Doctors, nurses, pharmacists, clinical assistants, Lab technician, clerical assistants	444 Doctors, nurses, pharmacists, clinical assistants, clerical staff, rural and environmental health workers (follow up of patients)
Approximate budget in US$	95,000	108,000	76,000	50,000	146,000	200,000
Approximate actual cost in US$	108,000	120,000	124,000	80,000	221,000	250,000

Table 2 continued

	Ghana (WHO)	Ghana (AMFm)	Kenya	Nigeria (pilot)	Nigeria (scale-up)	Zimbabwe
Sources of funding including commodities	WHO, FDA	Global Fund, Malaria control programme, FDA	EU, PPB, Malaria control	WHO, NAFDAC, Malaria control, SFH, YGC	Global Fund, Malaria control, NAFDAC, WHO, Sanofi Aventis	Global Fund, UNICEF, MCAZ

AA artesunate-amodiaquine, *ACTs* artemisinin combination therapies, *AL* artemether-lumefantrine, *AMFm* Affordable Medicines Facility for malaria, *EU* European Union, *FDA* Food and Drug Administration, *MCAZ* Medicines Control Authority of Zimbabwe, *NAFDAC* National Agency for Food and Drug Administration and Control, *PPB* Pharmacy and Poisons Board, *SFH* Society for Family Health, *WHO* World Health Organization, *YGC* Yakubu Gowon Centre

[a] A co-packaged formulation of AA (Arsuamoon®) was used in the pilot while a fixed-dose combination with reduced strength of amodiaquine (Winthrop ASAQ®) was used in the scale up

3.7 Duration of Enrolment

Table 3 shows the target and actual time taken to enrol the cohort. The time taken to complete enrolment exceeded the targeted timeframe by 50–100 % in all but one of the studies; only the Nigeria Pilot Programme was able to complete enrolment within the projected timeframe.

3.8 CEM Data Management

All responding countries reported using paper-based data collection forms. All completed CEM forms were sent to the NC for centralised data entry into CemFlow [16]—an electronic data management tool developed by UMC at the request of WHO, specifically for CEM studies. Completed forms were transmitted to the NC by a variety of means including courier, hand delivery by site staff, pick up by NC staff or leveraging of existing in-country distribution channels such as those used by Ministry of Health or public health programmes to distribute commodities within the system. The time required for data entry ranged from 4 weeks to 2 years. The number of people involved in data entry and the time taken to complete the task varied across the studies. Some studies such as the Kenya CEM programme for monitoring AL used dedicated data entry clerks to enter the CEM data over a period of 4 weeks, while other programmes such as the Nigeria Pilot CEM study used temporary staff to enter data over a long period of time. The Kenya NC reported that the CEM data management tool, CemFlow, "should be made more user-friendly" and the Ghana NC commented that the "data entry process has been one of the most challenging aspects of the study", citing concerns over the use of pharmacovigilance staff rather than data entry clerks for data entry, incomplete development of CemFlow and a lack of correlation between the data collection forms used in their programmes and the CemFlow data entry interface.

3.9 Cost of CEM

The actual cost of the CEM programmes exceeded the budgeted cost by 11.1–63.2 %. The funding sources for each programme are shown in Table 2. Two of the programmes also obtained non-monetary contributions such as insecticide-treated nets from stakeholders. The prolonged enrolment period and unexpectedly slow data entry added to the overall time and cost of the programme.

3.10 Effect of CEM on Spontaneous Reporting

The NCs of Nigeria and Zimbabwe reported a positive effect of CEM on spontaneous reporting of ADRs while Ghana and Kenya reported a reduction in the number of

Table 3 Planning and implementation of the cohort event monitoring (CEM) programmes

	Ghana (WHO)	Ghana (AMFm)	Kenya	Nigeria (pilot)	Nigeria (scale-up)	Zimbabwe
Ethical approval obtained and time taken	No	No	Yes, 1 mo	Yes, 2 mo	Yes, 9 mo	Yes, 1 mo
Requirement for patient consent	Verbal informed consent and universal enrolment with opt-out option	Verbal informed consent and universal enrolment with opt-out option	Written informed consent and universal enrolment with opt-out option	Verbal informed consent	Written informed consent	Written informed consent
Factors considered in site selection	Interest in participation; regional representation; quality of ADR reporting in previous year	Interest in participation; regional representation; quality of ADR reporting in previous year	Prevalence of malaria; willingness to participate; regional representation	Regional representation	Regional and health sector (primary, secondary, tertiary) representation	Prevalence of malaria; accessibility of sites (e.g. good roads)
Enrolment period: (actual no. of mo/target)	24/12	24/12	11/6	3/3	6/3	36/24
Data entry period	500 days	500 days	4 weeks	2 y	18 mo	2 y
Staff planned for or engaged in data entry	1 per site	1 per site planned	8	4 temporary staff with high turn over	4	3
Percentage loss to follow-up	5	5	0.3	15	0.5	30
Incentives for HCPs	Approx. US$30/mo	Approx. US$15 and US$30/mo	Approx. US$1.3/patient successfully followed up	Approx. US$70–320/mo	Approx. US$100–400/mo	Yes; amount not provided
Incentives for patients	Approx. US$0.3/patient for transport	Approx. US$0.3/patient for transport	Approx. US$1.3/patient/visit	Approx. US$1.5/patient for transport	Approx. US$3/patient for transport	No incentive given to patients

AMFm Affordable Medicines Facility for malaria, *HCPs* healthcare providers, *WHO* World Health Organization

Table 4 Key challenges and lessons learnt identified by each cohort event monitoring (CEM) programme

Programme	Comments
Ghana (WHO and AMFm)	Challenges: Sustaining enthusiasm of the study team; enrolling target number of patients into cohort due to seasonal variation of malaria, strike action by HCPs, delays in fund release and shortage of monitored medicines; delay in data entry and analysis due to CemFlow issues including access and lack of analysis capacity; use of pharmacovigilance staff rather than data entry clerks for data entry
	Lessons: Pretesting helped to appreciate the need to get a convenient time for follow-up call and obtain an alternate telephone number; increase patient enrolment sites in line with target cohort; ensure that fields in data collection tools are in line with fields in software to ensure seamless data analysis. NC and CEM site staff gained skills in implementing CEM
Kenya	Challenges: Inadequate funding; social, cultural and religious barriers (e.g. some women could not give informed consent without permission from their husbands and poor adherence to treatment during the Muslim Ramadan period when patients could only eat in the evening); strike action by HCPs; reduced malaria burden at some sites; staff turnover; data entry and limited analytical functions in CemFlow
	Lessons: A new treatment policy was implemented while CEM was ongoing that made it mandatory to test for malaria before treatment, This helped to determine a more realistic prevalence of malaria using CEM, which turned out to be less than projected. It also reduced unnecessary exposure of patients to antimalarial medicines
Nigeria (Pilot and Scale-Up)	Challenges: Insecurity in parts of the country; inadequate staff at some community pharmacies leading to increased workload; high personnel turnover; initial lack of cooperation by other staff at some sites; strike action by HCPs, more time required to explain CEM and obtain informed consent from patients; apprehension by some patients and unwilling to consent as they saw CEM as something new; reluctance by some patients to provide their phone numbers; preferential prescription of AL leading to early exhaustion of AL at some sites, poor recollection of other medicines taken prior to use of ACT; low literacy levels; faking of symptoms by patients to get incentives; lack of dedicated personnel for data entry including use of temporary staff; poor internet access
	Lessons: There is need to ensure timely supply of all study materials prior to commencement, ensure periodic review of progress, pre-test data collection tools and processes prior to commencement, sufficient funds are required and dedicated data entry personnel are invaluable for data entry. Increased awareness about pharmacovigilance in general
Zimbabwe	Challenges: Erratic and delayed disbursement of funds subject to satisfactory monthly acquittals before further disbursement, high staff turnover at all 84 sites and NC, inadequate funding for data entry clerks, additional funds required to pay data entry staff
	Lessons: The 6-month pilot phase indicated that CEM was feasible and could be scaled up. It also identified the need for quarterly re-training of healthcare professionals and monthly supervisory visit to sites due to high staff turnover at the monitoring sites. CEM was very good for monitoring safety of ACTs; however, it is very expensive and requires adequate staff and follow-up tools such as cell phones and internet which were not readily available in Zimbabwe at the time. Pharmacovigilance advocacy and sensitisation. NC gained confidence to conduct active pharmacovigilance

AMFm Affordable Medicines Facility for malaria, *HCPs* healthcare providers, *NC* National Pharmacovigilance Centre, *WHO* World Health Organization

ADR reports received by their national spontaneous reporting programme from sites participating in CEM.

3.11 Challenges and Lessons Learnt

The key challenges and lessons learnt identified by each of the NCs in the course of implementing CEM are summarised in Table 4.

4 Discussion

We report on the experiences of four African NCs that have implemented the newly described CEM method for active post-marketing surveillance of ACTs. Their experiences of undertaking a total of six CEM programmes provide useful information on the requirements and challenges of introducing safety monitoring of intensive medicines in

resource-limited settings. It is important to document the experiences of these early implementations to inform further development and refinement of the method and to shed light on some of the practical issues that need to be considered when planning such a programme in this setting. The survey focused only on practical issues of implementation and did not cover issues relating to data analysis or the study results.

Overall, each of the NCs reported similar experiences. All of the CEM programmes took longer than expected to complete. A number of unforeseen delays contributed to the prolonged timeframe for implementation, including the time required to obtain individual informed consent, strike action by healthcare workers, seasonal variation in malaria cases and lower than anticipated incidence of malaria in some regions (which prolonged the patient enrolment period in some programmes), shortage of monitored medicines, insecurity in some regions, delays in disbursement of funds, attrition of trained site personnel and insufficient data entry staff leading to unexpectedly slow data entry. One programme also reported that the time taken to obtain ethical approval was longer than anticipated, contributing to a delay in starting the study.

Although it is not possible to plan for all contingencies, awareness of potential pitfalls may help to avoid some of the factors that contributed to the extended study duration in these programmes.

4.1 Site Selection

To facilitate timely enrolment, the monitoring sites should be selected to include regions with the highest prevalence of the disease for which the monitored medicine is used. Site selection should also take into consideration the representativeness of the cohort, the willingness and capacity of the HCPs to participate in the monitoring and the accessibility of the sites. Selection of sites in these CEM programmes was predominantly influenced by a need for representative geographic distribution, although malaria prevalence and willingness of HCPs to participate were also seen as important factors. Less frequently reported factors were the prior experience of ADR reporting, accessibility of the sites and health sector representation.

Two of the CEM programmes (the Nigerian Scale-Up and Zimbabwe studies) engaged private-sector health facilities (community pharmacies) for monitoring the ACTs. Up to 82 % of all malaria episodes in sub-Saharan Africa are managed outside the official health sector and the private sector accounts for 40–60 % of all antimalarial drugs distributed, with unofficial sources such as street sellers and market stalls accounting for as much as 25 % [17, 18]. Including community pharmacies in the monitoring programme may help to increase the rate of enrolment and enhance the representativeness of the cohort. In the programmes where community pharmacies were engaged, enrolment still took longer than expected, but the NCs cited a number of other problems (Table 4) that delayed their progress.

4.2 Timing of CEM Implementation

The timing of the monitoring should allow for seasonal variation in the disease prevalence, and monitoring of ACTs should be planned to coincide with the peak malaria season. The CEM programme for ACTs in Kenya reported that a number of unforeseen delays (e.g. strike action by nurses, doctors and pharmacists and the Muslim Ramadan period in some areas) extended the planned monitoring period beyond the malaria season, thereby prolonging the overall time taken to complete the enrolment. Only three of the six programmes met their enrolment target, and only one (Nigeria Pilot study) achieved their target within the anticipated time frame.

4.3 Informed Consent

The time required to inform patients about the purpose of the monitoring and to obtain their informed consent was identified as a factor in prolonging the study duration in one of the studies. The CEM Handbook warns that explaining the rationale and requirements of the monitoring programme to individual patients will be time consuming, increase complexity and add to the cost—a concern that proved true in practice. A further caveat in the handbook stated that a requirement for formal informed consent could potentially compromise the validity of the results if many patients refused to be enrolled [5]. CEM is a non-interventional, observational study; all patients who are prescribed the monitored medicine during the course of routine clinical practice and who are willing to participate are eligible for enrolment in the cohort. Consent may be required to collect their personal health information and to be contacted for a follow-up interview. For CEM programmes where obtaining informed consent is a requirement by the ethics committee, NCs need to carefully plan how to obtain full informed consent, taking into consideration the time required to explain the purpose of the study to patients and how their data will be stored and used, so that sufficient resources can be allocated.

Unforeseen challenges that were reported in relation to obtaining informed consent included socio-cultural barriers such as women requiring their husband's permission to give consent, apprehension about signing the form, concerns about HCPs calling to enquire about treatment progress and communication barriers created by low literacy levels.

4.4 Data Management

The UMC, in collaboration with WHO, developed a data management tool, CemFlow, specifically for CEM studies. The tool was still under development at the time these CEM studies were implemented and was not fully optimised for data management. Direct data entry at the point of care was technically possible with CemFlow, but limited IT capacity at the monitoring sites made it impracticable; hence, all of the CEM programmes used paper-based data collection forms with subsequent centralised manual data entry into CemFlow.

All of the NCs reported experiencing challenges with data management. The CEM method requires data capture at each patient encounter. For ACTs, which generally involve a 3-day course of treatment, CEM requires a data collection form to be completed at the time of treatment initiation and at treatment review after a specified period of time, thereby generating at least two forms per patient. Consequently, the amount of data to be manually entered into the data management tool is very large. For example, the Nigeria Scale-Up programme, in which 10,260 patients were successfully followed-up after treatment initiation, necessitated manual data entry into CemFlow from at least 20,520 paper forms. All of the NCs reported that they had insufficient dedicated data entry clerks, and additional data entry clerks, including NC pharmacovigilance staff, were enlisted to complete the task.

It is worth noting that CEM of ACTs, with just two forms per patient, requires considerably less work than would be generated by a CEM study for a longer term therapy such as an antiretroviral medicine, in which patients would need to be followed up multiple times over a longer period (e.g. monthly for a year). NCs planning to implement CEM, especially when centralised manual data entry is unavoidable, must consider how to effectively manage the data that will be generated, including having an adequate number of staff for data entry.

The long-term solution may be the increased use of electronic health records (EHRs) that enable signal detection in longitudinal health data [19]. In the shorter term, EHRs and other digital technologies such as mobile phone applications that facilitate electronic data capture may be developed to reduce the workload associated with CEM. Access to computers, stable Internet connections and a constant electricity supply remain a challenge in many African countries [20, 21], but mobile phone technology is now widespread. Mobile phone ADR reporting apps have already been developed and are in use, for example in Kenya [22], and could be considered as a possible reporting tool for CEM studies.

4.5 Healthcare Providers' Participation

All NCs reported an initial high level of enthusiasm by HCPs, which waned with time to a level of almost reluctance to continue. The initial enthusiasm shows that HCPs in resource-limited settings are willing to participate in pharmacovigilance activities. The reasons behind the waning interest were not solicited in the questionnaire.

There appears to be a perception among HCPs, especially in developing countries, that CEM, and by extension pharmacovigilance, falls outside their scope of practice. This perception is reflected in the response to the question "How would the (monitoring) sites best describe the additional workload associated with CEM". All of the NCs responded that the monitoring sites considered that CEM interfered to a great extent with their routine work. These responses suggest that the HCPs involved in these CEM programmes had not fully appreciated the rationale for undertaking the CEM study and that pharmacovigilance activities should be considered an integral component of patient care. Although the number of developing countries that have joined the WHO Programme for International Drug Monitoring has increased sharply in recent years [23, 24], pharmacovigilance in many of these countries is not yet seen by HCPs as contributing to clinical decisions and improving treatment outcomes. There is a need for greater pharmacovigilance advocacy and training for HCPs to encourage their ongoing participation in future CEM studies.

The effect of diminishing returns may also have played a role in the loss of enthusiasm reported by each of the NCs. Many of the HCPs may have lost interest when the programme that was intended to be a short-term project extended beyond the expected timeframe. NCs that are planning to implement CEM need to carefully estimate the time commitment that will be required of participating HCPs, and endeavour to integrate data collection into their routine patient care activities.

Despite the waning of enthusiasm, the NCs reported positive experiences in relation to the participation of HCPs, including improved patient–HCP interaction, greater understanding of pharmacovigilance and more rational use of ACTs.

4.6 Cost of CEM

In all of the programmes, the actual expenditure on CEM exceeded the budget by 11.1–63.2 %. Factors that contributed to budget shortfalls included the unexpectedly prolonged study duration and the need to hire additional data entry clerks. A breakdown of the budget was not included in the survey questionnaire.

The use of incentives for HCPs (and, in most cases, patients) added to the cost of the CEM programmes. Although most NCs considered that implementing CEM would be difficult without the use of incentives, this is a potential target for cost reduction. Another target for cost reduction is the workload associated with patient enrolment and data entry. Electronic data capture in CEM studies would reduce the time and labour required for data processing.

4.7 Effect of CEM on Spontaneous Reporting

Two NCs reported a positive effect on spontaneous reporting of ADRs while two reported a reduction in the number of ADR reports from sites participating in CEM. The probable explanation for the observed reduction is that the same people who would have reported ADRs at the sites were engaged in CEM, thus leaving them with little time to routinely report ADRs. However, the survey responses indicate that the experience of implementing CEM helped to build pharmacovigilance capacity within the NCs and the monitoring sites, which can be expected to have a positive effect on routine pharmacovigilance activities in the long run [25].

4.8 Limitations of the Survey

The questionnaire was validated by the same people who completed the survey, but foreknowledge of the questionnaire content was thought unlikely to compromise the survey results in any way. Some of the questions were directed to the HCPs at the monitoring sites; however, it is not clear whether the NCs solicited responses for these questions from the sites or responded on their behalf. Thus, the responses may not be an accurate reflection of how CEM was perceived by the monitoring site personnel. The questionnaire was also limited in the depth of information required from respondents. It did not enable a probe into the reasons for issues such as the delay in obtaining ethical approval experienced by one of the NCs, information on individual cost items and their relative contribution to the total cost of CEM, and the waning interest of HCPs participating in the programme.

5 Conclusion

This survey documents the experiences of four African NCs that have implemented the CEM method for monitoring ACTs. Their experiences indicate that CEM has helped to build pharmacovigilance capacity within the NCs and monitoring sites, and HCPs are generally willing to be involved in implementing the CEM method. Pharmacovigilance advocacy and education towards integrating patient monitoring into the routine patient care activities of HCPs will improve appreciation of CEM as a complimentary tool for drug safety monitoring. Reducing the workload associated with CEM, for both the HCPs and NC staff, particularly in the area of data management, should be considered a priority for further development of the method.

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Authors' contributions CS and GH were the co-investigators for this study, designed the questionnaire, collected and analysed data and drafted the manuscript. GS, MD, GM, EA, AO, CE, PN and SK reviewed the questionnaire, provided country level data and National Centres' experience with implementing CEM and reviewed the manuscript. AD and SP reviewed the questionnaire and manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

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Conflicts of interest Comfort Suku, George Sabblah, Mimi Darko, George Muthuri, Edward Abwao, Adeline Osakwe, Cassandra Elagbaje, Priscilla Nyambayo, Star Khoza, Alexander Dodoo and Shanthi Pal have no conflicts of interest that are directly related to the content of this study. Geraldine Hill currently works with the Uppsala Monitoring Center (UMC) and undertook consultancy for the WHO to support development of CemFlow. She also provided training to National Phamacovigilance Centres on CEM method and use of CemFlow. Jayesh Pandit was with the National Pharmacovigilance Centre, Pharmacy and Poison Board, Kenya at the time the CEM programme was implemented in Kenya. He was employed by Bayer HealthCare, Middle Africa Region at the time of preparation of the manuscript. The work on the manuscript has no funding from either the UMC, WHO or Bayer HealthCare.

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Annex 20: Zimbabwe's Membership of the WHO International Monitoring Programme

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

Téléphone Central/Exchange: 791. 21.11
Direct: 791 36.81

In reply please refer to:
Prière de rappeler la référence: M19/286/3(IRN)
DRS/MtH/cfp

Your reference:
Votre référence:

Mr M. Dauramanzi
Register of Drugs
Drug Control Council
P.O. Box 48517
Union Avenue
Harare
Zimbabwe

23 October 1998

Dear Mr Dauramanzi,

I am pleased to inform you that the WHO Collaborating Centre on International Drug Monitoring has advised us that working relationships have been established with the Zimbabwe Drug Control Council.

We can thus confirm that Zimbabwe has been admitted, with immediate effect, as a full member of the WHO International Monitoring Programme.

We have added the Council's address to the mailing list to receive the WHO Pharmaceuticals Newsletter and drug safety Alerts.

I take this opportunity to extend our good wishes on behalf of the World Health Organization to the Council.

Yours sincerely,

Dr J. Idänpään-Heikkilä
Director
Division of Drug Management
And Policies

cc: Dr Moses Chisale, Regional Adviser, EDV, WHO/AFRO, Harare
Dr I. Ralph Edwards, Director, WHO Collaborating Centre for International Drug Monitoring, Uppsala
Ms Gugu Mahlangu, Drugs Control Council, Harare

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