



FOOD MEDICINE AND
HEALTH CARE
ADMINISTRATION
AND CONTROL
AUTHORITY OF
ETHIOPIA

Guideline for Adverse Drug Events Monitoring (Pharmacovigilance)

Third Edition

Food, Medicine and Healthcare
Administration and Control Authority of
Ethiopia

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Foreword

Medicines are one of the most essential components in the health care system. This indisputable fact makes rational selection, procurement, distribution, and use of medicines of paramount importance in health care. Worldwide, numerous numbers of drugs are being released into the market every day with incomplete knowledge as to their safety levels when used by wide variety of population category other than the one studied in the limited clinical trials making safety of medicines as one important concern. This concern calls for a Comprehensive pharmacovigilance system.

Hence a complete pharmacovigilance system needs an up to date and practical guideline to provide information and guidance to the various partners of pharmacovigilance as to what their roles and responsibilities should be towards the maintenance of a national drug safety.

It gives me a great pleasure to present this 3rd edition of Adverse Drug Event monitoring/Pharmacovigilance Guideline for all those involved which will be kept under review as necessary. I hope every partner will use this guideline effectively as a guide towards maintaining drug safety and ultimately improve the safety and quality of healthcare being provided.

I would like to take this opportunity to thank all those who contributed in developing and printing this Adverse Drug Event monitoring/Pharmacovigilance Guideline. I also call upon interested parties to continue their support by forwarding their comments and suggestions to the Ethiopian Food, Medicine and Healthcare Administration and Control Authority (FMHACA), p.o.box 5681 Addis Ababa, Ethiopia., Tel.251-115524122, e-mail regulatory@fmhaca.gov.et.

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Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AEFI	Adverse Events Following Immunizations
DTC	Drug and Therapeutic Committee
DIS	Drug Information Service
FMHACA	Food, Medicine and Healthcare Administration and Control Authority
IVD	In vitro Diagnostic Device
MAH	Market Authorization Holders
PHP	Public Health Programme
PSUR	Periodic Safety Update Report
PVDMS	Pharmacovigilance Data Management System
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

Definitions

Adverse drug event

“Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.”[1]

Adverse drug reaction

"A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[2]

Consumer

A consumer in a healthcare is anyone who uses, has used, or may use any health or health related service. It is not limited to those currently using a service. The terms "patients" and "users" generally apply only to those currently undergoing some form of treatment.[2]

Drug interaction

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

Health institution

A health institution is any governmental, non-governmental or private institution that carry out promotive, preventive, curative and rehabilitative activities or medicine trade or services.

Healthcare professional

Health professional means a person who is registered by the relevant body as a professional to protect human health or provide service

Medication errors

“A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.”[4] (National Coordinating Council for Medication Error Reporting and Prevention)

Medicine

“Medicine means any substance or mixture of substances used in the diagnosis, treatment, mitigation or prevention of a disease in human and includes narcotic drugs, psychotropic substances and precursor chemicals, traditional medicines, complementary or alternative medicine; poisons, blood and blood products, vaccine, radioactive pharmaceuticals, cosmetics and sanitary items and medical instruments” [5] (n. 6)

Pharmacovigilance

"The science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.”[6] (p. 7)

Product quality defect

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

Serious adverse event/reaction

“A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- * results in death,
- * is life-threatening (NOTE: The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- * requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
- * results in persistent or significant disability/incapacity,
- * is a congenital anomaly/birth defect,
- * is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.” [2] (p. 1, 2)

Signal

“is a Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.” An additional note says: “Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information.”[7]

Medical instrument

Means any instrument or supply that may be used on the inner or outer part of the body for diagnosis or treatment of a disease in human, and includes various diagnostic, laboratory, surgery, dental medical instruments and suturing materials, syringes and needles.

Scope of guideline

This guideline is written to outline the roles and responsibilities of stakeholders that are involved in monitoring medicines safety, pharmacovigilance, of which the objectives are listed below:

- detect previously unknown medicine-related problems as early as possible
- identify risk factors or risk groups of patients
- detect increased frequency of medicine-related problems
- improve knowledge of the clinical features of known serious adverse drug reactions
- Encourage reporting and strengthen of monitoring of ADEs

The findings are used to create awareness on and promote rational, safe and more effective use of medicines by health professionals, patients and consumers.

Stakeholders that are involved

A range of stakeholders are involved in pharmacovigilance activities:

- Patients and consumers
- Healthcare professionals
- Health facilities
- Market Authorization Holders (MAH)
- Public health programmes
- Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (FMHACA), responsible for that marketed medicines are safe and of quality for the public
- Academia and research institutions
- Professional Associations
- WHO Collaborating Center for International Drug Monitoring
- Community leaders
- Media

Including the patient or representative of the patient .(e.g., family member or referring physician).

Activities to promote medicines safety

Activities to promote medicines safety entails monitoring medicine use in order to detect potential medicine-related problems, further assesses and understand in order to develop prevention strategies to minimize patient harm. The strategies can be communicated, and then to monitor the impact of any action taken. The core activities that will work in a well-established system are outlined in Figure 1.

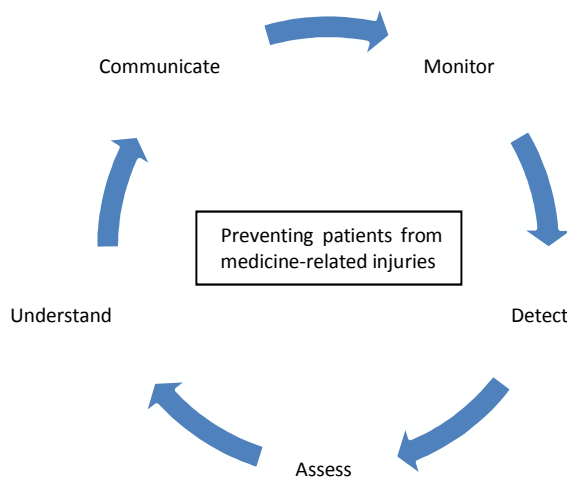


Figure 1. Activities to prevent medicine-related injuries and promote medicines safety

Medicines to be monitored

The medicines to be monitored are conventional, herbal, and traditional medicines, biologicals, medicated cosmetics and medical instruments (i.e. any instrument or supply that may be used on the inner or outer part of the body for diagnosis or treatment of a disease in human, and includes various diagnostic, laboratories, surgery, dental, medical instruments and suturing materials, syringes and needles).

An In Vitro Diagnostics is a device intended by a manufacturer for use for the *in-vitro* examination of specimens derived from the human body to provide information regarding a physiological, pathological or therapeutic state, as outlined in the medical device registration guideline. For this process to be effective it is important that the user, distributor/local agent and manufacturer have a clear understanding of what an incident is and the actions that must be taken on the discovery of an incident.

Outcome from the activities

Information from spontaneously reported ADEs, published literature, clinical and epidemiological studies is used as the primary basis for decision making within these activities. The findings can result in restricted use of the product in certain patient populations, dosage adjustments, added warnings, or withdrawal of the product.

Adverse drug events to be reported

Adverse Drug Events, i.e. medicine-related injuries, with at least a reasonable possibility to be caused by:

- The direct pharmacological mechanism of a medicine
- An individual's particular vulnerability
- Drug interactions
- Unexpected therapeutic ineffectiveness (e.g. resulting from drug interactions, product quality problems or antimicrobial resistance)
- Medication errors
- Product quality defects
- A malfunction or deterioration in the characteristics or performance of IVD.
- False positive or false negative test result falling outside the declared performance of the test.

In the context of reporting, in addition to ADRs ; ADEs include medication errors, treatment failures and product quality defects independent of whether the action or medicine reached or injured the patient.

Any of the above ADEs should be reported to the FMHACA using the Adverse Drug Event Reporting form, see Annex I.

Adverse Events Following Immunizations (AEFI) should be reported according to the “Guidelines for AEFI Surveillance in Ethiopia.[8]

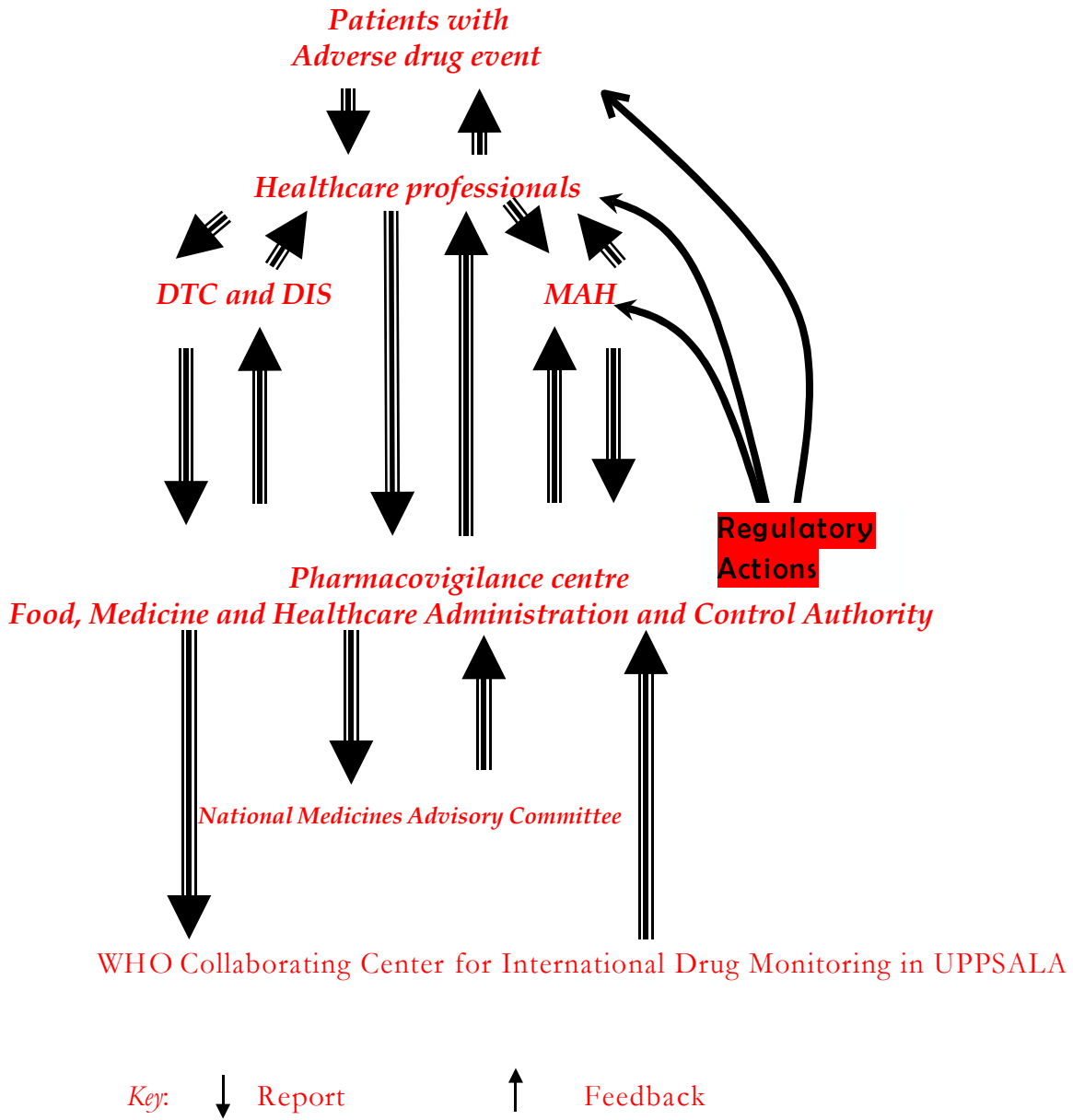


Figure 1. Schematic presentation of the ADE reporting system

Chapter One

Introduction

Medicines are essential for individual patients and public health. Medicinal products have undergone thorough pre-clinical and clinical studies to prove its quality, safety and efficacy before market authorization is granted. However, the product has only been tested on a restricted number and type of patients, for a limited length of time and used under strict protocols. Pregnant patients, children, elderly, and patients with certain diseases or medicines have often been excluded in these studies. These conditions make it unfeasible to detect rare Adverse Drug Reactions (ADRs), long-term effects, drug interactions and particular patient risk groups or risk factors. Marketed medicines are not used according to strict protocols as in the pre-marketing studies. In addition, problems can emerge from real-life medication use related to inadequate labeling, packaging, product information or product quality defects. The post-marketing period is therefore a very important period to detect medicine-related problems that were not possible to identify during the pre-marketing phases.

Even if the medicine previously has been marketed internationally, national post-marketing monitoring is necessary. The effect and safety of a medicine can be affected by population specific genetics, diet, malnutrition, and nation specific disease prevalence. Social and cultural traditions, healthcare systems and health professional practices can lead to sub-optimal use of medicines with increased risks for harm. National drug production, distribution and availability of medicines (or lack of availability) can also influence patient safety.

The drug delivery process is dependent on patients' and health professionals' vigilance in real-life settings to detect potential problems that need to be communicated to the national drug authority in order for preventative actions to be taken. Wherever medicines are being used there should be a readiness to monitor and report unwanted and unexpected medicine-related problems.

Article 31 of the Food, Medicine and Healthcare Administration Control Authority council of ministries regulation number 299/2013 gives FMHACA the mandate to carry out post-marketing surveillance in order to ensure the safety, efficacy and quality of medicines that are marketed in Ethiopia.

Accordingly,

1. The Authority shall undertake and coordinate post marketing surveillance on food or medicine supplied for sale, and based on the results, take necessary measure against non-compliance with the relevant requirements.
2. Any health institution shall have the duties
 - to report to the authority on any unprecedented adverse drug reaction ,product safety update or complaint on the safety efficacy and quality of medicine.
 - Refrain from distributing any medicine that the authority has notified as having safety, efficacy or quality defect.
3. Whereas the authority orders the recall of any medicine in accordance with this article the medicine manufacturer or its agent shall have the duty to recall and dispose the medicine.
4. Any medicine manufacturer, importer or distributor shall be responsible to establish a pharmacovigilance system for continuously monitoring the safety of the medicines for which it has obtained market authorization and to take corrective measures in case of irregularities.
5. Any health professional shall immediately inform the Authority any adverse drug effect as well as problems that he encounters with respect to the efficacy or quality of medicine

Adverse drug reactions

An ADR has been defined as "A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." [2]

Alphabetical categorization of adverse drug reactions

Two principal types:

Type A (Augmented) Related to the principal action of the medicine

- Can occur in anyone
- Dose related
- Pharmacodynamic effects
- Common
- Skilled management reduce their incidence

Type B (Bizarre) - Not related to the principal action of the medicine

- Will occur in some people
- Not part of the normal pharmacology of the medicine
- Not dose related
- Unpredictable
- Include idiosyncrasy and drug allergy
- Account for most drug fatalities

Four subordinate types:

Type C (continues)

- Reaction due to long term use

Type D (delayed)

- Effects like teratogenesis, carcinogenesis

Type E (ending of use)

- Abrupt discontinuation e.g. rebound adrenocortical insufficiency

Type F (failure of therapy)

Major factors predisposing to adverse effects

It is well known that different patients can respond differently to a given treatment regimen. For example, in a sample of 2422 patients who had been taking combinations of drugs known to interact only 7 (0.3%) showed any clinical evidence of interactions. In addition to the pharmaceutical properties of the drug therefore, there are characteristics of the patient which predispose to ADRs.

Extremes of age: The very old and the very young are more susceptible to ADRs. Medicines which commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal antiinflammatory medicines, antihypertensives, psychotropics and digoxin.

All children, and particularly neonates, differ from adults in the way they respond to medicines. Some medicines are likely to cause problems in neonates (for example morphine), but are generally tolerated in children. Other medicines (for example valproic acid) are associated with increased risk of ADRs in children of all ages. Other medicines associated with problems in children include chloramphenicol (grey baby syndrome), antiarrhythmics (worsening of arrhythmias), Aspirin (Reye syndrome).

Inter current illness: If the patient also suffers from another disease, such as kidney, liver or heart disease besides the condition being treated, special precautions are necessary to prevent ADRs. Remember also that, as well as the above factors, the genetic make-up of the individual patient may predispose to ADRs.

Drug Interactions: Interactions may occur between drugs which compete for the same receptor or act on the same physiological system. They may also occur indirectly when a drug-induced disease or a change in fluid or electrolyte balance alters the response to another medicine. Interactions may occur when one medicine alters the absorption, distribution or elimination of another medicine, such that the amount which reaches the site of action is increased or decreased. When two medicines are administered to a patient, they may either act independently of each other, or interact with each other. Interaction may increase or decrease the effects of the medicines concerned and may cause unexpected toxicity. As newer and more potent medicines become available, the number of serious drug interactions is likely to increase. Remember that interactions which modify the effects of a medicine may involve non-prescription medicines, non-medicinal chemical agents, and social drugs such as alcohol, marijuana, and traditional remedies, as well as certain types of food. The physiological changes in individual patients, caused by such factors as age and gender, also influence the predisposition to ADRs resulting from drug interactions.

Incompatibilities between medicines and IV fluids

Medicines should not be added to blood, amino acid solutions or fat emulsions. Certain medicines, when added to IV fluids, may be inactivated by pH changes, by precipitation or by chemical reaction. Benzyl penicillin and ampicillin lose potency after 6– 8 hours if added to dextrose solutions, due to the acidity of these solutions. Some medicines bind to plastic containers and tubing, for example diazepam and insulin. Aminoglycosides are incompatible with penicillins and heparin. Hydrocortisone is incompatible with heparin, tetracycline, and chloramphenicol.

Adverse effects caused by traditional medicines

Patients who have been or are taking traditional herbal remedies may develop ADRs. It is not always easy to identify the responsible plant or plant constituent.

The effect of food on drug absorption

Food delays gastric emptying and reduces the rate of absorption of many medicine; the total amount of drug absorbed may or may not be reduced. However, some medicines are preferably taken with food, either to increase absorption or to decrease the irritant effect on the stomach.

Medication errors

It is estimated that one in 10 hospitalized patients in industrialized countries are harmed because of patient safety issues. The number is estimated to be higher in developing countries.[9] Part of these patient safety problems can be caused by medication errors. Inadequate practice, products, procedures or systems can result in patient harm. A majority of these events can be prevented. Medication errors have been defined as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.”[4]

It is important that healthcare professionals alert responsible staff at health facilities and the regulatory authority of medication errors and near-misses detected during prescribing, transcribing,

dispensing and administration in order to prevent the error from occurring again. Important interventions to prevent medication errors are to provide oversight of physician ordering, especially in intensive care units; to simplify, standardize, and rationalize hospital systems involved in medicine formulation and administration; and to promote adequate staffing so that errors caused by undue haste or fatigue can be avoided.[1]

There are many causes of medication errors but majority are attributed to the following three factors:

- *Human factors*
 - Heavy staff workload and fatigue
 - Inexperience, lack of training, poor handwriting, and oral orders
 - Negligence
- *Workplace factors*
 - Poor lighting, noise, interruptions
- *Pharmaceutical factors*
 - Excessive prescribing
 - Confusing medicine nomenclature, packaging, or labelling
 - Frequency and complexity of calculations needed to prescribe, dispense, administer a medicine
 - Lack of effective policies and procedures.[1]

Product quality defect

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

Chapter Two

Roles and responsibilities in pharmacovigilance

The following section describes the roles and responsibilities for the stakeholders involved in activities to minimize the risk of medicine-related injuries or pharmacovigilance.

A. Patients and Consumers

Patients who suspect they have been affected by an ADE should report to any health care professional including the one that had prescribed, dispensed or administered the drug that has caused the ADE. This will then enable the health professional to report the medicine-related problems to the pharmacovigilance center at FMHACA.

B. Healthcare professionals

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

1. Being vigilant and detect adverse drug events

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

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

The possibility of an ADE should be the first differential diagnosis at all times in patients taking medicines.

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

Health professionals should make physical inspections of the medicinal product to be dispensed or administered. Pharmacy professionals have an important role in the work of detecting product quality defects. Color changes, separating components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling should be acknowledged.

2. Assessing the patient

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

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

3. Managing the encountered adverse event

If an ADR is suspected, the clinician should treat the patient and consider to:

- adjust the dose or
- replace the medicine or
- Withdraw the medicine.

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

If a medicine has caused an allergy, the FMHACA "Allergy card" is recommended to be used (see Annex 2). The purpose of the Allergy card is to prevent patients from being prescribed again the medicines for which they are allergic in the first encounter. Patients should then carry the card with them and present it to any health facility at upcoming visits.

The evaluation to determine if an event is at least possibly related to a medicine can be performed by the Drug and Therapeutic Committees (DTC), see further section C.

If the event is believed to be caused by a medication error, action should be taken according to the hospital or healthcare facility routines in order to avoid similar problems in the future. If an ADR, medication error or product quality defects are suspected they should be reported to FMHACA immediately as described below.

4. Reporting

Suspected ADRs, detected medication errors or product quality defects should be reported to the pharmacovigilance center at FMHACA. Reports can be sent either via:

- The yellow, prepaid report available at the facility (Annex I)
- Telephone 0115523142 (direct) or 0115524122 (via operator) or 8482 (toll free line)
- Download report form from website www.fmhaca.gov.et. and send via email regulatory@fmhaca.gov.et.

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

The reporter does not need to prove that there is a causal association between drug and adverse reaction. Therefore, uncertainty of the cause and effect relationship should not be a reason for not reporting.

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

Report as soon as possible

Any suspected ADR, medication error or quality defect should be reported as soon as possible after all relevant information is compiled. Delay in reporting will make reports inaccurate and unreliable. Reporting while the patient is still in the health institution will give chance to the reporter to clear any ambiguity by re-questioning or examining the patient. When the reports have been received by FMHACA, an acknowledgement letter will be sent to the reporter and follow-up questions might need to be answered.

Follow-up on a report that has already been reported

Any follow-up information for an event that has already been reported can be sent on a new ADE form to FMHACA. Clearly indicate that the report concerns:

- follow-up information
- the report case number, (available on the acknowledgement letter), so that this information can be matched with the original report.

It is very important that follow-up reports are identified and linked to the original report to avoid duplications of reports in the pharmacovigilance database.

C. Drug and Therapeutic Committee at the health facility

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

1. Processes to detect adverse drug events

The DTC should implement programs to track ADRs, medication errors and product quality defects and use the information to improve healthcare. Programs could involve review of ADEs, medication errors or near misses, patient chart review, or physical inspection of products. It needs the involvement of all health professionals as a team to identify problems with medicines, setting standards and monitoring practice. The facility should also assign a focal person to coordinate all ADE monitoring activities in the facility and serve as a link between the facility activities and the national pharmacovigilance centre.

2. Assessing adverse drug events

The DTC should be involved in the processing and analysis of spontaneous reports arising from patients and healthcare professionals. The evaluation to determine if an event is at least possibly related to a medicine can be performed by the DTC as follows:[1]

- Obtain a detailed history of the patient including current health status, current pharmaceutical therapy, and past medical history. Use an ADR reporting form to organize reporting. (See Annex 1.)
- Identify and document the clinical reaction.
- Check the product information:
 - o If the reaction is known to occur with the medicine. Note that if the reaction is not listed, it does not mean that the reaction cannot occur with that particular suspected medicine. Unlabeled and unexpected events are particularly important to acknowledge since these events could contribute to the detection of new ADRs that need to be further communicated.
 - o Any plausible mechanism of the medicine. Note that a suspicion should not be discarded even if a mechanistic explanation cannot be found because complete knowledge on the pharmacokinetic/dynamics of a medicine does not always exist.
- Establish the cause
 - o Use the Naranjo algorithm (or other system) for assessing the reaction and establishing the cause. This algorithm will assist in determining the probability that an ADR has actually occurred from the suspected medicine. The algorithm asks a number of questions about the adverse event and provides a numerical rating for the importance of each question. The scores for all items are added to give a probability of causality of the adverse event (See Annex 4).
 - o Evaluate the quality of the product from the manufacturer to rule out any adverse event occurring from a poor-quality product. This investigation should include the possibility of pharmaceutical counterfeiting and overt contamination of the product.

- o Does the underlying cause of the medical event result from a drug interaction, including consideration of traditional and over the counter medicines, or a medication error. Note, that these events should still be reported.
- o Are there other more likely explanations for the event?

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

3. Action in health facility

The DTC should initiate discussions about analyzed medicine-related problems on a regular schedule. The result of these discussions and analysis should then be used to design interventions, methods, procedures that will prevent similar errors to re-occur in the future at the facility. With the information obtained through this process, a definitive decision can be made upon the facts as presented. Determine if the reaction is an ADR, medication error, or a quality defect. The following actions are required by the DTC after the evaluation of any recurring event at the facility:

- Educate the health providers concerning ADEs in
 - o In-service education
 - o Face-to-face education with providers
 - o Medicine information bulletins
- Change facility specific medicine list if necessary, to obtain a medicine of proven safety.
- Modify patient monitoring procedures.

The actions taken should be followed-up to determine further improvement in their facility. Medication errors collected in the healthcare facility should be reported to FMHACA to allow exchange of experiences concerning management and prevention of recurrent medication errors. Medication errors, including near misses such as administering the wrong medicine, strengths or dose; confusion over look-alike and sound-alike medicines; incorrect route of administration; calculation or preparation errors; misuse of medical equipment; and other errors in prescribing, transcribing, dispensing and monitoring of medicines that necessitate action by the regulatory authority and/or the MAH should be reported to the FMHACA. It is recommended that associated materials, e.g. product photographs, containers, labels that would support the information, is submitted with the FMHACA report.

If a detected medication error that has not caused patient harm can be traced to a specific underlying cause following DTC investigation, and that cause can be corrected on a local level, e.g. stressing the importance of legible handwriting, or introducing routine procedures to prevent giving medicines to the wrong patient, these medication errors need to be reported to the FMHACA and the summarized information need to be used for educational purposes.

D. Marketing Authorization Holders

The marketing authorization holders (MAH) ;pharmaceutical industry, importer, wholesaler and distributor has the prime responsibility to monitor safety of their marketed products from the start of drug development and thereafter throughout the lifetime of the medicine.

1. Monitoring for adverse drug events

The MAH is required to have a pharmacovigilance system in place and to accept responsibility and liability for its registered medicinal products in Ethiopia. The MAH should ensure that information on ADEs are collected and collated and communicated to the FMHACA, according to the below specified timelines. The MAH should monitor international scientific literature for new reports at least monthly. Cases from the published literature originating from Ethiopia and where the authors of the publication have identified the MAH's medicine as the suspected should be reported to the

regulatory authority according to the below specified timeline. The report should be marked as a literature reports and a copy of the article should also accompany the report.

Reporting timelines

Any ADR with at least a reasonable possibility related to the MAH registered product should be reported accordingly:

- **Serious** ADRs, unexpected and expected, must be reported as soon as possible but no later than **15 calendar days of initial receipt of the information by the MAH**. Efforts must be taken to send a report that is as complete as possible.
- Non-serious ADRs must be sent within 90 days after he/she granted knowledge of the event.

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction.

Further explanation to the serious classification can be found on page 5. An ADR is expected if it is listed in the reference document, which is the approved product information or the Investigational Brochure for investigational drugs. The above time lines apply also to those cases detected in the published literature.

If the information first received by the MAH is incomplete, efforts must be made to seek the missing information, particularly for reports with serious and non-serious unexpected events, or for ADRs under special interest. Follow-up methods should be tailored to capture missing information particularly important for the monitored ADR. The use of targeted questionnaires or specific forms could be used to systematically collect additional information for ADRs under special monitoring.

Reports from post-registration studies

All suspected serious ADRs in post-registration studies should be reported according to the timelines given in the previous section. The report to FMHACA should include the study code. The study protocol must outline the reporting requirements and definitions of what constitutes a serious ADR.

Periodic safety update report

For new medicines, a Periodic Safety Update Report (PSUR) should be submitted to FMHACA every 6 months the first two years after market approval and thereafter annually for three years. If no ADRs have been received by the MAH, they are obliged to submit a “Null” report, i.e., a report stating that they have not received any ADR reports on their medicinal product.

Reporting of significant action taken by foreign agency

The MAH should also inform the FMHACA of any significant safety issue (from other than single case reports) or action taken by foreign agency, including the bases for such action **within 3 calendar days** of first knowledge by the MAH. Examples of new safety findings could be results from an in vitro, animal, epidemiological, or clinical study with significant human risk.

Information on withdrawal of the registration status in any country must be noted to FMHACA **within 24 hours** of the first knowledge by the MAH.

Action – notification of change in product safety profile

In the existence of a safety concern, manufacturers can change the label of the product voluntarily or by request from the FMHACA. This action requires changing the official labeling and changing the package insert to reflect the new safety concern and might involve changing indications, recommended dosage, contraindications, special precautions, warnings or the adverse drug reaction section. The action might also involve prompt notification by a “Dear Healthcare Professional” letter. In rare situations, medicinal products will need to be withdrawn from the market.

2. Risk management plan

Pharmacovigilance activities need to start early in the product development and at the time of license approval. Risk management should aid the planning and monitoring in particularly the early post-marketing period of new medicines.[10] Risk management involves:

- Characterization of what is known or not known about the risk
- Planning pharmacovigilance activities to gain more knowledge and new information about the risk
- Planning and implementing risk minimization strategies and evaluate the effectiveness of these activities.

A Risk Management Plan (RMP) should be prepared and submitted by the MAH at the time of

- New drug application
- Significant change in marketing authorization (new dosage form, route of administration, indication)
- Significant new safety concern
- Request by FMHACA

The regulatory authority will review the RMP and thereafter approve or request amendments to the document.

E. Public Health Programmes

The goal of Public Health Programmes (PHP) is to promote health and reduce spread of disease, premature death and disease-related discomfort and disability in the population. Large populations in disease specific PHP receive medicines, such as anti-retrovirals, anti-tuberculosis, anti-malarials, vaccinations and family planning products.

1. Monitoring medicines

FMHACA jointly with the PHP will decide priorities regarding monitoring of medicines to be conducted by the PHP, how the medicines should be monitored, the duration of the monitoring, when adverse reactions should be reviewed, and the time frames for reporting and actions if a safety concern emerges.

Reporting adverse drug events

Suspected ADRs, product quality defects and medication errors should be reported to the pharmacovigilance centre at the FMHACA. Therapeutic guidelines used in the PHP should include instructions on reporting. If the PHP independently detect safety issues, these should be communicated to the FMHACA.

F. Food, Medicine and Healthcare Administration and Control Authority of Ethiopia

The primary role and mandate of FMHACA is to ensure that marketed medicines are safe and of quality for the public. The authority has the responsibility to investigate safety concerns and take action to prevent and minimize medicine-related harm.

1. Report entry

Pharmacovigilance experts at the center enter the incoming reports into the national pharmacovigilance database PVDMS according to internal routines. Each report is classified as an ADR, medication error or a product quality problem. The recipient of the report will carefully review the report for the quality and completeness of the medical information.

The center then provides feedback to the reporter and might request information in case of missing pertinent data. Causality assessment is performed and the report is classified according to the WHO-UMC causality criteria.[6]

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

2. Monitor to detect signals

The pharmacovigilance experts at the FMHACA review each incoming report (ADR, medication error, product quality defect) individually to detect any medicine-related problems that need immediate action.

The authority works towards detecting new potentially causal drug and event associations, or a new aspect of a known association, i.e. a signal

- Previously unknown ADRs
- Increases in frequency of known ADRs
- Risk groups, risk factors and possible mechanisms underlying ADRs.

A signal can initially be detected in a single incoming report. The literature, the WHO Signal document and the WHO Pharmaceutical Newsletter are regularly screened to detect medicine-related problems relevant for the nation. Each year, a summary of the reports received during the past year is produced and evaluated.

Post marketing surveillance to detect product quality defects is performed by the FMHACA. Samples of any product in the market are collected from various premises in a determined frequency per year. The samples are tested in the FMHACA laboratory. Regulatory inspection is also carried out by regional responsible offices to detect product quality defects.

3. Assessing potential signals

Each detected potential signal will undergo further evaluation. The national and WHO-ADR databases, published literature and information from the MAH are reviewed for similar cases. The National Drug Advisory Committee is provided summary information for evaluation. The committee recommends what action needs to be taken, i.e. if it is a signal that needs to be acted upon, no signal, or if further monitoring is needed. (See section G for details about the National Drug Advisory Committee).

Signals related to medication errors will be evaluated to determine whether preventative actions can be made. Depending on the nature of the safety concern, assessment will be performed in collaboration with the MAH or health facility.

Product quality problems are communicated to the relevant directorates at the authority for testing.

Signals might need formal studies or might require intensive monitoring of a certain reaction and/or a medicine. The MAH can be enforced to conduct these studies. Further investigation can also be performed by the FMHACA in collaboration with a research institution.

4. Preventative action

When a signal has been confirmed, action is taken either directly by the FMHACA or by enforcing the MAH to take action:[1]

- Letters to healthcare providers about the safety concern describing how it may affect present patients on the medicine and future prescribing. The action needed might only be a warning of a possible safety concern that have been detected and may recommend a continued vigilance in prescribing and dispensing the medicine.
- Package insert revisions – when safety concerns become significant, manufacturers must change the label of the product. This action requires changing the official labeling and changing the package insert to reflect the new safety concern. Regulatory officials typically approve the change.
- Modifying inadequate designs of product labeling, packaging, product formulation, medical device, or product/technical information.
- Medicine recalls – When the risk of ADRs or product quality issues outweighs the benefits, withdrawing the medicine from the market might be necessary. Medicine recall can be voluntary or imposed by regulatory authorities.

In case of a product quality defect, corrective actions will be taken in collaboration with the MAH, the FMHACA regional branch offices and the regional health regulatory offices.

The above actions should be taken rapidly and systematically.

G. The National Drug Advisory Committee

National Medicine Advisory Committee is composed of Medical, and Pharmacy professionals established by the Food, Medicine and Health Care Administration and Control Authority to advise or make recommendations on matters relating to drug evaluation, clinical trials, pharmacovigilance and other related issues. The composition includes Internists, Psychiatrist, Obstetrics and Gynaecology specialist, Paediatrician, Ophthalmologist, Dermatologist, Pharmacologist and representative from the Regulatory Authority. Members of the National Medicine Advisory Committee are appointed by the Authority pursuant to their professional competence.

The National Drug Advisory Committee evaluates drug safety concerns highlighted by the FMHACA and recommends what action to be taken by the authority.

Assessing potential signals

The National Medicine Advisory Committee is regularly consulted regarding questions on individual case reports or summaries of ADE reports provided by the FMHACA. They investigate the question in concurring medical literature, reactions listed for medicines within the same pharmacologic class and search additional databases for further investigation.

Action recommended

Following their assessment, the committee communicates their findings and recommendations to the FMHACA as early as possible.

H. Academia and research institutions

The educational system plays an important role in pharmacovigilance to provide training about safe and rational use of medicines, the nature of ADRs, the specifics of medication errors, and the importance to be vigilant of product quality problems.

Action to promote safety of medicines

The science and activities of pharmacovigilance should be included into the course content of the health professional's curricula. Research and postgraduate training in the field should also be considered. The FMHACA has developed a training manual "Adverse drug event monitoring system, Pharmacovigilance" to be a guide in the teaching about pharmacovigilance.[11].

I. Professional Associations

Professional associations play a valuable role towards the maintenance of drug safety by building the capacity of their members in their respective associations.

Action to promote safety of medicines

Various types of trainings on pharmacovigilance and continuing Education programmes should be designed so that members become aware of the importance of pharmacovigilance and the activities at the national pharmacovigilance system. This will then enable them to contribute their individual share and carry out their professional responsibilities properly.

J. WHO Collaborating Centre for International Drug Monitoring i.e. the Uppsala Monitoring Centre

As a means of pooling existing data on ADRs, WHO's Programme for International Drug Monitoring was started in 1968. Initially a pilot project in 10 countries with established national reporting systems for ADRs, the network has since expanded significantly as more countries worldwide developed national pharmacovigilance centres for the recording of ADRs. Currently, 86 countries participate in the programme, which is coordinated by WHO together with its collaborating center in Uppsala, Sweden. The collaborating center is responsible for maintaining the global ADR database, Vigibase. At present the database contains more than three million ADR reports.

The majority of national contributing centers have easy electronic access to these. The UMC has established standardized reporting by all National Centers and has facilitated communication between countries to promote rapid identification of signals.

The WHO Collaborating Centre analyses the reports in the database to:

- Identify early warning signals of serious adverse reactions to medicines;
- Evaluate the hazard;

- Undertake research into the mechanisms of action to aid the development of safer and more effective medicines.

Through an advisory committee, WHO plays an important role in the provision of expert advice on all matters relating to the safety of medicines. The Committee also exists to facilitate consistent policies and action among member countries and to advise those who may be concerned about action taken in another country. [13]

K. Other partners.

The contribution of other partners in drug safety including the media, advocacy groups, and lawyers needs to be acknowledged. These partners in pharmacovigilance could directly or indirectly facilitate the development of new and robust drug policies and decisions, while highlighting deficiencies and weaknesses in existing drug safety policies. In many instances these groups or individuals have the capacity to voice, and often change public opinion. Moreover, they often facilitate active public debate and discussion of issues, which have direct relevance to their health. In many countries, policy-makers engage pro-actively with these partners when important matters of public interest are being considered. Co-operation and open lines of communication with non-governmental agencies including the media and consumer advocacy groups is likely to facilitate the creation of policies and legislation on pharmacovigilance which will enjoy widespread public support and confidence. [14]

Communication

The findings collected through pharmacovigilance activities are used to educate and promote rational, safe and more effective (including cost effective) use of medicines by health professionals and patients. This promotion is done through communication.

The preamble in the Erice declaration states “Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties – consumers, health professionals, academia, media, pharmaceutical industry, drug regulators, governments and international organizations – working together. [12]

Depending on the safety issue, the FMHACA uses the ‘Pharmacovigilance newsletter’, ‘Dear Doctor letters’, the FMHACA webpage, and, on occasion, the media to communicate safety concerns and regulatory measures taken to health providers, health professionals and patients/consumers. The MAH and PHP should transfer any new safety knowledge about their products/products in use to the pharmacovigilance centre at the FMHACA so that collaborative actions can be taken.

Confidentiality

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

The original report form is kept under a strict condition in a locked cabinet. The details of the report are stored in the national pharmacovigilance database. The information stored in the database can be accessed only by authorized personnel. The data can be exported to different data analysis tools. Report details will also electronically be sent to the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Sweden. The UMC regularly screens compiled case reports for new and incompletely documented safety concerns on an international level. The UMC also provides web-based access to the internationally collected reports via the WHO-ADR database to member countries.

Annex 1. Adverse Drug Event Reporting Form

Adverse drug events can be reported to FMHACA via 3 ways:

- Yellow, prepaid report available at the facility (Annex I)
- Telephone 01115523142 (direct) or 0115524122 (via operator) or 8482 (toll free line)
- Downloaded report form from website www.fmhaca.gov.et/adrreport form and sent via email regulatory@fmhaca.gov.et.

Direction for completing the ADR reporting form

General

The ADE reporting form (Annex I) comprise basic information about the patient, the drug, the adverse event, the action taken and the outcome

- The age, sex, description of the adverse reaction, information on suspected medicine, and outcome are all considered essential and should be completed.
- The form can be completed by all Health Professionals in the country such as Physicians, Pharmacists, Nurses, Health Officers, Dentist, etc.
- Complete the form to the best of your abilities.
- Avoid non-standard abbreviations.
- Use a separate form for each patient.
- Write legibly.

Specific

The patient's identity

Information about the patient's identity, and habit should be provided. It is not necessary to write patient's full name. Use Patients name initials only. E.g. ASZ for Addis Solomon Zerga. The card number have to be stated as the card number and patient's identity are useful to solicit additional information if necessary and also for retrospective and prospective study of adverse drug reaction.

Description of the adverse event

Clear and brief description about the nature of adverse event, the date of onset, duration, time course and laboratory test results including "negative" and normal results of any relevant test performed should be reported. The severity of the reaction i.e. weather it has necessitated prolonged hospitalization or not, discontinuation of the medicine or not, etc. have to be reported.

Information on suspected medicine

Drug Information

Write all drug identifying information i.e.; the brand name of suspected medicine(s),batch number, manufacturer and manufactory and expiry dates. Avoid non-standard abbreviations such as PPF, CAF, MTC, TTC, etc.

The dosage form such as tablet, capsule, syrup, suspension, elixir, emulsion, injection, eye drop/ointment, topical crème/ ointment, otic drop, nasal drop, suppositories rectal/ vaginal etc. should be stated. The strength must also be expressed in metric system. e.g. 500mg tab, 250mg/5ml syrup, 1gm rectal suppository etc. Sometimes strength can be expressed in % e.g. 2% hydrocortisone ointment.

Frequency of drug administrations should be clearly notified using standard abbreviations.

e.g. 3 times a day as tid or 8 hrly ,
2 times a day as bid or 12hrly,
4 times a day as qid or 6 hrly etc.

Route of administration expressed using standard abbreviation. E.g. Per os as PO, Intramuscular as IM, Intra-Venus as IV, Per-rectal as PR, Topical as TO etc.

It is also useful to indicate whether the medication is taken before or after meal using Latin abbreviations such as ac, pc etc.

Date

The date the medicine was started and discontinued is an important data to assess the cause and effect relationship of the medicine and adverse reaction. Therefore it has to be stated clearly on the report form as date/ month/ year.in European Calender. If the medicine has not been discontinued at the time of reporting, write continuing.

Dechallenge and Rechallenge

If the reaction subside after discontinuation of the suspected medicine (dechallenge), check Y (yes) and if not, check N (No). If the reaction reappear after the suspected medicine is restarted (if rechallenge done),, check Y (yes) and if not, check N (No). If there is no dechallenge and rechallenge then check NA (Not available).

Drug used concomitantly

List any other prescription or non- prescription medicines used concomitantly (designated as 'C') with the suspected (designated as 'S')medicine with all description i.e. brand name, route, dosage form, strength, frequency, indication, date started and date stopped. This information is useful for evaluation of possible drug interaction.

Indication

Write the reason why the medicine was used or the diagnosis for which the medicine prescribed for both suspected medicine and other medicines concurrently used.

Treatment

The treatment of the reaction, the final outcome of the reaction and sequelae has to be entered.

Additional information

Any reaction the patient may have experienced previously, particularly similar to the current adverse event, either caused by the same or different medicine has to be reported. Other relevant medical history, such as allergy, chronic disease, pregnancy and other factors, which may contribute i.e. herbal products, foods and chemicals, should be included under this heading.

The National Adverse drug Event Reporting form

**Food Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA)
Adverse Drug Event reporting form**

Patient Name (abbreviation)	Card No	Age, Date of birth	Sex	Weight	Height	
Ethnic group		Substance of abuse				
Information on suspected drug/vaccine		S=suspected drug		C=concomitantly used drugs		
Drug name(write all information including brand name batch no and manufacturer)	S/C	Dose/dosage form, route, frequency	Date drug taking was started (D/M/Y)	Date drug reaction started (D/M/Y)	Date drug taking was stopped (D/M/Y)	Indication (Reason for drug use)

Adverse drug event description(include all available laboratory test results)

Reaction necessitated: Discontinuation of drug/s <input type="checkbox"/> YES <input type="checkbox"/> No Hospitalization prolonged <input type="checkbox"/> YES <input type="checkbox"/> No	Reaction subsided after D/C of suspected drug? <input type="checkbox"/> YES <input type="checkbox"/> No <input type="checkbox"/> Information not available Reaction reappeared after restart of suspected drug? <input type="checkbox"/> YES <input type="checkbox"/> No <input type="checkbox"/> Information not available		
Treatment of reaction: <hr/> <hr/>			
Outcome: <input type="checkbox"/> Died due to the adverse event <input type="checkbox"/> Died, drug may be contributory <input type="checkbox"/> Not yet recovered <input type="checkbox"/> Recovered without sequelae <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Unknown			
Sequelae: Relevant medical conditions such as allergies, renal disease, liver disease, other chronic diseases, pregnancy etc <hr/>			
Reported by: Name	Profession:	Email address:	Telephone
Name of health institution:	Date		







Annex 2. Allergy Card

የመድኃኒት አለርጂ መታወቂያ ካርድ

የባለመታወቂያው ስም _____ ያታ _____
 እድሜ/የተወለዱበት ቀን _____
 አድራሻ ወረዳ _____ ተቦሌ _____ ቤቱ _____
 ካርዱ የተሰጠበት ቀን _____
 አለርጂውን ያስከተለው መድኃኒት ስም
 1 _____
 2 _____
 3 _____
 በአለርጂው ምክንያት የደረሰው ችግር ዝርዝር

 ተጨማሪ አስተያየት

እባክዎ ከካርዱ ጀርባ ያለውን መመሪያ ይመልከቱ

መመሪያ

ለግንኛውም ጤና ባለሙያ

- እባክዎ ሕክምና በሚሰጡ ወይም መድኃኒት በሚያድሱበት ወቅት ታካሚዎ ለየትኛው መድኃኒት አለርጂ እንዳልባቸው ይጠይቁ :: ከዚያም በዚህ መታወቂያ ካርድ ላይ ይመዝግቡላቸው ::
- ታካሚው ከዚህ በፊት ያጠማቸውን አለርጂ አስመዝግበውም ከሆነ ካርዳቸውን እንዲያሳዩዎት ይጠይቁ :: ለአለርጂው ምክንያት የሆነው መድኃኒት በድጋሚ እንዳይታዘዝ ወይም እንዳይሰጥ ይከላከላል::

ለግንኛውም ታካሚ

- እባክዎ ወደየትኛውም የሕክምና መገልገያ ተቋም ማለትም ሆስፒታል፣ ጤናጣቢያ፣ ጤና ኪላ፣ ክሊኒክ ለመታከም ወይም መድኃኒት ቤት መድኃኒት ለመግዛት ሲሄዱ አለርጂ ካጋጠመዎት አለርጂውን ያስከተለው መድኃኒት ስም በዚህ መታወቂያ ካርድ ላይ እንዲመዘገብዎት ይጠይቁ ::
- በሌላ ጊዜም ለመታከም ወይም መድኃኒት ለመግዛት ሲሄዱ ለጤና ባለሙያ ካርዱን ማሳየትን አይርሱ :: ለአለርጂው ምክንያት የሆነው መድኃኒት በድጋሚ እንዳይታዘዝዎት ወይም እንዳይሰጥዎት ይከላከላል::

Annex 3. Naranjo Algorithm for Assessing Probability of an ADR

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected medicine was administered?	+2	-1	0
Did the adverse reaction improve when the medicine was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the medicine was re-administered?	+2	-1	0
Are there alternate causes (other than the medicine) that could solely have caused the reaction?	-1	+2	0
Was the medicine detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicines in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Total the score to determine the category of the reaction. The categories are defined as follows—

Definite	> 9
Probable	5–8
Possible	1–4
Doubtful	0

Annex 4. WHO-UMC Causality Criteria

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

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