Product safety Directorate,

Ethiopian Food and Drug Authority

Pharmacovigilance Training for Healthcare Professionals

Participant's Manual

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National Pharmacovigilance Training for Healthcare Professionals

Participant's Manual

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Foreword

Ethiopian Food and Drug Authority (EFDA) is the national regulatory authority vested by law to control medicines and food that aim to improve the quality, safety, and efficacy of medicines and food to ensure the safety and quality of health services throughout the country. It is widely known that the sector is growing in line with the overall growth and transformation plan of the country and that the sector is being guided by the health regulatory sector transformation plan (HRSTP), which is consistent with the national focus on quality improvement, patient safety and considers the national priority public health programs.

Access to medicine, in general, is increasing but inadequate pharmacovigilance (PV) capacity to effectively monitor, prevent, detect, manage, and report adverse drug events (ADEs) locally remains a challenge. The increasing number of clinical trials, the introduction of new drugs/regimens in major public health programs (PHPs) including HIV and TB, the large-scale mass drug administration and immunizations programs being deployed through PHPs in the country need to develop/strengthen the PV system for patient safety.

The EFDA has been leading the efforts to strengthen the national PV system in the health care system. As part of these efforts, the development of training material to build the capacity of healthcare professionals on PV was determined to be necessary. PV is ‘‘the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.”

Thus, the development of this training manual is an important step to addressing knowledge, skill, and attitude gaps identified to enhance the national monitoring and reporting of ADE thereby improving patient safety. Since this PV training material was designed as an answer to observed gaps, it is my belief that health system/program managers and experts involved in education, mentoring, and supportive supervision of PV at the health facility level will find it useful.

I would like to take this opportunity to thank all who participated in the design and development of this training manual. I would also like to encourage users of the manual to send their comments regarding the manual to the authority via the website: http://www.efda.gov.et or P.O. Box 568 , Addis Ababa, Ethiopia.

Heran Gerba (B. Pharm, MSc)

Director General, Ethiopian Food and Drug Administration (EFDA)

APPROVAL STATEMENT OF THE MINISTRY

The Federal Ministry of health of Ethiopia has been working towards standardization and institutionalization of In-Service Trainings (IST) at national level. As part of this initiative the ministry developed a national in-service training directive and implementation guide for the health sector. The directive requires all in-service training materials fulfill the standards set in the implementation Guide to ensure the quality of in-service training materials. Accordingly, the ministry reviews and approves existing training materials based on the IST standardization checklist annexed on the IST implementation guide.

As part of the national IST quality control process, this National Pharmacovigilance Training IST training package has been reviewed based on the standardization checklist and approved by the ministry in May, 2022.

Assegid Samual Cheru

Human Resource Development Directorate

Director
Ministry of Health, Ethiopia

Acknowledgment

EFDA would like to express its gratitude and appreciation to all participants and their respective health institutions who contributed to the preparation of this training material. The shared technical knowledge, experiences, and perspectives have produced training material that will have a positive impact on the practice and capabilities of PV across the country. We extend our gratitude to the following individuals and institutions whose role was central to the analysis, design, development, coordination, and finalization of the training material:

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Acronyms/Abbreviations

ADR/E	Adverse Drug Reactions/Events
DTC	Drug and Therapeutic Committee
DTP	Drug Therapy Problem
EFDA	Ethiopian Food and Drug Authority
EHSTG	Ethiopian Hospital Service Transformation Guideline
EPSA	Ethiopian Pharmaceutical Supply Agency
ESA	Ethiopian Standard Agency
MOH	Federal Ministry of Health
HSTP	Health Sector Transformation Plan
IST	In-service Training
KAS	Knowledge, Attitude and Skill
MDT	Multidisciplinary Team
MRN	Medical Registration Number
OPD	Out-patient Department
SOP	Standard Operating Procedure
USAID	United States Agency for International Development
PV	Pharmacovigilance

Contents

Introduction to the manual

Monitoring the safety and quality of medicines after they are put on the market is a key regulatory function towards ensuring rational medicine use and meeting the goal of protecting the public from drug-related harms. To ensure this goal, various activities have been implemented in the national PV system.

As awareness creation and training on PV is vital to enable healthcare providers to understand and practice ADE monitoring and reporting. Hence, various events of training and face-to-face discussions at facilities have been conducted for healthcare professionals. In addition, tools necessary for executing PV including ADE reporting forms, allergy cards and IEC materials have been revised, printed, and distributed.

Inclusion of topics on PV into the pre-service curriculum of health teaching institutions was also a milestone activity performed during the past few years. The establishment of six decentralized PV centers at selected university hospitals in the country, development of a roadmap for the national PV system, establishment of electronic reporting and mobile application to report ADEs carrying out of several investigations on serious ADEs and performing of causality assessment to obtain the necessary scientific recommendations were also other significant system strengthening activities carried out .

Additional capacity building activities such as assessment and supportive supervision have also been carried out to strengthen the adverse event following immunization (AEFI) monitoring and reporting. Further, active surveillance as a cohort event-monitoring program (CEM) on ART medicines, active drug safety monitoring and management (aDSM) on MDR-TB medicines and adverse event following immunization on anthelmintic mass drug administration (AE-f-MDA) programs have also been conducted.

Reports were monthly received and those reports with serious ADEs have been analyzed. Regulatory measures were taken on medicines that have caused ADRs and on product quality defects. The measures have been communicated to the various stakeholders. This drug safety information has also been shared to the WHO database VigiFlow on a routine basis so that the country could benefit from receiving and sharing information with the international world.

Despite the efforts made to strengthen the national PV system, still there are many challenges remaining. The national PV system situational analysis conducted in 2018 and feedbacks of experts working in the area identified the following gaps, including:

- Low number and variety of ADEs reporting by healthcare providers.
  - According to WHO, the expected number of ADE reports is 200 per 1 million inhabitants in a country (Ethiopia is expected to generate at least 20,000 reports annually).
    - currently the number of reports being received is very low (less than 1000 per year).

Poor knowledge and attitude regarding the importance of PV at all levels.

- Inadequate ADE monitoring, diagnosis, management, and prevention in health facilities.
- Poor level of awareness on electronic reporting mechanisms among healthcare providers.
- Poor collaboration between PV and the various public health programs.
- Absence of standardized in-service training programs on PV for healthcare providers.

In an attempt to address such problems, various activities are being conducted by EFDA and stakeholders. In line with this, a national PV in-service training material has been developed to build the capacity of healthcare professionals (HCPs). By following the principles of instructional design, a group of experts in this area designed and developed a draft training material based on the national guideline on PV, ADE monitoring system/ PV training manual for health teaching institutions, national SOPs on PV, different national PHP guidelines including HIV, TB, malaria, non-communicable diseases (NCD), mass drug administration (MDA) for neglected tropical disease (NTD) and guidelines issued by WHO.

The syllabus was designed to enhance HCPs knowledge, skills, and attitude in critical areas of PV competencies so that they could meaningfully contribute to patient safety. The training material was further enriched by appropriate experts from MOH, EFDA, universities, hospitals, and development partners. This training material contains Participant's Manual, Trainers' Guide, and PowerPoint presentations. The training course considers participants as the focus of the learning process and activities in the sessions are designed to be more trainee-focused. A modular approach is followed in the material design and development and will be implemented in the delivery. This course requires a Training of Trainers (TOT) and basic training to be conducted in all regions. The training will be given in selected training centers with proper infrastructure and facilities.

Core Competencies

Upon completion of this course, trainees are expected to attain the following core competencies:

- Differentiate ADE, ADR, and medication error
- Manage ADEs
- Report ADEs using different reporting mechanisms
- Investigate ADEs
- Perform causality assessment
- Recognize the role of PV in major PHPs
- Identify the roles and responsibilities of national key stakeholders in PV

Course Syllabus

Course Description: This 4-days course is designed to equip participants with the knowledge and skill on monitoring, diagnosis, management, and reporting of ADEs to improve patient safety. The course addresses a brief overview of Pharmacoepidemiology (PE) and its relationship with PV, basic concepts of PV, ADE components, investigations and causality assessment of ADR, diagnosis, management and prevention of ADRs, monitoring and ensuring medication safety, the national PV system and PV in PHPs.

Course Goal

To provide participants with the necessary knowledge, skill, and attitude required to ensure safety and quality of patient care within the healthcare continuum.

Course objectives

At the end of this course, participants will be able to:

- Identify the link between Pharmacoepidemiology and PV
- Discuss the need and importance of PV in health care system
- Differentiate the components of ADEs
- Describe the national PV system in Ethiopia
- Monitor, diagnose, manage, and prevent ADEs
- Report ADEs using different reporting mechanisms
- Explain how to investigate ADEs
- Perform causality assessment
- Recognize the rationale of PV in PHPs
- Identify the roles and responsibilities of national key stakeholders in PV

Training methods

- Interactive lecture/presentation
- Reflection
- Small group discussions
- Brainstorming
- Exercises
- large group discussions
- Case study
- Demonstration
- Video
- Reading

Training materials

- Participant's manual
- Trainer's guide
- PowerPoint presentations
- National ADE reporting form
- National pharmacovigilance guideline
- National aDSM SOP
- Computer with LCD Projector
- White board and white board markers
- Flipchart, flip chart hanger and writing Marker

Participant selection criteria

The primary target group for this course are HCPs working in health facilities. In addition, experts working in EFDA, MOH, university, Regional Health Bureaus (RHBs), Zonal Health Departments (ZHDs), Woreda Health Officers (WoHOs) and partners who are supporting the PV system and capacity are target audiences.

Facilitator/Trainer selection criteria

Trainers for this course should be HCPS who have TOT training certificate in this PV training course. For the first round, experts participated in material development will be served as trainers.

Methods of evaluation

A. Participant

- **Formative**
  - Observation through checklists
  - Group activities and presentations
  - Individual reflections for questions
  - Case studies
- **Summative**
  - Progressive assessment (trainee daily performance): 20%
  - Post-test (written exam) - 80%
  - For TOT: progressive assessment (20%), Teachback-20% and Post-test (60%)

Course

- Daily evaluation
- End of course evaluation
- Post-test

Certification criteria

- for basic and TOT training trainees, the certificate will be provided to those who have scored ≥70% and ≥80%, respectively on summative assessment and who have 100% attendance on the course for both basic and TOT trainings. .
- Continuing educational Unit (CEUs) =15 CEUs

Course Duration

- Four days (4) for the basic training and six days (6) for the TOT.

Suggested class size

- suggested training class size shall be 20 - 25 participants per training venue.

Training Venue

- The training will be conducted at a nationally recognized CPD center.

Course Schedule

Training Course on Pharmacovigilance for healthcare professionals

Time	Topic	Presenter	Facilitator
Day 1: _____			
8:30-8:45 AM	Registration of participants	Organizer	
8:45-9:00AM	Welcoming Address /Opening Speech	EFDA	
9:00-9:10 AM	Introductory activity	Facilitator	
9:10-9:40AM	Pre-test	Facilitator	
	Overview on Pharmacoepidemiology		
9:40-10:00AM	Introduction	Presenter	
10:00 AM-10:15 PM	Study designs and measurements in epidemiology	Presenter	
10:15AM-10:30AM	**Health Break**	**Organizer**	
10:30AM-11:15AM	Surveillance systems in monitoring adverse health events	Presenter	
11:15AM-12:20AM	Types of surveillance system for medication safety	Presenter	
12:20AM-12:30AM	Chapter summary	Presenter	
12:30-1:30PM	**Lunch Break**	**Private**	
	Basic concepts of Pharmacovigilance		
1:30PM-1:35PM	Introduction	Presenter	
1:35-PM-1:45PM	Overview on drug development process	Presenter	
1:45PM-2:30PM	Pharmacovigillance	Presenter	
2:30PM-3:25PM	Components of adverse drug events (ADEs)	Presenter	
3:25PM-3:30PM	Chapter summary	Presenter	
3:30PM-3:45PM	**Health Break**	**Organizers**	
	Diagnosis ,management, prevention ,investigation and causality assessment of ADEs		
3:45PM-5:30PM	Diagnosis, Management, and Prevention of ADEs	Presenter	
Day 2: _____			
8:30-8:45AM	Recap of day one	Participants	
8:45-9:50AM	Investigation of ADEs	Presenter	
9:50-10:30AM	Causality assessment of ADEs	Presenter	
10:30-10:45AM	**Health Break**	**Organizers**	
	ADEs Monitoring and Reporting in Ethiopia		
10:45AM-11:00AM	Introduction	Presenter	
11:00AM-12:30PM	The national ADE monitoring and reporting system	Presenter	
12:30PM-1:30PM	**Lunch Break**	**Private**	
1:30PM-3:30PM	Demonstration of reporting tools	Presenter	
3:30PM-3:45PM	**Health Break**	**Organizers**	

3:45PM-5:20PM	Roles and responsibilities of stakeholders in national PV system	Presenter	
5:20PM-5:30PM	Chapter summary	Presenter	
Day 3: _____			
8:30AM-8:45AM	Recap of day two	**Participants**	
	PV in public health programs		
8:45AM-9:45AM	Pharmacovigilance in expanded program of immunization (AEFIs)	Presenter	
9:45AM-10:30AM	PV in Anti -TB medicines	Presenter	
10:30AM-10:45AM	**Health break**	**Organizer**	
10:45AM-11:45AM	PV of medicines used in HIV	Presenter	
11:45-12:30PM	PV for Anti- malaria medicines	Presenter	
12:30PM-1:30PM	**Lunch Break**	**Private**	
1:30PM-2:30PM	PV in mass drug administration (MDA)	Presenter	
2:30PM-3:30PM	PV in non-communicable diseases (NCD) medicines	Presenter	
3:30-3:45PM	**Health Break**	**Organizer**	
3:45-5:00PM	PV in reproductive, maternal ,neonatal and child health medicines	Presenter	
5:00-5:15PM	Daily evaluation	Participants	
Day 4: _____			
8:30-9:15AM	Post- test	Participants	
9:15-9:45AM	End of course evaluation	Participants	
9:45-10:30AM	Closing remark and certification	**Organizer**	
10:30-10:45AM	**Health Break**	**Organizer**	
10:45-12:30AM	Admin issues and End of program	Participants	

Chapter 1: Brief overview on Pharmacoepidemiology

Chapter Description

This chapter introduces basic concepts of epidemiology with a specific focus on description of Pharmacoepidemiology (PE), explaining types of pharmacoepidemiologic study designs, overview on important epidemiologic measurements used in epidemiology and the role of surveillance for monitoring of adverse health effects. Participants will develop an understanding of how to plan, implement, analyze, and criticize pharmacoepidemiologic studies and methods for monitoring medicine safety.

Primary Objective:

At the end of this chapter, participants will be able to:

- Describe the concepts and practice of PE and Epidemiology in relation to medicine safety.

Enabling Objectives:

- Recognize the role of PE in medicine safety
- Differentiate epidemiologic study designs and measurements used in PE
- Discuss the role of surveillance for monitoring of health adverse events

Chapter Outline

1.1 Introduction

Group Exercise

What do you understand about the term PE and PV and their relationship?

Time: 10 mins

Epidemiology deals with the study of the frequency, distribution, and determinants of health-related events in specified populations. Regarding the scope, epidemiology has been used in several ways in the planning and evaluation of health intervention in an effort to improve the health status of the population including:

- Elucidation of the natural history of the disease •
  Description of the health status of the population •
  Establishing causation of disease
- Evaluation of intervention
- Monitoring adverse health event

On the other hand, Pharmacoepidemiology (PE) deals with the study of the utilization and effects of drugs in large groups of people. It is viewed as an epidemiological discipline with particular focus on drugs that applies epidemiological techniques to study drug use in a large population. PE studies quantify drug use patterns and adverse drug effects including;

- Understanding the patterns of drug prescribing
- Appropriateness of drug utilization,
- Medication adherence and persistence patterns, and
- Identification of predictors for medication use

PE enables safety studies of drug use in large populations, with special focus on common, predictable adverse drug reactions (ADRs) as well as uncommon and unpredictable ones. Epidemiologic and PE methods have become increasingly recognized as a valuable tool for

better characterizing the benefit risk profile of the product throughout its life cycle. One of the objectives of PE and pharmacovigilance (PV) is to identify and gather consistent evidence on the associations between drug use and the occurrence of adverse events. Such evidence grounds decision-making processes with regard to health surveillance.

Phase IV studies consists of pharmacoepidemiologic studies to evaluate the safety of drugs in larger populations, under real life situation and PE evaluates the use and effects of drugs in large populations during the post-marketing phase. In short, it is PV that happens in the post marketing surveillance phase. Both PV and PE together play an influential part in minimizing the adverse reactions and ensure the safety and efficacy of drugs.

PE through its population-based studies and the possible use of a comparison group, enables quantification of risks that is impossible to carry out using spontaneous reporting alone. It also enables highlighting and quantification of safety signals for events that are frequent and multifactorial, where the role of a drug in individual cases can be difficult to detect, and therefore difficult to identify from spontaneous reporting.

In general, PE together with a successfully implemented PV system can minimize, prevent, and improve the use of drugs by discovering at the post-marketing phase, the adverse effects at the level of public use. This will ensure the safety and better use of drugs towards the needed efficacy for treating illnesses. In short, PE is PV that happens in the post-marketing surveillance phase. Overall, this is the major contribution of PE to PV, where it complements PV in drug safety monitoring but in no way could replace it and play an influential role in minimizing the adverse reactions and ensure the safety and efficacy of drugs.

1.2 Study designs and measurements in epidemiology

As in all clinical research study designs, PE studies are broadly of two types, namely experimental and observational studies. While experimental studies randomize patients to either the treatment or the control group, observational studies observe patients either on or not on the treatment of interest to find out the association between exposure and disease. Observational studies are operationally simple, shorter in time duration and less costly as compared to experimental studies. Observational studies are useful to prove the effectiveness of drugs at

times. Observational studies include descriptive and analytical studies. Analytical studies include ecological (correlational), cross-sectional, cohort, and case-control studies.

Varieties of measures are employed in epidemiology during characterization of the likelihood of developing a disease within a specified period. Careful and accurate measurement of disease occurrence (morbidity and mortality) constitutes fundamental basis of studies. The use of measurement in epidemiological studies is designed to: describe & compare disease trends, identify disease determinants, and evaluate public health interventions aimed at controlling health problems.

Three categories of Epidemiologic measures;

A. Measures of disease frequency

It includes Prevalence and Incidence. It measures of disease frequency in mathematical quantity includes count, proportion (percentage), rate and ratio

B. Measures of association

A measure of association quantifies the relationship between exposure and disease between the two groups. Measures of association can be expressed using the following methods.

- Relative risk (RR)
- Odds ratio (OR)
- Attributable risk/population attributable risk percent
- Standardized mortality ratios

C. Measures of potential impact

It reflects the expected contribution of a study factor to the frequency of a disease in a particular population and useful for predicting the efficacy or effectiveness of therapeutic maneuvers and intervention strategies within a specific population, e.g., vaccine. Essentially, potential impact measures are a combination of frequency and association measures.

1.3 Surveillance Systems in Monitoring Adverse Health Events

Epidemiological surveillance is the systematic collection, analysis, interpretation, and dissemination of health data in an ongoing basis. Surveillance provides "***information for action"***

which can be used to investigate, prevent, and control disease in communities. Its purpose is to provide a factual basis for setting priorities, planning programs, and taking action to promote and protect community health.

Health events are monitored for the following main purposes:

- To detect sudden changes in disease occurrence and distribution
    - Determines the need for epidemic investigation and control and;
    - Ensure that effective action to control the disease is being done
- To follow secular (long-term) trends and patterns of disease
    - Alerts decision makers of the need to reallocate resources or shift policy
- To detect changes in health care practices
    - Points up the need for changes in preventive measures

Key sources of surveillance data include:

- Mortality reports (birth and death certificates, autopsy reports)
- Morbidity reports (notifiable disease reports)
- Hospital data (discharge diagnoses, surgical logs, hospital infection reports)
- Absenteeism records (school, workplace, compensation claims)
- Epidemic reports
- Laboratory test utilization and result reports
- Drug utilization records
- ADR reports

Activities in surveillance/monitoring adverse health event:

- Data collection and recording, reporting and notification
- Compilation, data analysis, and interpretation
- Dissemination of findings for action
- Uses a combination of possible and active mechanisms to collect data
- Timely reporting
- Timely and comprehensive action targeted to the control of the adverse health event
- Strong laboratory services for accurate diagnosis the health problem

Types of Surveillance system for medication safety

When a drug reaches the market, a good deal is known about its therapeutic activity but rather less about its safety when used in large numbers of patients with a variety of diseases, for which they are taking other drugs. Over a number of years, increasingly sophisticated systems have been developed to provide surveillance of drugs in the post-marketing phase.

Drug surveillance systems may be classified as either **passive or active**. A **passive surveillance system** relies on health professionals and patients to voluntarily report suspected drug-associated adverse events to the relevant health authorities. In contrast, an **active surveillance system** employs automated monitoring of public health databases to proactively infer associations between drugs and adverse events.

Passive surveillance system: *Spontaneous reporting (SR)* and *Case series* are the most common examples of passive surveillance

Spontaneous reporting (SR):

- It is unsolicited communication by a Healthcare professionals (HCPs) or consumer to a company, regulatory authority or other organization that describes one or more adverse 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
- Events or reactions that are voluntarily reported either to pharmaceutical manufacturers, to national or regional PV centers, or to national regulatory authorities by health care professionals, other professionals or consumers.
- It is the most common method of surveillance.

Advantages of SR:	**Disadvantage of SR:**
• Easiest to establish and cheapest to run • Least labour intensive, covers the whole population • Includes all medicines • Detects signals of new, rare or, serious ADRs • Play a major role in the identification of	• Data accompanying spontaneous reports, are often incomplete • Very low reporting • Captures only suspected ADRs • Subject to strong biases and there is no database of all users or information on overall drug utilization

safety signals once the drug is marketed • Can also provide important information on at risk groups, risk factors and clinical features of known serious adverse reactions	• Denominator (total number of subjects exposed to the drug) unknown • Difficult to detect delayed ADRs and ADRs with high background incidence

Case Series

- Series of case reports can provide evidence of an association between a drug and an adverse event.
- More useful for generating hypotheses than for verifying an association between drug exposure and outcome.
- There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens - Johnson syndrome. When events such as these are spontaneously reported, pharmacovigilance centers should place more emphasis on these reports for detailed and rapid follow-up.

Active surveillance: It involves regular systematic collection of clinical information on a population of patients who receive drugs that are on the market. It seeks to ascertain completely the number of adverse events via a continuous reorganized process which gives more comprehensive data on individual adverse event reports than passive reporting system. In active or proactive safety surveillance, active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. There are several ways by which this clinical information may be collected such as:

- Sentinel sites,
- Drug event monitoring (DEM),
- Cohort event monitoring (CEM),
- Clinical trials, observational studies and
- Registries

Cohort Event Monitoring (CEM)

- It is a prospective, longitudinal, observational, cohort study adverse events associated with one or more monitored medicines
- An active PV method promoted by the WHO and other agencies
- In CEM, patients on a particular drug or groups of drugs are recruited at time of initiation of e.g. ART and followed up by way of clinic or home visits or where appropriate by phone calls.
- CEM is an early warning system that interviews patients on a certain treatment (the cohort), for capturing problems (the events) with new medicines in public health programs; the patients are interviewed before and after starting treatment.
- CEM captures all medicine-related events, including medication errors, problems due to poor storage conditions, poor quality or counterfeit medicines, and drug interactions.
- Patients may be recruited from all health facilities involved in providing the medicines, or patients may be recruited from selected health facilities that are representative of the whole country.

Advantages of CEM	Disadvantages of CEM
- Ability to produce rates and complete profile of the adverse events and/or ADRs for the medicines of interest - Very effective in identifying signals at an early stage - Ability to associate reactions with risk factors and make accurate comparisons between medicines - Can detect reduced or failed therapeutic effect and can raise suspicion of medication errors, interactions, emerging resistance or poor-quality or counterfeit medicines - Ability to record and examine details of all	- Labour-intensive, needs dedicated staff to perform treatment initiation (baseline) and treatment follow-up interviews - More costly than spontaneous reporting - Patients may not turn up for follow-up; potential for loss to follow-up - Patients may 'opt-out' and refuse to be part of the CEM; this might make it difficult to reach the required cohort size - Takes certain expertise in recording adverse events, training will be necessary - Cannot detect very rare problems with medicines

deaths and provide rates of death	

Registries

- A list of patients presenting with the same characteristics will be studied or followed.
- Characteristics can be disease (disease registry) or a specific exposure (drug) registry or pregnancy (pregnancy registry).
- Collect information using standardized questionnaires in prospective fashion. Disease registries, such as registries for blood dyscariasis, severe cutaneous reactions or congenital mal-formations can help collect data on drug exposure. Disease registry can also serve as a base for a case control study.
- Exposure/drug registry addresses population exposed to medicinal products of interest to determine if the drug has a special impact on this group of population
- Some exposure registries address drug exposures in specific populations such as pregnant women
- Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires

Sentinel sites surveillance

- It is selected reporting units, with a high probability of seeing cases of the disease in question, good laboratory facilities and experienced well-qualified staff, identify and notify on certain diseases.
- A sentinel system deliberately involves only a limited network of carefully selected reporting sites. For example, a network of large hospitals might be used to collect high-quality data on various diseases and their causative organisms, such as invasive bacterial disease caused by Hemophilus influenzae type b, meningococcus or pneumococcus.
- A sentinel surveillance system is used when high-quality data are needed about a particular disease or medicine that cannot be obtained through a passive system.
- 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.

- Data collected in a well-designed sentinel system can be used to signal trends, identify outbreaks and monitor the burden of disease in a community, providing a rapid, economical alternative to other surveillance methods.
- Because sentinel surveillance is conducted only in selected locations, however, it may not be as effective for detecting rare diseases or diseases that occur outside the catchment areas of the sentinel sites

1.4 Chapter Summary

- Epidemiology concerned with the study of the distribution and determinants of the health related states or events in specified
- PE applies epidemiological techniques to study drug use in a large population
- Types of epidemiological studies categorized under two main categories as interventional and observational.
- Descriptive epidemiology can identify patterns among cases and in populations by time, place and person while analytic epidemiology based on is a comparison group
- Epidemiologic measurements aid in describing the occurrence of morbidity and mortality in population and provides information on frequency of disease, association between exposure and health outcome and strength of the relationship an exposure and a health outcome
- Surveillance is critical for public health aimed at gathering of relevant information that drives action, require data of sufficient quality and with a resolution and timeliness that match public health objectives.
- Drug safety surveillance systems can be classified as either passive or active surveillance

Chapter 2: Basic concepts of Pharmacovigilance

Duration: 2:10 HRs

Chapter Description: This chapter deals with basic concepts of pharmacovigilance (PV). The chapter discusses the gaps in drug development processes and how post-marketing safety surveillance bridges the gap. The chapter enables the participants to identify the limitations of pre-marketing safety studies, appreciate the importance of post-marketing drug safety (PV) monitoring and understand, drug safety monitoring methods.

Primary Objective:

At the end of this chapter, participants will be able to:

- Explain the significance of PV pharmacovigilance in drug safety monitoring.

Enabling Objectives:

- Describe drug development process, pre-marketing, and post-marketing surveillances (PMS)
- Discuss importance of PV
- Recognize components of ADEs

Chapter Outline

2.1. Introduction

2.2.Overview of drug development process

2.3. Post Marketing Safety Surveillance

2.4. Pharmacovigilance

2.5. Terminologies in pharmacovigilance

2.6. Chapter Summary

2.1. Introduction

Group discussion and reflection

- What do you know about thalidomide tragedy?
- Time: 5 minutes)

Medicines save lives and have become one of the most essential components of health care systems worldwide. In addition to the primary therapeutic function, medicines have undesired side effects that can be beneficial or harmful, desired or undesired, harmless or serious, predictable or unpredictable, dose dependent or dose independent. Sometimes side effects indicate new therapeutic uses and stimulate the development of new drug design. Unfortunately, it is less common for side effects to be beneficial as there are ADEs.

Thalidomide tragedy was the greatest of all drug disasters in 1961-62. Thalidomide was introduced, and welcomed, as a safe and effective hypnotic and anti-emetic. It was rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10, 000 children in the countries in which it was widely used in pregnant women.

Figure 2.1: Picture showing thalidomide tragedy

The thalidomide disaster led to the establishment of the drug regulatory mechanisms of today. These mechanisms require the new drug shall be incensed and authorized byell-established

regulatory authorities before introduction to clinical use. It also triggered a chain of activities that were part of a global effort to avert a recurrence. Australia, Canada, several European countries, New Zealand, and the United States of America established monitoring schemes based on reporting of suspected ADRs. This culminated in the setting up of the WHO Programme for International Drug Monitoring.

In the past fifty years, there has been a steady growth in the science now known as PV with an exponential turn in recent years. In the course of this growth, various terminologies and parameters have been introduced to enable communication and exchanges among workers in the field. PV has attained the maturity and stature of a discipline that has a significant impact on patient care and public health. An effective PV system ensures the monitoring of medicines, their availability, and safe use.

2.2. Overview of drug development process

- **Individual reflection**
  - Do you think that drug safety information collected during animal studies and clinical trials is adequate to reflect their safety in clinical practice?

If No, Why?

Time : 10 Minutes

Drugs may be discovered by different methods such as modification of structure of a known drug**,** random screening, synthesis of substances using biological processes that start with known physiological actions seeks to identify their chemical basis and serendipity. Once drugs dare discovered in any one of the above methods, they will be prepared at a laboratory scale. After discovery, they will undergo a wide variety of preliminary screening before the trial preparation is given to human subjects.

The Pre-clinical trial evaluates the efficacy and safety of the new compound. The pre-clinical trial includes pharmacological and toxicological studies.

With regard to pharmacology, the new drug will be studied its pharmacodynamics and pharmacokinetic properties. On the other hand, a toxicological study will be done to determine the toxicity of drugs and/or their metabolites in the experimental animals to evaluate their safety.

Some of the toxicological Studies includes;

- Acute Toxicity Study
- Sub-acute Toxicity Study
- Long term or Chronic Studies
- Special Toxicological Studies
- Studies on prenatal and postnatal

The aims of pre-clinical studies include:

- Identification of target organ toxicities
- Identification of dose-response relationships
- Assessment of systemic exposure and relationship with pharmacological and toxicological responses
- Assessment of reversibility of effect
- Provision of a basis for assessment of safe starting dose for human trial
- Identification of parameters for safety monitoring in human trials.

Limitations of pre-clinical studies:

- Need for a large number of animals of different species
- Time-consuming and expensive nature of toxicity studies
- Unreliable data extrapolation to humans
- Lack of relevancy to physiology and disease in some cases

Once the new drug passed the preclinical studies and the pre-clinical experiments are foundbe adequate, the new compound becomes a candidate to be tested in human being called called Clinical Trials.

Phases of clinical trial

Phase I:

- Also known as First in Human Drug Administration.
- New medicine is administrated to man for the first time
- Most often phase I clinical trial is conducted in about 20-50 healthy volunteers
- Aim: To make a preliminary evaluation of human pharmacologic properties of the new drug such as;

- Pharmacodynamics effects
- Adverse reactions
- Pharmacokinetic behavior of the drug
- Safe dosage range in man

Phase II:

- The new medicine will be tested on limited number of selected and willing patients (150-350) suffering from the diseases for which the drug is intended to treat.
- **Purpose:**
  - To establish or determine possible therapeutic uses.
  - To refine therapeutic dosage range.
  - Further evaluate the safety and pharmacokinetics

NB: Phase I and II of clinical trials together are usually known as early clinical studies in man.

Phase III:

- Known as broad clinical trial or large scale, controlled trial.
- Carried out on much larger (250-4,000) and more varied patients over a long period.
- It provides additional data, which are statistically satisfactory to the verification of the efficacy and safety.
- Generally, requires comparison of the new treatment with already established terms of treatment.

Limitation of pre-marketing studies (clinical trial)

- Too few (limited sample size)
- Too simple:
  - Exclude complicated medical histories or populations who are receiving drugs
- Too Medium (narrow population): In general exclude neonatal, pediatric and geriatric patients
- Too narrow: Pre-marketing trials generally investigate a drug for a single indication.
- Too brief (short duration): ADRs that occur with chronic or long-term use cannot be detected in the short term.

Due to the above limitations of pre market studies, it is clear that not all possible drug uses and potential adverse reactions may be identified when the drug is first available for prescribing. It is in view of this fact that further studies must continue and a special vigilance is needed to complement available knowledge of the various adverse reactions.

2.3. Post marketing surveillance /Phase IV

Uncommon ADRs or manifestations of chronic toxicity may become apparent only after the drug has been used in a large number of subjects for long periods.

Once medicines released onto the open market, it will be used not only by more people, but also by older and sicker people, different ethnic groups, pregnant women, and children and prescribed in many different dose regimens. These circumstances inevitably lead to a potential for more ADRs. Because knowledge about the clinical toxicity of a new drug will always be incomplete at the time of marketing, further investigation of frequency and determination of ADRs must be pursued in the post-marketing safety studies. There are basically two broad types of post-marketing surveillance for ADE monitoring, they are ***Active surveillance*** and ***Passive surveillance*** which are described in detail in chapter 1 of this manual.

PMS is the systematic surveillance and scientific study of all intended and unintended effects of medicines on human health, after their release for marketing. In this definition PMS refers to PV as well as to PE.

2. 4. Basics of Pharmacovigilance

2.4.1. Definition of Pharmacovigilance

PV is defined by WHO as “the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems”. PV can also be defined as the process of evaluating as well as improving the safety of drugs. In other words, it can be called as the practice of using the scientific methods for tracking, recording and analyzing, the effects of various pharmaceutical products. PV is also known as 'Drug Safety' that should be applied throughout the life cycle of a medicine.

2.4.2. Aims of pharmacovigilance

The major aims of PV are:-

- Early detection of unknown reactions and interactions.
- Detection of increase in adverse drug reactions frequency
- Identification of risk factors.
- Quantification of risks.
- Preventing patients from being affected unnecessarily.
- Rational and safe use of drugs.

2.4.3. Scope of pharmacovigilance

The scope of pharmacovigilance has grown remarkably in recent times and is now considered to include the following domains (Figure 2.1):

Figure 2.1: Scope of Pharmacovigilance

The products under consideration go beyond conventional medicines and include herbal medicines, other traditional and complementary products, biologicals, vaccines, blood products and possibly medical devices (Figure 2.2.)

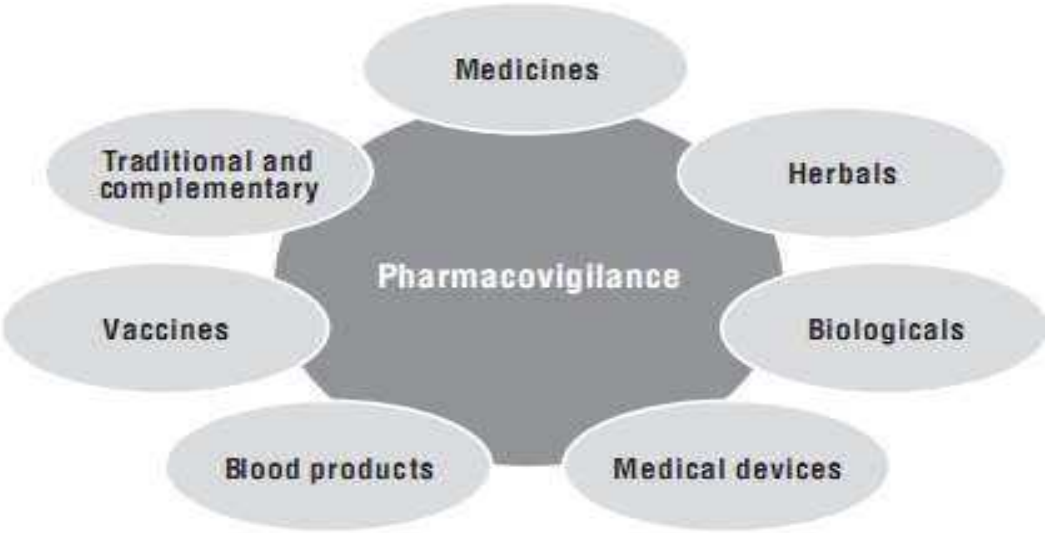

Figure 2.2: Products covered by Pharmacovigilance

2.4.4. Common Terminologies in Pharmacovigilance

- **Adverse Drug Event (ADE):** Any untoward medical occurrence that may be presented during treatment with a medicine but does not necessarily have a causal relationship with the treatment.
- **Adverse Drug Reaction (ADR):** A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
- **Medication Error (ME):** 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.
- **Product Quality Defect (PQD):** Quality problems of products i.e; suspected contamination, questionable stability, defective components, poor packaging or labeling, or unexpected therapeutic ineffectiveness.
- **Serious Adverse Event (SAE):** A serious adverse event or reaction is any untoward medical occurrence that at any dose:
  - Results in death
  - Requires hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity

- Congenital abnormality (birth defect)
- Life-threatening

- **Side effect**: Any unintended effect of a pharmaceutical product occurring at normal dose that is related to the pharmacological properties of the drug.
- **Signal:** Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.
- **Unexpected adverse reaction:** An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization or expected from characteristics of the drug.

2.5. Components of Adverse drug events (ADEs)

- ADE is an injury resulting from medical intervention related to a drug. This includes; ADR, medication error and product quality defect.
- It can be any untoward medical occurrence that may be presented during treatment with a medicine but does not necessarily have a **causal** relationship with the treatment

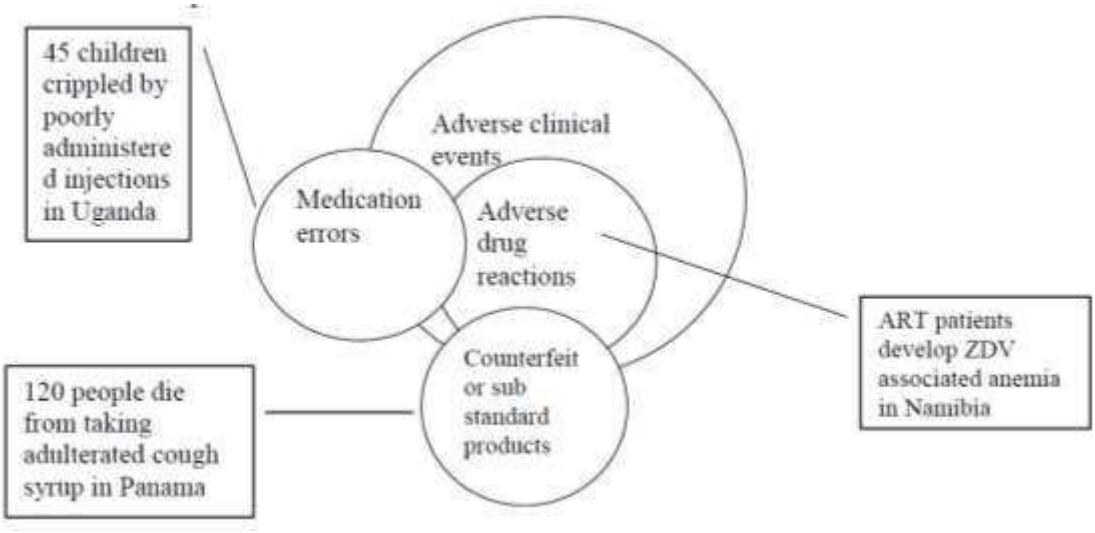

Figure 2.3: Components of ADEs

2.5.1. Adverse Drug Reactions (ADRs)

- ADR is a noxious, unintended, and occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
- An ADR in contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.
- The American Society of Health-System Pharmacists defined ADR as any unexpected, unintended, undesirable, or excessive response to a medicine that
  - Requires discontinuing the medicine (therapeutic or diagnostic)
  - Requires changing the pharmaceutical therapy
  - Requires modifying the dose (except for minor dosage adjustments)
  - Necessitates admission to a hospital
  - Prolongs the patient's stay in a health care facility
  - Necessitates supportive treatment
  - Significantly complicates diagnosis
  - Negatively affects prognosis
  - Results in temporary or permanent harm or disability, or in death

Classification of ADRs

ADRs can be classified into different types based on different criteria.

I. Classification of ADRs by type

Table 2.1: Classification of ADRs by type

Types	Features	Examples	Management
A: Dose related (Augmented)	Common Related to the pharmacologic action of the drug - exaggerated pharmacologic response Predictable Low mortality	Dry mouth with tricyclic antidepressants, respiratory depression with opioids, bleeding with warfarin, serotonin syndrome with SSRIs, digoxin toxicity	Reduce dose or withhold drug Consider effects of concomitant therapy

B.Non-dose related (Bizarre)	Uncommon Not related to the pharmacologic action of the drug Unpredictable High mortality	Immunologic reactions: anaphylaxis to penicillin Idiosyncratic reactions: malignant hyperthermia with general anaesthetics	Withhold and avoid in future
C. Dose Related and Time Related (Chronic)	Uncommon Related to the cumulative dose	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with bisphosphonates	Reduce dose or withhold; withdrawal may have to be prolonged
D. Time Related (Delayed)	Uncommon Usually, dose-related Occurs or becomes apparent sometime after use of the drug	Carcinogenesis Tardive dyskinesia Teratogenesis Leukopenia with lomustine	Often intractable
E. Withdrawal (End of use)	Uncommon Occurs soon after withdrawal Of the drug	Withdrawal syndrome with opiates or benzodiazepines (e.g., insomnia, anxiety)	Reintroduce drug and withdraw slowly
F. Failure of therapy	Common Dose related Often caused by drug interactions	Inadequate dosage or oral contraceptives, particularly when used with specific enzyme inducers	Increase dosage Consider effects of concomitant therapy

II. **Classification of ADRs by severity**

Assessment of ADRs is largely subjective. These reactions can be classified as **Mild**, **Moderate**, **Severe,** and **lethal** (deadly) based on severity.

- **Mild ADRs:** Mild reactions usually described as of minor significance include:

- Digestive disturbances (such as nausea, constipation, diarrhea), Headaches, Fatigue, Vague muscle aches, Malaise (a general feeling of illness or discomfort), Changes in sleep patterns, etc.
- However, such reactions can be very distressing to people who experience them. As a result, people may be less willing to take their drug as instructed, and the goals of treatment may not be achieved.

- **Moderate ADRs:** Are with moderate risk and the points listed are typical examples
  - Rashes (especially if they are extensive and persistent)
  - Visual disturbances (especially in people who wear corrective lenses)
  - Muscle tremor
  - Difficulty with urination (a common effect of many drugs in older men)
  - Any perceptible change in mood or mental function
  - Certain changes in blood components, such as a temporary, reversible decrease in the white blood cell count or in blood levels of some substances, such as glucose
  - Reactions that are described as mild might be considered as moderate if the person experiencing them considers them distinctly annoying, distressing, or intolerable.
- **Severe ADRs:**
  - Severe reactions include those that may be life-threatening (such as liver failure, abnormal heart rhythms, certain types of allergic reactions), that results in persistent or significant disability or hospitalization, and that cause a birth defect.
  - Severe reactions are relatively rare. People who develop a severe reaction usually must stop using the drug and must be treated.
  - However, some high-risk medications (for example, chemotherapy to people with cancer or immunosuppressant to people undergoing organ transplantation) might be given when their benefit outweighs their risk.
- **Lethal ADRs**
  - Lethal reactions are those in which a drug reaction directly or indirectly caused death.
  - These reactions are typically severe reactions that were not detected in time or did not respond to treatment.

- Lethal reactions can be the reasons that some drugs are withdrawn from the market (such as troglitazone and terfenadine).

Risk factors for the occurrence of ADRs

Risk factors for the occurrence of ADRs includes the following points:

1. **Hereditary factors:** Make some people more susceptible to the toxic effects of certain drugs.
2. **Age**: Extreme age groups are particularly vulnerable to ADRs because drugs are less likely to be studied extensively in these patients, and drug absorption and metabolism are more variable and less predictable in both of these groups.
3. **Gender:** The biological differences between males and females affect the **PK** and **PD** of many drugs.
4. **Pregnancy status:** the physiologic change might affect the **PK** and **PD** of many drugs. Drugs during pregnancy might affect either the mother or the embryo or both
5. **Alcohol drinking: PK** and **PD** interactions with certain drugs facilitate the development of ADRs.
6. **Race and ethnicity:** Evidence suggests that ethnicity (genetic variation) exerts a substantial influence on drug response and action.
7. **Smoking:** One of the risk factors for many diseases like peptic ulcers, cancer and cardiovascular diseases. It also affects the metabolic process by affecting liver enzymes
8. **Poly-pharmacy**: The number and severity of ADRs increase disproportionately as the number of drugs taken increases.
9. **Drug dose and frequency:** risk of ADR is higher when drugs are given at higher doses more frequently
10. **Disease related factors (accompanied diseases):** Concomitant disease may also influence susceptibility to ADRs.
11. **Incompatibilities between medicines and IV fluids:** May lead to the development of more toxic product
12. **Drug Interactions**: Interactions may lead to change in PK or PD of the drug this intern may cause increased ADR risk

2.5.2. Medication Errors (ME)

- ME 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 HCPs, patient, or consumer. •

One of the important missions of the healthcare providers is to help patients make the best use of medications and very importantly, strive to ensure patient safety.

- Medication safety is one of the major components in patient safety but unfortunately, medication errors do occur and often go undetected.

Table 2.2: Types of medication error

No	Types of ME	Description
1	**Prescribing Error**	Incorrect drug product selection (based on indications, contraindications, known allergies, existing drug therapy, and other factors), dose, dosage form, quantity, route of administration, concentration, rate of administration, or instructions for use of a drug product ordered or authorized by physician (or other legitimate prescriber); illegible prescriptions or medication orders that lead to errors.
2	**Dispensing error**	Dispensing without checking legibility of prescriptions, quality of products, appropriateness of prescribed drugs and other relevant information
3	**Administration Error**	Failure to give medications to the correct patient, at the correct time, correct dose, frequency, route, administration technique.
4	**Transcribing error**	Failure of the intermediary (a clerk/nurse in a hospital setting or a pharmacy technician in reading and interpreting the order in a paper-based system correctly
5	**Monitoring error**	Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy.
6	**Others**	Any medication error that does not fall into one of the above predefined types.eg. non-compliance

Factors that may influence Medication errors

- **Factors associated with HCPs**
- Lack of therapeutic training
- Illegible writing and use of non-standard abbreviations
- Inadequate drug knowledge and experience
- Inadequate knowledge of the patient
- Inadequate perception of risk

- Overworked or fatigued health care professionals
- Physical or emotional health issues
- Poor communication between HCPs with patients
- **Factors associated with patients**
  - Patient characteristics (e.g., Personality, literacy and language barriers)
  - Complexity of clinical case including multiple health conditions, poly pharmacy and high-risk medication
  - Incomplete patient data
- **Factors associated with the work environment**
  - Workload and time pressures
  - Distractions and interruptions (by both health care staff and patients)
  - Lack of standardized protocols and procedures
  - Insufficient resources
  - Issues with physical work environment (lighting, temperature and ventilation)
- **Factors associated with medicines :** Naming of medicines **,** Labelling and packaging

2.5.3. Product quality defect (PQD)

- A quality defect in a medicinal product may be defined as an attribute of a medicinal product or component which may affect the quality, safety and/or efficacy of the product, and/or which is not in line with the approved product authorization (PA).
- Reports of quality defects are received from a number of sources, such as manufacturers, pharmacists and members of the public.
- There are three classes (or ratings) of quality defects and these are classified according to their potential risk to patient and health.
  - **Critical Quality Defects:** defects which are potentially life-threatening or could cause a serious risk to health
  - **Major Quality Defects:** defects which could cause illness or mistreatment but are not critical

- **Minor Quality Defects:** defects which may not pose a significant hazard to health

  - As part of the concept of applying risk-based regulatory oversight as per the quality risk management principle, the EFDA is providing guidance so that stakeholders may be better able to determine which types of quality defects are required to be reported to the EFDA and which ones are not.
  - **Quality defects that should always be reported**- These are types or categories of defect which should always be reported to the EFDA, as they are (potentially) serious in nature and have a high associated risk. These include:
    1. **Product mix-up issues:** Reporting of a potential product mix-up is considered mandatory, as the administration of an incorrect product or an incorrect strength of a product to a patient could lead to serious situations such as overdose, under dose, allergic reaction or interaction with another contraindicated medicine.
    2. **Product contamination:** The risk posed by a bacterial, fungal, viral, chemical or certain other type of contaminant may vary. All contaminants should be viewed as potentially harmful.
    3. **Non-adherence to cold chain:** Any breach of cold chain that is identified after a product has been distributed onward in the supply chain should be reported to the EFDA.
    4. **Illegal or counterfeit product:** A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to its identity and/or source (WHO definition).
    5. **(Potential) lack of sterility assurance:** Defects that may affect the sterility assurance of a medicinal product, for example cracks in vials and leaking infusion bags, are deemed reportable, especially if the defect issue is not isolated in occurrence.
    6. **Unauthorized product on the market:** A product which does not have an Ethiopian product authorization.
  - **Quality defects that may need to be reported are packaging and/or labeling defects**
    - Defects associated with product packaging and labeling constitute the highest proportion of reports received by the EFDA.
    - Medicinal products usually have multiple packaging and labeling components and can display large volumes of text, so there is the potential for wide variety of defects to occur.
    - These defects may not affect the product quality directly, but have an impact on the manner in which the product is prepared, administered or used.

2.6. Chapter Summary

- Premarketing safety and efficacy information does not necessarily predict the safety or efficacy of medicine in the real clinical practice.
- Uncommon ADRs or manifestations of chronic toxicity may become apparent only after the drug has been used in a large number of subjects for long periods of time.
- Because knowledge about the clinical toxicity of a new drug will always be incomplete at the time of marketing, further investigation of frequency and determination of adverse drug reactions must be pursued in the post-marketing safety studies through pharmacovigilance system
- ADEs are medicine related problems having direct adverse patient response, errors occurs during medicine use process and defective products.
- Collectively the problems are categorized under ADR, ME and PQDs)

Chapter 3: Diagnosis, Management, Prevention, Investigation and Causality Assessment of ADEs

Duration: 3:30 HRs

Chapter description: This chapter discusses the components of ADEs, and describes diagnosis, management approaches of ADRs. Besides, it also deals with ADE investigation and causality assessment methods.

Primary Objective:

At the end of this chapter, participants will be able to:

- Describe ADEs, conduct diagnosis, management of ADRs, and ADE investigation and causality assessment.

Enabling Objectives: at the end of this chapter, participants will be able to:

- Explain diagnosis, management, and prevention of ADRs
- Describe the process of ADE investigation.
- Discuss causality assessment of ADRs

Chapter Outline

3.1. Diagnosis, Management, and Prevention of ADEs

Introductory Case study

- **Instruction:** Read the case carefully and discuss the questions that follows
  Time : 10 minutes

K.J., a 48-year-old woman, seeks care at an urgent care center. She presents with impaired speech, but is able to swallow; she has red and swollen lips and tongue, and puffy eyes. Her medical history includes hypertension, atrial fibrillation, and a new diagnosis of hypercholesterolemia (plasma cholesterol 290 mg/dL). Although her BP had been well controlled on hydrochlorothiazide, her diuretic was discontinued about a week ago because of its effect on cholesterol, and enalapril 5 mg daily was started. K.J. also takes a multivitamin (one tablet each day) and warfarin (5 mg daily). Her physical examination shows BP 130/87 mmHg; heart rate 70 beats/minute; lungs clear to auscultation and percussion; respirations 12 breaths/minute; and skin without rash or urticaria.

Discuss:

A. What is going on in this patient?
B. How do you analyze the situation?
C. How do you manage if the patient is experiencing ADR?
D. Was it possible to prevent this? How?

3.1.1. ADR diagnosis approach

The diagnosis of an ADR is part of the broader diagnosis in a patient. If a patient is taking medicines, the differential diagnosis should include the possibility of ADR. Besides, ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following steps may be helpful in assessing possible ADRs:

A. Collect the relevant information by reviewing medical history including the patient's subjective report of symptoms, medication list, allergy history and objective findings including relevant laboratory investigations.

B. Ensure medicine ordered is received and actually taken by patient at dose advised. Consider all drugs / medicines possibly taken by the patient.

C. Verify that the onset of suspected ADR was after drug was taken, not before.

- Discuss carefully observation made by patient.
- Determine the time interval between beginning of drug treatment and onset of event.
  - Was the event present before the patient began the medicine?
  - Did the event occur within a plausible time of starting the medicine?
  - Was it dose related?

D. Consider whether the event pharmacologically plausible

- Is it a side effect (class A reaction) of the drug(s) in question or the class?
- Is it a known allergic (class B) reaction of the drug(s), class or previous exposure

E. Consider the background frequency of the event and how often it is associated with the drugs.

- Eg. Headache is relatively common, so its association with medicine may be by chance. In contrast, aplastic anemia has a low background incidence and is often associated with medicines; it is therefore more likely to be an ADR.

F. Evaluate suspected ADR after discontinuing drugs or reducing dose and monitor patient's status (de-challenge)

- Trial withdrawal: Is the time to recovery consistent with the action of the drug?
- Re-challenge : same pattern? Or No effect?
- De-challenge**:** withdrawal of a product from the patient's therapeutic regimen
  - Positive de-challenge: improvement of reaction when de-challenge occurs. Resolution of suspected ADR when the drug is withdrawn is a strong, although not conclusive indication of drug-induced reaction
  - Negative de-challenge: continued presence of an adverse experience after withdrawal of the drug.
- Re-challenge**:** reintroduction of a product suspected of having caused an adverse event following a positive de-challenge.
  - Negative re-challenge*:* failure of the product when reintroduced to produce signs or symptoms similar to those observed when the product was previously introduced.
  - Positive re-challenge*:* reoccurrence of similar signs and symptoms upon reintroduction of product.

Note: Re-challenge is only justifiable when the benefit of re-introducing the drug to the patient outweighs the risk of recurrence of the reaction. This is rare. In some cases, the reaction may be more severe on repeated exposure. Re-challenge, therefore, requires serious ethical considerations.

G. Consider the possibility of a drug interaction

- Remember:
  - OTCs
  - Contraceptives
  - Herbals / traditional
  - Drugs of abuse / alcohol
  - Long term medicines
- No problems observed with the first drug but problems occur when a second drug is commenced
  - Is it the 2nd drug or is it an interaction?
  - Has the patient taken the 2nd drug before?
  - Timing of the introduction and withdrawal of interacting drug fit
  - Knowledge of the metabolism of the two drugs

H. Analyze alternative causes (other than the drug) that could on their own have caused reaction

I. Use relevant up-to-date literatures like product inserts, Med Watch reports, and personal experience on drugs and their ADRs. Verify if there are previous conclusive reports on this reaction. The National PV Centre is one resource for obtaining information on ADRs.

3.1.2. Management of ADRs

ADRs should be quickly identified and managed to limit their detrimental effects on the patient. Most of the time the management of ADRs is supportive and removal of the culprit. Rapid action is sometimes important because of the seriousness nature of the suspected ADR. Example, anaphylactic shock.

Decisions for the management of ADRs are made by considering:

A. Seriousness / severity of ADR

B. Seriousness of disease

C. Benefit / harm assessment

A. If the reaction is serious

- Withdraw suspected (all?) drugs

- Treat urgently
- Use alternative drug, if any

If the reaction is mild;

- Continue treatment if necessary
- Consider dose reduction
- Reassure
- Symptomatic treatment if warranted

B. If the disease is serious

- Consider the effect of not having treatment
- Continue treatment and treat symptoms of reaction if necessary
- Consider an alternative drug

C. Benefit/risk assessment

- Whenever a drug is given to a patient, the prescriber should have a clear idea of what is to be achieved, the likelihood of success, and the chance of doing harm and try to balance these factors.
- Although general knowledge about a drug may not be sufficient to cover a particular patient's situation, the benefits and risks of the drugs would be determined from available literature including the enclosure with the drug produced by the manufacturer.
- For each drug prescribed the prescriber should consider the medicines use in reducing the seriousness of the disease, how long will the disease last, and how much reduction can be expected from the drug? In the case of prophylaxis, how prevalent is the disease and what reduction can be expected? , seriousness, frequency and duration of ADR
- Report the ADR

3.1.3 ADE prevention strategies

Prevention of some ADEs is possible and should be a necessary function of the HCPs. Because many ADEs are related to the ME and PQD . The following measures would help to reduce the incidence of ADEs:

- Build the capacity of health care providers on monitoring, prevention of ADEs, and to make it part of their routine practice.
- Be aware of the general predisposing factors to ADEs. These include;
    - Extremes of age, liver and kidney disease, previous history of allergy or reaction to drugs.
    - Co-morbid conditions such as AIDS increase the incidence of ADEs (e.g. AIDS patients have a propensity to have allergic adverse reactions). Drug therapy should be adjusted to the individual.
    - Be particularly careful when prescribing for children, the elderly, the pregnant and lactating, the seriously ill and patients with hepatic and renal diseases. Careful ongoing monitoring is essential in these patients.
- Counsel patients about potential common and severe ADRs that may occur, actions to prevent or minimize their occurrence, and actions to take if they occur, including notifying the prescriber, pharmacist, or other health care provider.
- If the ADR is preventable give appropriate prophylaxis
- Do not change therapy from known drugs to unfamiliar ones without good reasons
- Always consider the risks and benefits of any drug that you plan to use. Make comparisons among drugs for the same indication before deciding what is best to use for a particular patient.
- Take extra care when you prescribe drugs known to exhibit a large variety of interactions and adverse reactions (e.g., anti-coagulants, anti-epileptics, hypoglycemic drugs) with careful monitoring of patients with such reactions.
- Beware of the interaction of drugs with certain foods, alcohol and household chemicals
- Drugs should always be of the best possible quality
- Avoid poly-pharmacy. Use few drugs whenever possible. The incidence of adverse reactions increases with the number of drugs.
- Review the entire drugs used by patients regularly, taking special notice of those bought without a prescription (OTC, herbal preparations).
- If patients show signs or symptoms not clearly explained by the course of their illness, think of ADRs
- If you suspect an ADR, take an appropriate measure as soon as possible.

- Refer to textbooks and other reference materials providing information on ADRs (eg. Medwatch, standard reference books on ADRs like meyler's side effect of drugs, The side effect of drug annuals (SEDA), Martindale: the complete drug reference, Davies text book of ADR) and interactions (eg. Micromedex)
- Avoid nonstandard abbreviations and recheck the prescriber if the prescription is illegible
- Recheck the calculation to ensure that the patient will get the right therapeutic dose.

The importance of preventing ADEs

- Reduces the risk of a patient harm
- Can prevent unnecessary hospital admissions or re-admissions
- Can prevent prolonged hospital stays
- Reduce unnecessary costs to the health system
- Increase staff confidence and morale
- Reduces risk of litigation for clinical negligence
- Reduce risks of harm to Trust reputation
- Provide reassurance to regulatory bodies and commissioners

Case studies

- **Genera instruction:**
  - Read the following cases individually and reflect in group what you understand
  - Answer the discussion questions following each case
  - **Time allotted**: 20 minutes

Case-1

A 30-year-old man newly diagnosed with HIV infection [CD4: 20 cells/mm3; HIV-1 RNA: 32,388 copies/mL] developed skin rash and fever 11 days after starting the combination of Efavirenz (600 mg), Tenofovir (300 mg), and Lamivudine (300 mg) once daily. He was also being treated with Pyrimethamine (75 mg/day) and sulfadiazine (6 g/day) for toxoplasmosis and azithromycin and fluconazole for prophylaxis against opportunistic infections, all of which had been started four weeks before the Antiretrovirals. He denied alcohol use or exposures to viral hepatitis. Physical examination showed a generalized erythematous rash. Therapy was continued. One week later he complained of abdominal pain, nausea and fever, and blood tests showed

marked elevations in serum aminotransferase levels (Table). All medications were stopped. Serum enzyme elevations peaked 5 days after stopping antiretroviral therapy and he recovered slowly but completely. Serum lactate levels were normal, and tests for viral hepatitis A, B and C and autoantibodies were negative. He was subsequently treated with Tenofovir, Lamivudine and Atazanavir without recurrence of the liver abnormalities.

Key Points

- Medication: Efavirenz (600 mg daily)
- Pattern: Cholestatic
- Severity: 4+ (jaundice, hospitalization, and coagulopathy)
- Latency: 11 days to onset of rash, 18 days to onset of jaundice
- Recovery: Yes, time to recovery not available
- Other medications: Pyrimethamine, Sulfadiazine, Azithromycin, Fluconazole, Tenofovir, Lamivudine, Efavirenz

Table 3.1: Laboratory Values

Time after starting	Time after stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
18 days		699	1073	3.0	
3weeks	0	1181	1362	4.2	Temperature 39.5^{o}c
	5days	2132	760	10	Ammonia 119, INR 2.6
4weeks	4weeks	488	840	7.5	
Normal values		**<40**	**<117**	**<1.2**	

Questions for discussion

A. How would you analyze this situation? What investigations would you carry out?

B. If you think it is an ADR, which medicine or medicines might be responsible? How did you arrive at this conclusion?

C. If you think it is an ADR, how do you manage it?

Case 2

A.K., a 36-year-old Ethiopian man, is seen in the ED with a 2-day history of fever, chills, and bouts of diarrhea following his return from Afar region, where he was visiting his parents for 3 weeks. A.K. had not taken any prophylaxis for malaria. A blood smear stained with Giemsa solution demonstrated P. vivax, and A.K. was given chloroquine 1 g (600 mg base) initially, to be followed by 500 mg (300 mg base) 6 hours later and 500 mg at 24 and 48 hours. On completion of the chloroquine regimen, A.K. was instructed to take primaquine 52.6 mg/day (30 mg base) for 14 days. However, A.K. was seen again in the ED a day later with complaints of abdominal pain, severe headache, vomiting, and a "bitter taste" in the mouth.

Questions for discussion

A. How do you analyze the situation?

B. How do you manage if the patient is experiencing ADR?

C. Was it possible to prevent this? How?

Time: 15 minutes

Summary: Diagnosis, Management, and Prevention of ADEs

- ADEs are medicine related problems having direct adverse patient response, errors occur during medicine use process and defective products.
- Collectively the problems are categorized under ADR, ME and PQDs.
- ADE prevention is an integral part of patient care
- Correctly defining and classifying an ADR can help determine management
- Health professionals should be equipped with the knowledge and skill of ADR diagnosis and management

3.2. Investigation and causality Assessment of ADEs

Individual reflection

- Have you ever encountered a SAE or PQD that was being investigated?
- Were you involved? What are your experiences?

3.2.1. Introduction and rationale for investigation of ADEs

Investigation of post market medicine related problems(ADEs) is the systematic process to find out all the details or facts about the event to discover (understand) what led to the event, and provides an opportunity to introduce changes in practice and reduce the likelihood of recurrence.

SAEs are required to be promptly reported to regulatory authorities and need to be investigated to establish any linkage with the drugs used (causality assessment). Successful response to SAEs is dependent on early identification, early action, having a plan in place, and detailed reporting.

The ultimate goal of an investigation is to determine whether the medicine in the process is responsible for the reported event(s) or to find another and correct it if possible, and reassure the public. SAEs, critical product quality problems, MEs and clusters in the case of vaccine and mass drug administration (MDA) are subject for investigation.

Before the start of the investigation, procedures to be followed, experts responsible to conduct the investigation, and tools used during theinvestigation are important to be identified and prepared.

The rationale for investigating ADEs:

- To confirm a reported ADEs and clarify the details and outcome
- To determine whether there is the same event occur within the community attributable to another cause
- To determine the link between the product and the event reported
- To determine the contribution of operation related problems
- To determine whether a reported event was isolated or part of a cluster for SAEs
- To determine the cause of the ADEs so as to provide corrective and preventive actions to the responsible stake holders
- To decrease distrust of the patients (users) toward the healthcare system

3.2.2. Investigation of ADEs

All ADEs that are encountered, reported and eligible are subject to investigation.

Determine Case Eligibility for Investigation

Cases that are eligible to investigation include:

- All PQDs,
- MEs which cause SAEs
- SAEs,
- Cluster of events (in the case of vaccine and MDA), and
- All events causing significant parental or community concern (in the case of AEFI, MDA).

Determining who should investigate

- There should be an investigator with adequate training and resources for the investigation at each major administrative unit (e.g. National, region, Zone or woreda).
- When embarking on an investigation, peripheral level investigators should ensure that the national level is aware and regularly updated throughout the investigation.
- A decision should be made as early as possible about who is taking up the role of spokesperson about the investigation.

Steps in conducting investigation for SAE and medication errors

Serious adverse event and MEs that causes SAE should be investigated as soon as possible and the following steps outline a typical investigation:

A. Confirm the information provided in the report and add missing information (if any).

B. Check if more than one case should be included in the same investigation and gather and verify basic information on each case.

- Age, sex, place of residence, pregnancy and lactation history (if applicable)
- Signs and symptoms in chronological order from the time of drug administration
- Family history
- Recent clinical features, details of first examination including name, profession and address of the examiner
- Type and description of the encountered serious adverse event, date of appearance, duration, and treatment of the clinical event, date and time of hospitalization (if applicable)
- History of the patient including past medical history,
- previous allergies or reactions to medicines

- Preventive chemotherapy history: type of medicine(s) taken, date of the last and previous (if any) doses, type of previous reaction (if any)
- In the event of death, date and time of death, a full autopsy report as much as possible (or reason why it is not available), toxicological screening, and pathological findings

C. Direct observation of treatment site (institution).

- Ask to be shown treatment procedures, medicine administration techniques and how the dose was calculated
- Determine if the number of persons to treat was greater than usual.
- Check if the medicine administered was obtained from the original medicine container or not and if the labeling is legible or not.
- Check for up-to-date guidelines on medicine handling and treatment procedures
- Observe all medicine storage facilities and the available practice
- Observe whether the physical environment of the treatment area is hygienic and compatible with appropriate drug administration
- Check the presence and completeness of record of medicines that are received and used in treatment operations

D. **Gather information on the suspected medicine and obtain a sample** if necessary (preferably from and with the container of the suspected medicine):

- Medicine name (Generic and brand name)
- Medicine strength(s)
- Pharmaceutical/ dosage form
- Pack size
- Batch number(s) and/or lot number
- Manufacturing and expiry date
- Name and address of the MAHs (Manufacturer, Importer and Wholesaler
- Total received quantity of packs

3.2.3. Product Quality Defect Investigation

PQD is defined as attributes of a medicinal product or component which may affect the quality, safety and/or efficacy of the product, and/or which are not in line with the approved for Market Authorization (MA). According to their potential risk to patients there are three classes of quality

defects and these are classified as critical quality defects, major quality defects, and minor quality defects**.**

EFDA investigates all quality defects on a case-by-case basis. Quality defects can result in batch or product recalls, in the issuance of communications to healthcare professionals and responsible market authorization holders. The important part of the quality defect investigation is to ensure that a plan of timely corrective actions is put in place at the manufacturing site, transportation or storage condition in order to prevent a recurrence of the defect.

Investigation of PQD include collection of information on the following:

- The nature of observed quality defect
- Collecting all pertinent information about specific product
    - Product name (generic and brand)
    - Active substance name(s)
    - Product strength(s)
    - Dosage form
    - Pack size
    - Batch number(s) and /or lot number
    - Production and expiry date
- Ensuring that the product is registered in the country and purchased from the right supplier
- Name and address of the MAHs (Manufacturer, Importer and Wholesaler)
- Total quantity of packs of affected batch (es)
- Conducting facility inspection to identify facility level
- Conduct inspection in other facility who had the same product but not report a defect
- Taking adequate sample of the product after visual inspection
- Conduct visual inspection and take product sample (if needed) in consultation with the laboratory

E. Using the available form (investigation form)

- Fill all the information stated above in the available investigation form
- Attach copies of all available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports).
- Complete additional information not available in existing documents from family and caregiver

- Information not available during the first investigation should be collected in repeated visits.
- In the case of PQD take a photo of the product and it's package which is reported as defected
- If the SAE is a cluster provide details of number of people who has taken the same medication, same batch at each site/other site. And attach record if available
- When specific training is required, investigate on details of staff training (When and where they trained? To do what? and obtain verification)

Summary of Investigation of ADEs

- Serious Adverse Events, MEs which causes SAE and PQDs need to be investigated to establish any linkage with the medication.
- Successful response to SAEs is dependent on early identification, early action, having a plan in place, and detailed reporting
- Investigation should be conducted as soon as possible, by the appropriate bodies and up to satisfactory level.

3.2.3. Causality assessment of ADEs

Introductory discussion points

- Have you ever encountered a SAE where causality was assessed at national level and categorization was provided to stakeholders?

3.2.1.1. Introduction

Causality assessment of ADEs is a method used for estimating the strength of relationship between drug(s) exposure and occurrence of adverse event(s). Causality assessment means **t**he evaluation of the likelihood that a medicine was the causative agent of an observed adverse drug event (ADE).

Based on the reported cases causality assessment can be conducted at individual, regional, or national level and the conclusion obtained from the causality assessment, can help regulatory

authorities work on in signal detection and risk-benefit decisions regarding medicines and share the report to Uppsala Monitoring Center (UMC) and other stakeholders as necessary.

Different methods are used in conducting causality assessment. Among others, WHO-UMC system uses combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

3.2.3.2. Determining who should conduct causality assessment

Non-SAEs causality assessment can be conducted at each level by health-care providers, when dealing routinely with ADRs in patients by using WHO-UMC causality criteria.
Causality assessment of SAEs should be undertaken by the national committee and regional P centers experts composed of clinicians with variety of specialization, academicians and statisticians.

3.2.3.3. Rationale (Importance) of causality assessment:

Causality assessment has a huge importance in defining relationship between drug and adverse event, signal detection and evidence based risk minimization. Causality assessment is crucial for risk benefit assessment, particularly when it involves post marketing safety signals and the causality finding can also use to make changes on the product labeling.

3.2.3.4. Methods for conducting Causality

1. **WHO-UMC Causality Categories**

EFDA uses the WHO UMC causality categories for the evaluation of the relationship between an encountered ADE and the responsible medicine. The causality categories are assigned based on the assessment criteria provided for each.

Table 3.2: WHO-UMC Causality Categories

Causality category	**Assessment criteria***
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically,

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

*** All points/criteria should be reasonably complied**

After a causality category is reached for the encountered ADE, the committee provides a set of recommendations for the stakeholder involved to be implemented and prevent any future recurrence of the ADEs.

2. Naranjo method

Developed in 1991 by Naranjo is often referred to as the Naranjo Scale. This scale was developed to help standardize assessment of causality for all ADE. It is simple to apply and widely used. Probability is assigned via a score termed definite, probable, possible or doubtful. See Annex 1 of this chapter in the manual

Summary of causality assessment

- Causality assessment means the evaluation of the likelihood that a medicine was the causative agent of an observed ADE.
- Based on the reported cases causality assessment can be conducted at individual, regional, or national level.
- Different algorithms and criteria are used in conducting causality assessment.

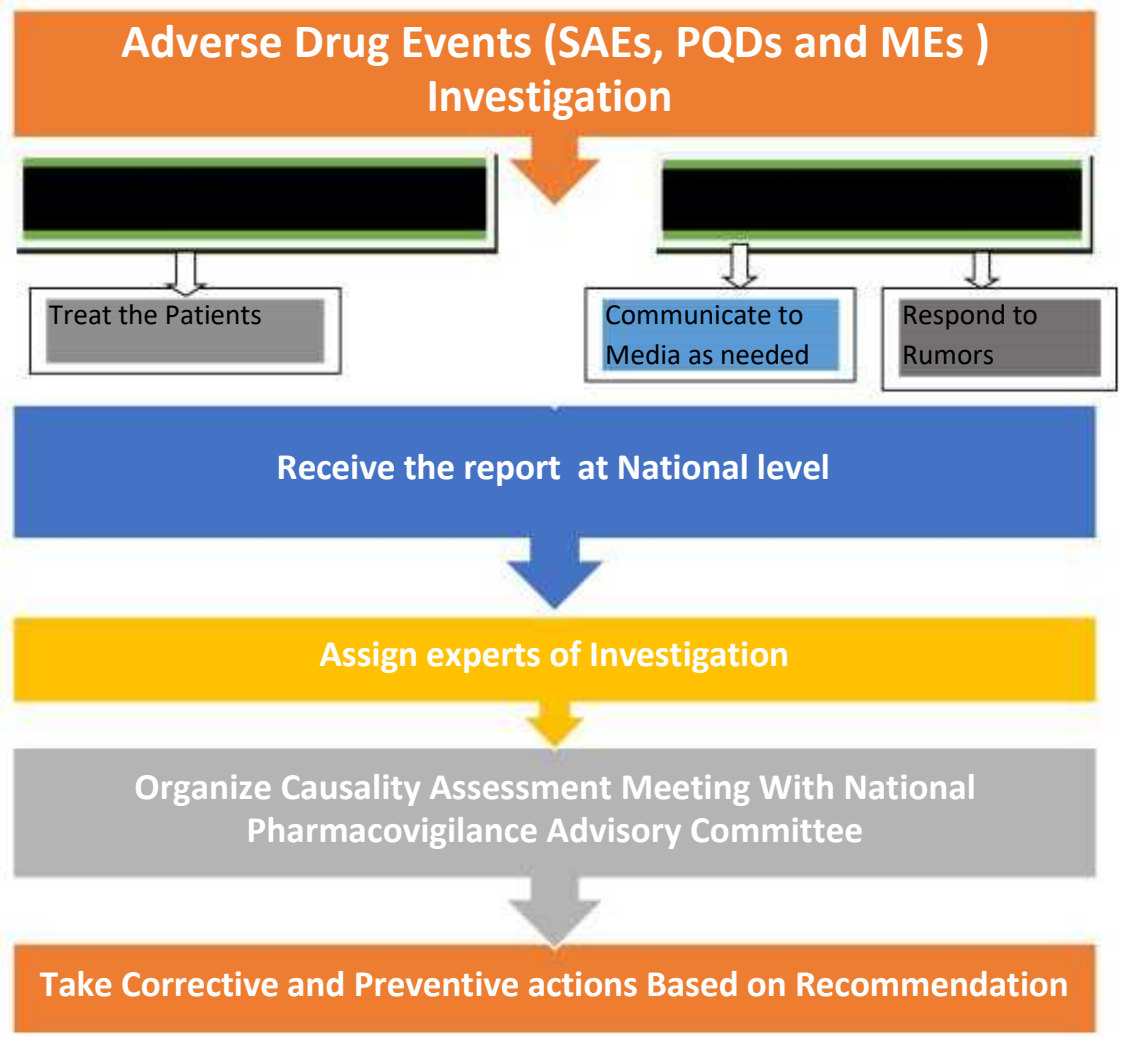

Fig. Adverse Drug Events (SAEs, PQDs and MEs) Investigation

Table 3.3: Naranjo Algorithm for Assessing Probability of an ADR Occurrence

Questions	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

Chapter 4: Adverse Drug Events Monitoring and Reporting in Ethiopia

Duration: 3:10 HRs

Chapter Description

This chapter describes about the national ADE monitoring and reporting system and provides explanation about the role and responsibility of each stakeholder in the national pharmacovigilance system. It also familiarizes the various ADE reporting tools and process of reporting and feedback giving.

Primary objective:

At the end of this chapter, participants will be able to:

- Describe the national ADE monitoring and reporting system.

Enabling objectives: At the end of this chapter, participants will be able to:

- Identify the importance of ADE monitoring
- Describe the national ADE monitoring and reporting system
- Complete the ADE reporting tools
- Identify the roles and responsibilities of stakeholders in national PV system

Chapter outline

4.1. Introduction

Individual reflection

- Have you ever had an experience of an ADE that occurred on a patient? What did you do about it?
- Do you think you have a role in the national PV system? If yes, what type of roles do you have?

Time: 5 minutes

EFDA, a national regulatory authority, is mandated as per the proclamation number 1112/2019, to ensure the safety, quality and efficacy of medicines by undertaking the major regulatory functions. One of these regulatory functions is adverse events monitoring and reporting system. National pharmacovigilance /PV/ system was started in 2002 and Ethiopia becomes the 88th full member of the WHO Program for International Drug Monitoring in 2009.

Overall ADEs monitoring and reporting system is coordinated by national PV center in EFDA. In addition to national pharmacovigilance center, there are 6 regional pharmacovigilance centers established in 2020 at university-based referral hospitals located at Gonder, Mekelle, Hawassa, Haromaya, Jimma, Addis Ababa.

The legal mandates enabling the regulatory authority to execute ADE monitoring which are provided through the **proclamation 1112/2019**are stated as follows.

Article 4: Sub article (9)

- The Authority shall undertake or order post-marketing surveillance to ensure safety, efficacy and quality of medicines and take appropriate legal measures.

Article 4: Sub article (10)

- Ensure that evidence of existing and new adverse events and information about pharmacovigilance of globally monitored products are followed upon and, as appropriate take the necessary legal measure.

Article 24:

- Every health professional working for a medicine or medical device institution shall have the duty to immediately report risks of public health significance related to the quality, safety and efficacy of medicine or quality safety and effectiveness of a medical device to the executive

Article 38:

- The manufacturer and importer of any medicine or medical device shall be responsible for damages caused as a result of quality and safety problem associated with the product. Implementation details shall be determined by the regulation

4.2. The National ADE monitoring and reporting system.

The system relies mainly on Passive surveillance /health professionals spontaneous reporting but active surveillance has also been performed as Cohort Event monitoring on ART, TB and other mass drug administration.

ADE reporting routes in the National PV system are diagrammatically presented as follows:

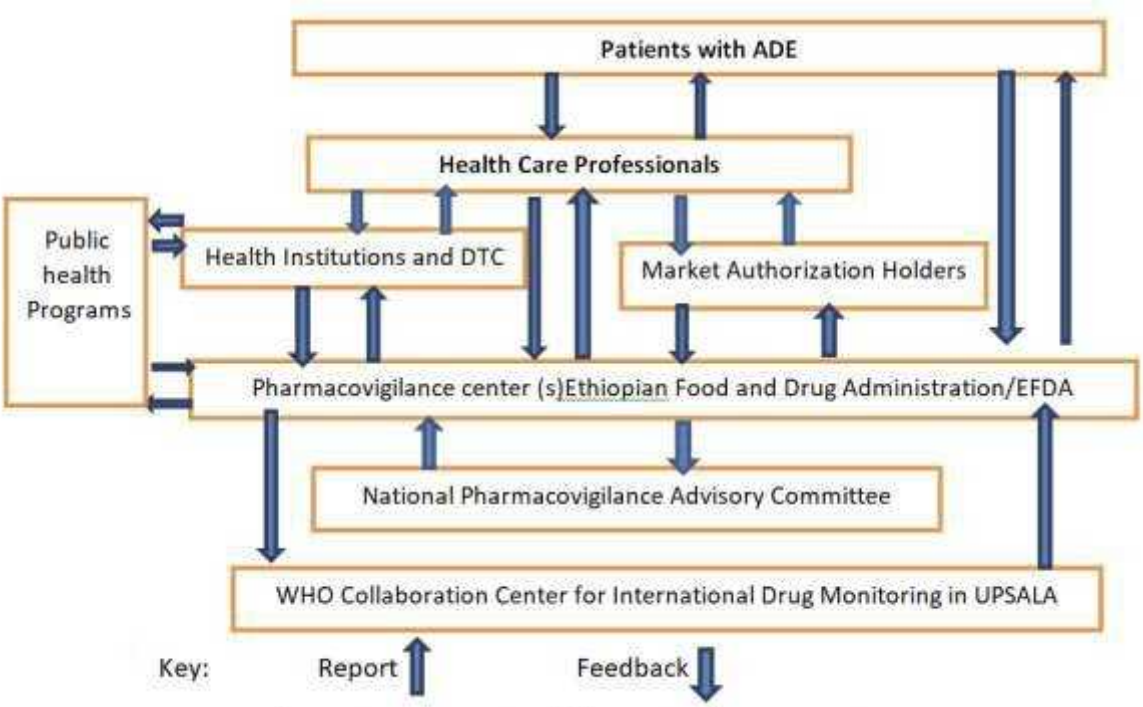

Figure 4.1: *The National ADE reporting and feedback mechanism*

4.2.1. What to report?

It is mandatory to report all adverse drug events which contain adverse drug reactions, product quality defects and medication errors and are provided in detail as follows:

- **ADRs**
  - All suspected reactions to drugs
  - Unknown or unexpected reactions
  - Serious adverse drug reactions
  - Unexpected therapeutic effects
  - All suspected drug interactions

- Treatment failures

- **Product quality defects**
- **Medication errors:** Medication error of any type

In addition, any Adverse Event Following Immunization (EEFI) should be reported according to the guideline for AEFI Surveillance in Ethiopia by HCPs engaged in national expanded program for immunization /EPI/

The reporter does not need to prove that there is a causal association between medicine /vaccine and adverse reaction. Therefore, uncertainty of cause and effect relationship should not be a reason for not reporting and only suspecting that the drug may cause the ADE is enough to report

4.2.2. Who should report?

HCPs including physicians, dentists, health officers, nurses, pharmacists and other pharmacy personnel should report ADEs to regional/national PVcenter. Market authorization holders: Being primarily responsible for safety of their products, they are obligated to report serious ADRs that they receive to nationa PV center. While non-serious ADEs should be included in the periodic sfaety up-date reports (PSURs) that are also sent to EFDA

4.2.3. When should be reported?

- Any suspected ADE (ADR, ME or PQD) should be reported as soon as possible after all relevant information is compiled. Delay in reporting will make reports inaccurate and unreliable
- Serious ADRs, unexpected and expected, must be reported within 24 hrs after identification by HPs.
- Reporting while the patient is still in the health institution will give a chance to the reporter to clear any ambiguity by re-questioning or examining the patient
- Any follow-up information for an event that has already been reported can be sent on a new adverse drug event report form to national PV center. Clearly indicate that the report

concerns follow-up information and include 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.

4.2.4. How to report?

The national PV system has reporting tools to receive encountered and observed ADEs from health professionals. (Annex I to III). Reporting can be done using any of the four available mechanisms or tools described below:

- **The yellow**: prepaid report form available at the facility (Annex 1). After the form is filled and folded, it needs to be sent to the post office so that it could reach EFDA
- **8482 (toll free line):** Collect the necessary patient information, drug information, reaction information, reporter information call the number and inform the trained experts who can receive the report at the Health regulatory Information center of EFDA.
- **Online reporting:** Using online reporting system available from the website www.fmhaca.gov.et-serivces-e-Reporting ADR, creating an account using an email address and then entering the required information in the reporting page (See instructions on Annex II).
- **Medsafety:** Using a mobile application **Medsafety** that can be downloaded from Google play store for Android phones or and **the APP store for IOS users,** creating an account using an email address and then entering through the "new report" button and filling the information on the adverse drug event that is going to be reported (See instructions on Annex III).

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

If the event occurred in a university hospital, it is very important to communicate focal person available in hospital PV center to get the necessary support in the reporting process. These focal persons are also available in other health facilities and are designated by the facility to support Pharmacovigilance activities.

4.2.5 What happens after a report sent to national PV center?

As the primary role and mandate of EFDA to ensure that marketed medicines are safe and of quality, the experts at the PV center perform the necessary data management activities after an adverse drug event report is received. These activities are:

1. Information validation, verification and report entry

The recipient of the report will carefully review the report for the quality and completeness of the filled information obtained in the report form. The reporter might also be requested for information in case of missing pertinent data by using the address he/she has provided. Each report is classified as an adverse drug reaction, medication error or a product quality problem. Pharmacovigilance experts enter the incoming reports into the national Pharmacovigilance database which is vigiflow.

2. Acknowledgment feedback to the reporter

The center then provides feedback in the form of an acknowledgment package to the reporter. The acknowledgment package contains formal letter from the authority and Information Education and communication materials prepared by pharmacovigilance center.

3. Investigation

Each individual case safety report is investigated further to gather further information on the case for further analysis. If it is ADR and medication error then the occurrence of the case is searched and additional data is solicited from other health care facilities so that the rate and variety of the available data is increased to be subjected to analysis. If the case is adverse event following immunization, the case is investigated by examining the clinical record of the victim, the vaccinators, the vaccine handling and the vaccine identifying information and interviewing all healthcare providers, the family and all that were involved during the immunization programme. If the case is a product quality defect further investigation is carried out by taking samples from other facilities and subjecting it to laboratory analysis

4. Causality assessment

Causality assessment is performed and the report is classified according to the WHO causality criteria. Causality assessment can also be performed at the regional Pharmacovigilance centers that are sending reports to the national PV center. The assessment can then be verified and

finalized to be sent to Uppsala monitoring center of WHO and also to be used for recommendation for regulatory measure.

5. Report analysis

The outcome of the report, together with relevant information including background rate relating to the event will be used to analyze as to its rate and relevancy.

6. Assessing for potential signals

The Pharmacovigilance experts at the EFDA review each incoming report (adverse drug reaction, 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 which could be-

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

A signal can initially be detected in a single incoming report. The literature, the WHO Signal document and the WHO Pharmaceutical Newsletter should be 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.

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

Each detected potential signal will undergo further evaluation. The WHO database published literature and information from the market Authorization Holder are reviewed for similar cases. The National Pharmacovigilance safety 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, it is not signal, or if further monitoring is needed.

7. Taking regulatory measures

Based on the result of the different evaluations carried out and if necessary using the quality control laboratory investigation results, and the recommendation obtained from the Pharmacovigilance advisory committee, regulatory measures will be taken on the specific medicine used so that appropriate actions are taken. The regulatory actions might range from warnings on the use of the specific medicine to the withdrawal or recall of the medicine and suspension from use.

8. Communication with stakeholders

After all those processes are completed, the final decision and/ or regulatory measures will be communicated to all concerned bodies or stakeholders who are involved in the national PV system.

4.3. Demonstration of reporting tools

- In Ethiopia, currently there are at least 3 ways of reporting ADE to the authority; these are:
    - Paper based ADE reporting,
    - Mobile based reporting, and
    - E-reporting

Components of ADE report

The ADE reporting form should be completed in as much detail as possible as shown below.

- **An identifiable patient:** name, card number, sex, age, weight, height, ethnic group, substance of abuse
- **Suspected medicine:** Name, strength, batch number, manufacturers dose, dosage, route of administration, indication for use, duration of use, date started, date stopped,
- **Suspected drug reaction:** Description of the reaction, seriousness of the reaction, date of the reaction started and stopped, date of drug withdrawn or continued after suspected ADR, treatment provide to the reaction and relevant tests/laboratory data (if available), outcome of the reaction.
- **An identifiable reporter:** Name, initials, profession, e-mail address, telephone, Name of health institutions, and date of report
- **Product quality problem:** Describe the quality problem as per the reporting format, Drug name, dosage form and strength, batch number, and size /type of package

Demonstrate to the participants using the annexed ADE reporting tools. Provide with a fake case of ADE and help them to fill the required data fields and the necessary report sending procedures

Paper based ADE reporting tool

Ethiopian Food and Drug Authority (EFDA)
Suspected Adverse Drug Event (ADE) reporting form

Patient Name (initial)	Card no/MRN	Age, Date of birth	Sex	Weight	Height

Report type □ Initial □ Follow up	Substance of abuse

Information on suspected drug/vaccine

Drug name(write all information including brand name, batch no and manufacturer)	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)

Information on concomitant drug/vaccine, including herbal medicines

Drug name(write all information including brand name, batch no and manufacturer)	Dose/dosage form, route, frequency	Date drug taking was 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)

Was the reaction serious? □ YES □ No Reason for seriousness □ Death □ Hospitalization/prolonged □ Disabling □ Congenital anomaly □ Life threatening □ Other medically important conditions	Reaction subside after D/C of suspected drug □ YES, Date □ No □ Unknown Reaction reappear after restart of suspected drug □ YES □ No □ Information not available

Treatment of reaction

Outcome: □ Died due to the adverse event □ Died, drug may be contributory □ Not yet recovered
□ Recovered without sequelae □ Recovered with sequelae* □ Unknown

*Sequelae

Relevant medical conditions such as allergies, renal disease, liver disease, other chronic diseases, pregnancy etc

Reported by: Name	Profession:	Email address:	Telephone

Name of health institution	Date

Product quality problem: Color change, separating of components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling, etc (Write if anything different than given above)

Drug name	Batch No	Manufacturer	Dosage form and strength	Size /type of package

For office use only	
Received on:	Registration no:
Key: D/M/Y ; Date /Month/Year D/C; Discontinue treatment Y;YES N;NO	

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What to report?

- All suspected reactions to drugs
- Unknown or unexpected reactions
- Unexpected therapeutic effects
- All suspected drug interactions
- Product quality problems
- Treatment failures
- Medication errors

NB. Drugs includes

- Conventional drugs
- Herbal drugs
- Traditional medicines
- Biologicals
- Medical supplies
- Medicated cosmetics

This ADE reporting form was prepared & printed by EFDA in collaboration with ....

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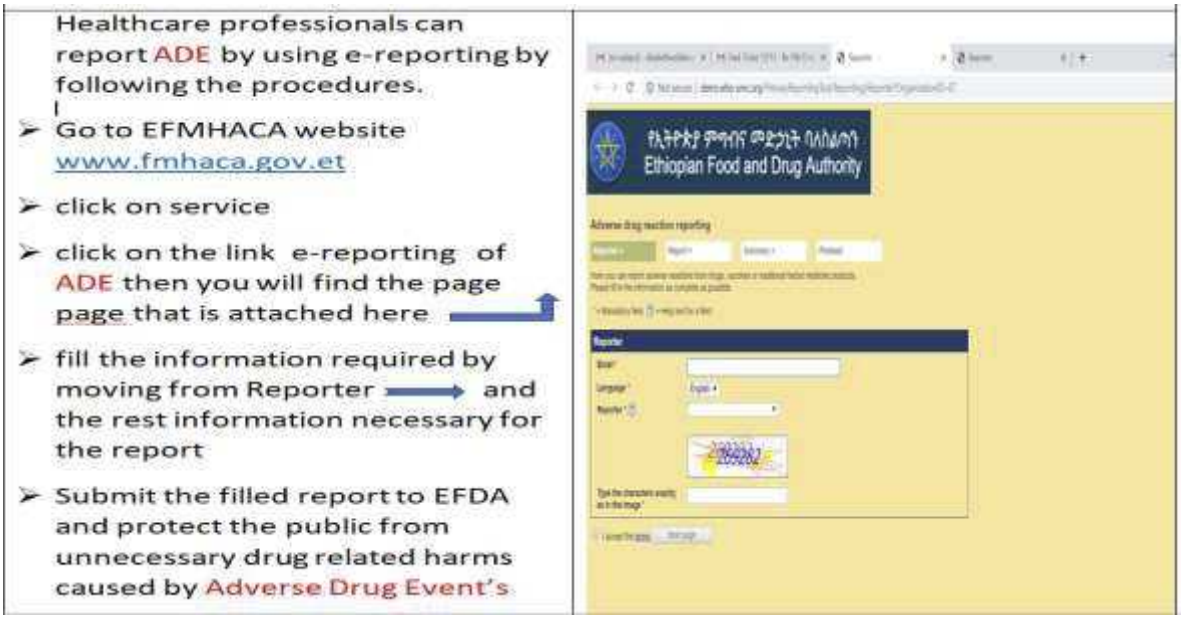
E-reproting tool

Instructions on how to use the e-reporting tool



AE line listing form

AE Line listing Form

Region:_____ Zone:_____ Woreda:_____ Name of Health Facility:_____

Reporter Name:_____ Profession:_____ E-mail Address:_____ Cell phone:_____

S.NO	Patient ID No	Age	Sex	Regimen	Suspected Drug	Concomitant medications	AE Description	AE Date	AE Number	Severity Grading	Causality Result	Measures taken	Outcome

Case studies: Demonstration

Case 1: Product quality defect

A pharmacist working in Bole 100 HC named XXX, 0911111111 discovered that one of the oral live Bivalent poliomyelitis type 1& 3 vaccine that was stored in the refrigerator of the store has shown color change. When he see it closely the brand name of the vaccine was BipolioB1/3, its batch number B68018029A, manufactory date 08/19, expiry date 09/21 and was manufactured by Bharat biotech international ltd. How would you enter this data in the reporting form and other reporting tools?

Case 2: Adverse drug reaction

A 33 years old man named XXX was treated at a health facility called XXX for infection. He was treated by a physician named Dr YYYY, telephone no. 090000001 and email address eyyyy@gmail.com and his clinical records were recorded in the card number 39944. He was prescribed with Ceftriaxone sodium 1gm iv inj/day. At the facility pharmacy dispensary, he was given Ceftriaxone with brand name Ceftazone, batch number 6591903823, manufacture date 05/19, and expiry date 03/23 and manufactured by WWW pharma chime plc. At the time of the treatment, his weight was 68, height 160cm, ethnic group XXX and had a substance abuse of chat. He also informed the physician that he had a chronic liver disease and is on treatment.

He was given the first injection on 14/2/13, and developed reactions with symptoms of rash, itching, swelling tongue swelling, redness in all parts of the body, back pain and chest pain after 30 minutes. Laboratory test done during the treatment showed that SGPT, SGOT were raised, He immediately went back to the health facility and informed the physician about the situation and the drug was stopped from being given again.

The reaction subsided after the discontinuation of the drug and he was treated with Hydrocortisone 100mg injection IM stat, Chlorpheniramine 10mg tablet one per day for the reaction.

He came back the next day and informed the physician that he has recovered but has observed that he has black spots in his skin where the rash has been during the reaction

4.3. Roles and responsibilities of stakeholders in national PV system

What makes PV effective and efficient is the shared responsibility among the different stakeholders. Each of these stakeholders has a fundamental roles and responsibilities to play in the system to safe the patients from untoward effects of medicines. The Uppsala monitoring center/UMC/ is the major international stakeholder for Ethiopian pharmacovigilance system

4.3.1. National regulatory Authority/national PV center/

- Develop and provide ADEs collection tools, methods and procedures for regional pharmacovigilance centers and health professionals.
- Collection of ADEs reports from voluntary health professionals
- Perform active surveillance on selected drugs ADEs
- Enter ADE reports to international pharmacovigilance data base,
- Disseminate new ADR information from global community to other stake holders and the public.
- Collaborative work with public health programs to maintain safety of their medicines
- Analyze ADEs in collaboration with national pharmacovigilance advisory committee.
- Make regulatory decisions based on the results of ADEs analysis
- Alert prescribers, manufacturers and the public to new risks of adverse reactions.
- Communicate health professionals, patients and the public about benefit, harm, effectiveness, and risk of medicines
- Give feedback and acknowledgements for ADEs reporters.

- Conduct gap identification assessments of health professionals and coordinate the capacity building training.
- Coordinate pharmacovigilance/drug safety/ harmonization meeting for different stake holders.

4.3.2. Regional PV centers

- Awareness creation and training for health professionals
- Collection of ADE reports.
- Conduct causality assessment
- Documenting and reporting of ADE reports

4.3.3. Uppsala monitoring center/UMC/

- Provides technical support and guidance to national PV centers.
- Maintain the global ADR database
- Analyze the reports from ADR data base to identify early warning signals of serious adverse reactions
- Evaluate the hazard
- Undertake research in to the mechanisms of action to aid the development of safer and more efficient medicines.

4.3.4. Pharmaceutical industry

- Manufacturers are uniquely placed for monitoring the safety of medicines, from the start of drug development and thereafter throughout the lifetime of the drug.
- Pharmaceutical companies should establish pharmacovigilance system and employ trained medical representatives on pharmacovigilance or qualified professional for pharmacovigilance (QPPV) so that they are able to recognize and capture safety information appropriately
- Develop and maintain the Pharmacovigilance System Master File (PSMF) in accordance with the guideline on good pharmacovigilance practices/GVP/
- Collect, compile and submit ADE reports to national PV center.
- Produce and submit periodic safety reports such as periodic safety update reports/PSUR/ to national PV center.

4.3.5. Health facilities

- Initiate and conduct their own PV activities in collaboration with regional and/ or national PV center
- Develop the standard operating procedure/SOP/ for management and reporting of ADEs to regional or national PV center.
- Coordinate in service training on medicine safety and the national and global PV system for healthcare professionals in collaboration with national PV center and other partners.
- Provide drug safety information and safety alerts for their health professionals.
- Change facility specific medicine list if necessary.

4.3.6. Academia

- Provide training on pharmacovigilance for graduating health students
- Incorporate the detail pharmacovigilance science and global pharmacovigilance system into the course contents of the health professional's curriculum
- Conduct different studies in collaboration with different stakeholders to strengthen the national PV system

4.3.7. Health professionals

- Inspect the medicinal product to be dispensed or administered to patient.
- Being vigilant and detect adverse drug events
- Identify medication errors and product quality defects
- Adjust the dose or replace or stop the treatment for ADR suspected patient
- Complete yellow (ADE reporting) form and/or other electronic reporting tools for all ADEs and submit them to national PV center(decentralized Pv centers)
- Document the management of suspected ADR on patient's history file
- Report SAEs to national PV center as soon as possible.

4.3.8. Patients

- Patients who suspect that they have been affected by any ADEs should report to their health care providers to enable the health professionals to identify, manage and report it to the pharmacovigilance center.

- Record basic components of ADE information used for further investigations such as name suspected medicine, onset of reaction (exact time), duration of the reaction(period of reaction),any concomitant medicines and their previous health status.

4.3.9. National pharmacovigilance advisory committee

- Review individual serious and unusual ADE and other safety reports referred to it by the Secretariat in order to assess a potential causal link between the event and the medicine.
- Provide recommendations for further investigation, education, corrective action and communication.
- Advise the national program managers and Regulatory Authority about ADE related issues when requested by those institutions.
- Make final decision on causality assessment of inconclusive investigations and ensuring quality control of pharmacovigilance system.
- Provides professional advice on the dissemination of drug information to the general public
- Provides recommendations on measures to be taken on drugs with safety and efficacy problem
- Give other drug related advice as needed

4.4. Chapter Summary

- National PV center has the overall responsibility to coordinate pharmacovigilance activities for: prevention or minimization of the future occurrence of the medicine-related injuries.
- Health professionals need to be vigilant on adverse drug reactions, medication errors and product quality defects identification
- Health professionals need to report all suspected cases of ADEs
- The success of pharmacovigilance system depends on the active participation of all stakeholders.

Chapter 5: Pharmacovigilance in Public Health Programs

Duration: 6:00 HRs

Chapter Description:

This chapter highlights the importance, rationale and peculiar activities in ADE prevention, detection, monitoring and reporting and implementation of PV activities for selected public health programs.

Chapter Objective:

At the end of this chapter, participants will be able to:

- Explain the importance, rationale and peculiar activities of pharmacovigilance in national public health programs.

Enabling Objective: at the end of this chapter, participants will be able to:

- Explain the importance of PV in selected public health programs
- Explain the rationale of PV in selected public health programs
- To know the peculiar activities of PV in selected public health programs.

Chapter Outline:

5.1. PV in Vaccines (Adverse Event Following Immunization-AEFI)

5.2. PV in Anti-TB medicines

5.3. Pharmacovigilance of medicines used in HIV, malaria, mass drug administration, non-communicable diseases and RMNCH

5.4. Summary

5.1. Pharmacovigilance in Expanded Program of Immunization (AEFI)

Individual activity:

What makes vaccine different from other conventional medicines?

Why we give peculiar attention for vaccine safety?

Time: 5 Minutes

5.1.1. Introduction

A vaccine is a biological product that produces and enhances immunity to the particular vaccine preventable diseases (VPD) for which it is targeted. A vaccine contains the disease-causing microorganism (virus or bacteria), or a portion of it, in a form that is incapable of causing the actual disease. In addition to the primary antigen(s), vaccines contain small quantities of other substances. Sometimes AEFI can result from one of the other substances.

Table 5.1: Additional vaccine components

Vaccine Components	Examples of substances	Benefit
Adjuvants	Aluminum salts (aluminum hydroxide, aluminum phosphate or potassium aluminum sulfate)	Enhance the immune response by degree and/or duration- reduce the amount of immunogenic per dose or the total number of doses needed to achieve immunity
Antibiotics	Neomycin	To prevent bacterial contamination of the tissue culture cells in which the viruses are grown during manufacturing
Preservatives	chemicals (e.g. thiomersal, phenol derivatives)	to inactivate viruses, detoxify bacterial toxins, and remain in the vial to prevent serious secondary infections in multidose vials
Stabilizers	potassium or sodium salts, lactose, human serum albumin and a variety of animal proteins, such as gelatin and bovine serum albumin	Controlling acidity (Ph); stabilizing antigens through necessary steps in the manufacturing process, such as freeze drying; and preventing antigens from adhering to the sides of glass vials with a resultant loss in immunogenicity

5.1.2 Vaccine Classification

Table 5.2: Vaccine classification

Class of vaccine	Type of vaccine	Common AEFIs
Live attenuated vaccines(LAV)	**Bacteria:**	
	BCG vaccine	Suppurative lymphadenitis, BCG osteitis, Disseminated BCG infection
	Virus:	
	Oral poliovirus vaccine	VAPP
	Measles, mumps, rubella vaccine	Febrile seizures, Thrombocytopenia, Anaphylaxis, Encephalopathy
	Rotavirus vaccine	Intussusception
	Yellow fever vaccine	
Inactivated (killed antigen) vaccines	**Bacteria:** Whole-cell pertussis (Wp)	Persistent (>3 hours) inconsolable screaming, Seizures, Hypotonic, hypo responsive episode(HHE), Anaphylaxis, Encephalopathy
	Virus: Inactivated poliovirus vaccine (IPV)	None
Subunit vaccines (purified antigens)	**Protein-based:**	
	Hepatitis B vaccine	Anaphylaxis
	Acellular pertussis vaccine(Ap)	
	Polysaccharide:	
	Meningococcal polysaccharide vaccine	
	Pneumococcal polysaccharide vaccine	
	Conjugate vaccine: Haemophiles type b (Hib) conjugate vaccine,	None
	meningitis A and B conjugate vaccine	Anaphylaxis and syncope
	Pneumococcal conjugate vaccines	None
Toxoids	Tetanus toxoid	Brachial neuritis, Anaphylaxis
	Diphtheria toxoid	Brachial neuritis, Anaphylaxis

5.1.3. Adverse Events Following Immunization (AEFI)

An adverse event following immunization is any untoward medical occurrence (unfavorable or unintended sign, abnormal laboratory finding, symptom or disease) which follows immunization and **which does not necessarily have a causal relationship** with the usage of the vaccine.

Serious AEFI are serious adverse event/reaction can be death, hospitalization, or prolongation of existing hospitalization (e.g., encephalopathy, seizures, aseptic meningitis), persistent or significant disability or incapacity (e.g., paralysis), congenital anomaly, and life-threatening adverse reactions.

A cluster of AEFIs is two or more cases of the same adverse event related in time, place or vaccine administered. It is aggregation of relatively uncommon events or diseases in space and/or time in frequency that are believed or perceived to be greater than could be expected by chance.

AEFIs can be classified into five categories based on their causes as described in the table below.

Table 5.3: Cause specific AEFI classification

Cause-specific type of AEFI	**Definition**
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. **e.g. anaphylaxis, vaccine-associated poliomyelitis (LAV)**
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer. **e.g. wild polio virus (**Insufficient inactivation of wild-type vaccine agent**), AE due to contamination of the vaccine**
Immunization error-related reaction (formerly "program error")	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable. **e.g. Error in vaccine handling, prescribing and administration**
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization. **e.g. Fainting (vasovagal syncope or syncope), hyperventilation**
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. **e.g. sudden infant death syndrome**

	Group discussion and reflection
	• When parents bring their children for immunization, why may they have a low tolerance for any AEFIs?

Why AEFI Monitoring

- Vaccines are almost always biological products - Subject to widespread variation even between batches
- All vaccines require special conditions of storage - usually cold storage
- Vaccines are large molecules usually administered parenterally - Some vaccines may be given orally
- Vaccines are normally given in "schedules" which must be adhered to - For whole populations and/or age groups
- Vaccines given mostly to PREVENT disease
- Vaccines are supposed to protect whole populations ("herd immunity")

Table 5.3: Key difference between vaccine and medicines

VACCINES	OTHER DRUGS
Who gets them?	
Usually, healthy people including infants. Often most of the population, birth cohort, or group at high risk for disease or complications.	Usually, sick people.
Why?	
To prevent disease.	Usually to treat disease.
How do they get them?	
Vaccines are often administered through public health programs. In some countries, vaccination may be a prerequisite for enrolment in school.	Often administered by a medical doctor or pharmacist.
When do they get them?	

VACCINES	OTHER DRUGS
Most childhood vaccines are administered at specific ages, or in relation to special circumstances such as outbreaks or travel. The age at the time of vaccination may coincide with the emergence of certain age-related diseases (e.g. neuro developmental disorders). Sometimes they also administered in adults to prevent specific diseases	Normally at time of illness.
What about adverse events?	
Low acceptance of risk. Intensive investigation of severe AEFIs, even if rare, is necessary. Minor AEFIs also should be carefully monitored because they may suggest a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.	Acceptance of adverse events often depends on the severity of illness being treated and the availability of alternative treatment options.
How many?	
8-15 Childhood vaccines globally recommended. and around 30 vaccines are exist currently	Thousands of drugs are available.

5.1.5 AEFI Surveillance

The main objective of AEFI surveillance is to detect early and appropriately respond to adverse events following immunization. It results in reduction of the negative impact on the health of individuals and on the immunization programs thereby enhancing program credibility and to provide country-specific data on vaccine risks.

5.1.6. Immediately Reportable AEFIs

- Serious AEFI,
- AEFI as a result of potential immunization errors,
- Clusters,
- AEFI causing parental or community concern resulting in the family notifying the case back to the healthcare system,
- Those that are unexpected, and
- Those that are known but occur with unexpected frequency.

N.B. all reportable AEFIs are mandated to detail investigation and causality assessment

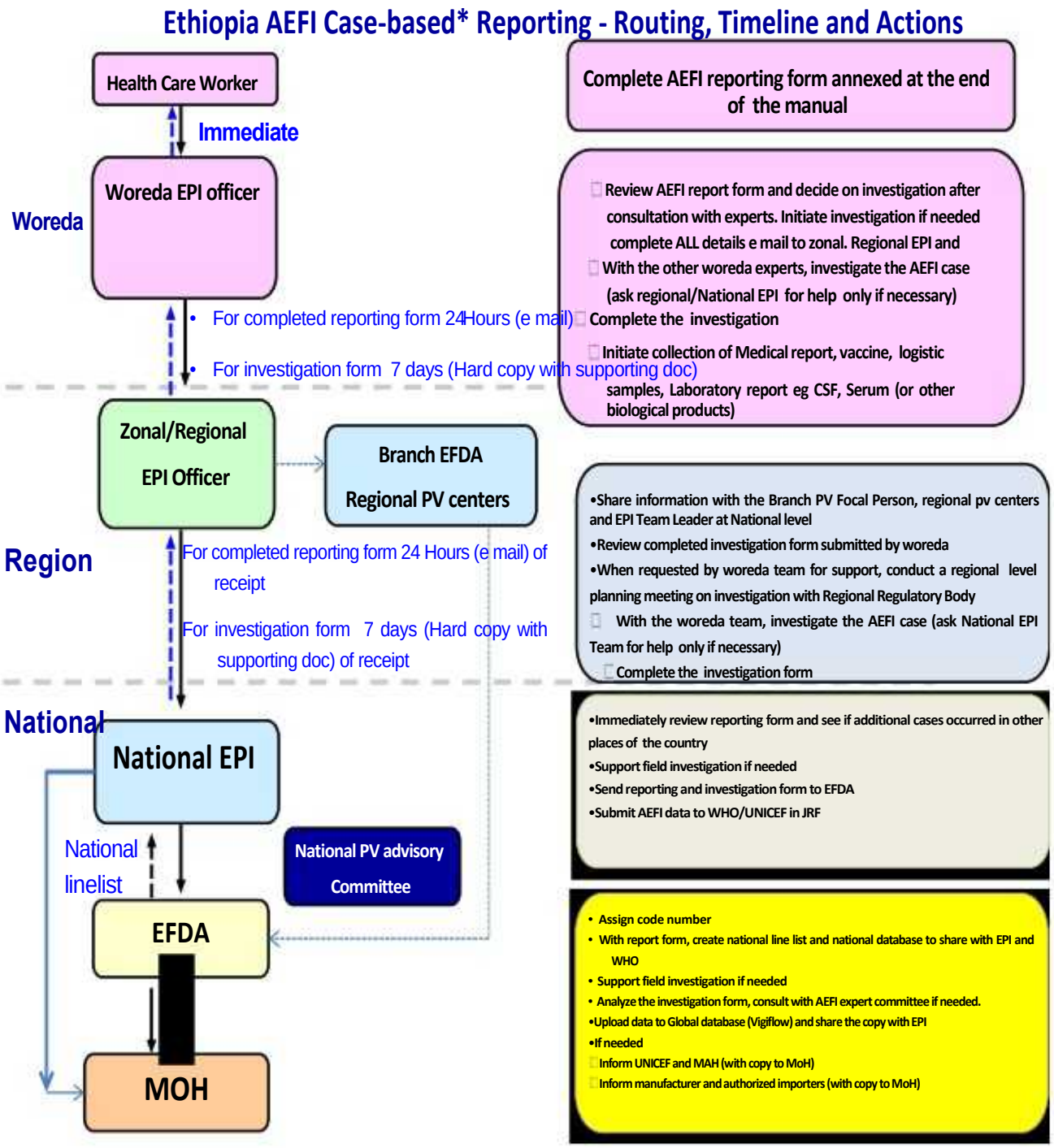


Fig 5.2: AEFI Case based reporting

5.1.7. AEFIs Investigation

The report of an AEFI will usually be followed by a case investigation or, when there is a cluster of AEFIs, by a series of case investigations. The ultimate goal of a case investigation is to find the cause of an AEFI or cluster of AEFIs and thereafter conduct follow-up activities. Investigation should identify any immunization related errors or vaccine product related reactions because these are preventable, and if co-incidental events are recognized then demonstrating this will be important to maintain public confidence in the Immunization Program.

The investigation of AEFI report is critical in identifying and correcting the problem(s) in order to ensure trust among clients and the different EPI actors.

Who should be involved in AEFI investigation?

The health worker will complete the AEFI **Reporting Form (Annex xxx)** and report to WEO. The WEO along with the woreda rapid response team (RRT) will carry out the investigation.

Expert support from zonal to national levels and close communication among all levels are important.

EFDA, national AEFI Committee, National EPI, regional AEFI task forces and zonal regulatory bodies are expected to support investigation of the case according to their capacity at their level if desired by WEO. Technical supports from partner organizations like WHO may be sought as and when needed. If necessarily they will also participate in investigation activity.

What should be investigated and when?

The following medical incidents, i.e., trigger events, should be investigated;

- All serious cases of AEFIs
- Clusters and events above the expected rate and severity
- Evaluation of suspected signals
- Other AEFIs
    - Immunization error is suspected (e.g. injection site abscesses, sepsis)
    - Significant events of unexpected cause within 30 days of vaccination

- Events causing significant parental and community concerns (e.g. febrile seizures, hypotonic hypo-responsive episode

When to investigate?

Investigation should begin as soon as possible, ideally in24 hours but maximum within seven days of notification to the health worker, to identify any immunization error(s) that might be present, to correct them before other people are exposed to the same error, and to show members of the community that their health concerns are taken seriously.

How to investigate AEFI?

An AEFI investigation follows standard epidemiological investigation principles. It is important to investigate suspected adverse events promptly and completely. The investigator will need to look directly at the reported reaction as well as gather information from the client/parent, health workers and supervisors, and community members. The information collected (and conclusions) should be recorded on an AEFI Investigation Form (Annex xxxx).

Immunization related errors and coincidences are the most likely causes of adverse events. Therefore, the investigator should suspect immunization errors as the cause and examine the evidence for any errors in the storage, handling, or administration of vaccines. Attention can then focus on finding out more about the particular error and taking the necessary corrective action. The investigators should seek to identify system problems rather than to find individuals to blame.

Steps in Investigating AEFIs

1. Confirm information in report
2. Investigate and collect data
    a. About the patient
    b. About the event
    c. About the suspected vaccine(s)
    d. About other people
3. Assess the immunization service by
    a. Making enquiries
    b. Observing the service in action

4. Specimen collection
    a. From Patient
    b. Vaccine and logistics
5. Conclude Investigation

5.1.8. AEFI causality assessment

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that the event might have been caused by the vaccine/s received. 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. Nevertheless, causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization program and regulation of the safety and quality of the product. Vaccine recipients want to know whether what they have experienced was due to the vaccine. They may believe that because one event followed another, it was causal. It can be difficult to explain that might not have been the case. Causality assessment may provide a more descriptive explanation that may reassure the vaccine and lead to better management of the event that ultimately helps the vaccine. Causality assessment is important for:

- Identification of vaccine-related problems;
- Identification of immunization error-related problems;
- Excluding coincidental events;
- Detection of signals for potential follow-up, testing of hypothesis and research; and

Validation of pre-licensure safety data with comparison of post-marketing surveillance safety data

Preparation for AEFI causality assessment

There are three prerequisites that every AEFI report should fulfill before causality assessments going to be conducted:

- The AEFI case investigation should have been completed. Premature assessments with inadequate information could mislead the classification of the event.

- All details of the case should be available at the time of assessment. They should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate.

- There must be a "diagnosis" for the adverse event, clinical sign, abnormal laboratory finding, symptom and/or disease in question. In other words, the event being assessed should be clear - it should be understood both which vaccine is being associated with what specific event that was reported.

Causality assessment team

Causality assessment in should be done by the National AEFI Committee who are independent, free of real or perceived government, industry conflicts of interest, and broad range of expertise in the areas (including infectious diseases, paediatrics, epidemiology, microbiology, pathology, immunology, neurology, forensic medicine, dermatology, internal medicine and vaccine program). The committee has written terms of reference (ToR)

Case eligibility and causality assessment method

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
- 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.

There are four steps in causality assessment. The steps and their purpose are outlined below:

Step 1: Eligibility: To determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.

Step 2: Checklist: To systematically review the relevant and available information to address possible causal aspects of the AEFI (Annex I).

Step 3: Algorithm: To obtain a direction as to the causality with the information gathered in the checklist.

Step 4: Classification: To categorize the AEFI's association to the vaccine / vaccination based on the direction determined in the algorithm.

The final classification is based on the availability of adequate information. It is for the benefit of the final classification that all relevant information should be collected ahead of time during the investigation

I. A Case with adequate information for causality conclusion can be classified as follows:

A. Consistent causal association to immunization

A1: vaccine product- related reaction or A2: vaccine quality defect-related reaction orA3: immunization error-related reaction or A4: immunization anxiety-related reaction.

B. Indeterminate

B1. Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (may be new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.

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

C. Inconsistent causal association to immunization (coincidental)

C1. Underlying or emerging condition(s), or

C2. Conditions caused by exposure to something other than vaccine.

II. A case without adequate information for causality conclusion is

"Unclassifiable" and requires additional information for further review of the causality.

This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine. A case without adequate information for causality conclusion is “unclassifiable” and requires additional information for further review of the causality. The available information on unclassifiable cases should be placed in a repository or an electronic database which should be periodically reviewed to see if additional information is available for classification and to perform analyses for identifying signals.

It is strongly encouraged to adopt the new revised causality assessment process during the expert committee reviews. Final classification (step 4) is critical, as it provides direction to the follow-up actions. It is important to note that the final classification of a given AEFI may change with updated knowledge and information.

When AEFIs occur as clusters, it is important to consider each case separately and do an independent causality assessment for each case in the cluster and classify. After classification, the cases should be line listed to see if a pattern emerges. Pattern identification is important for action to be taken as well as identifying signals.

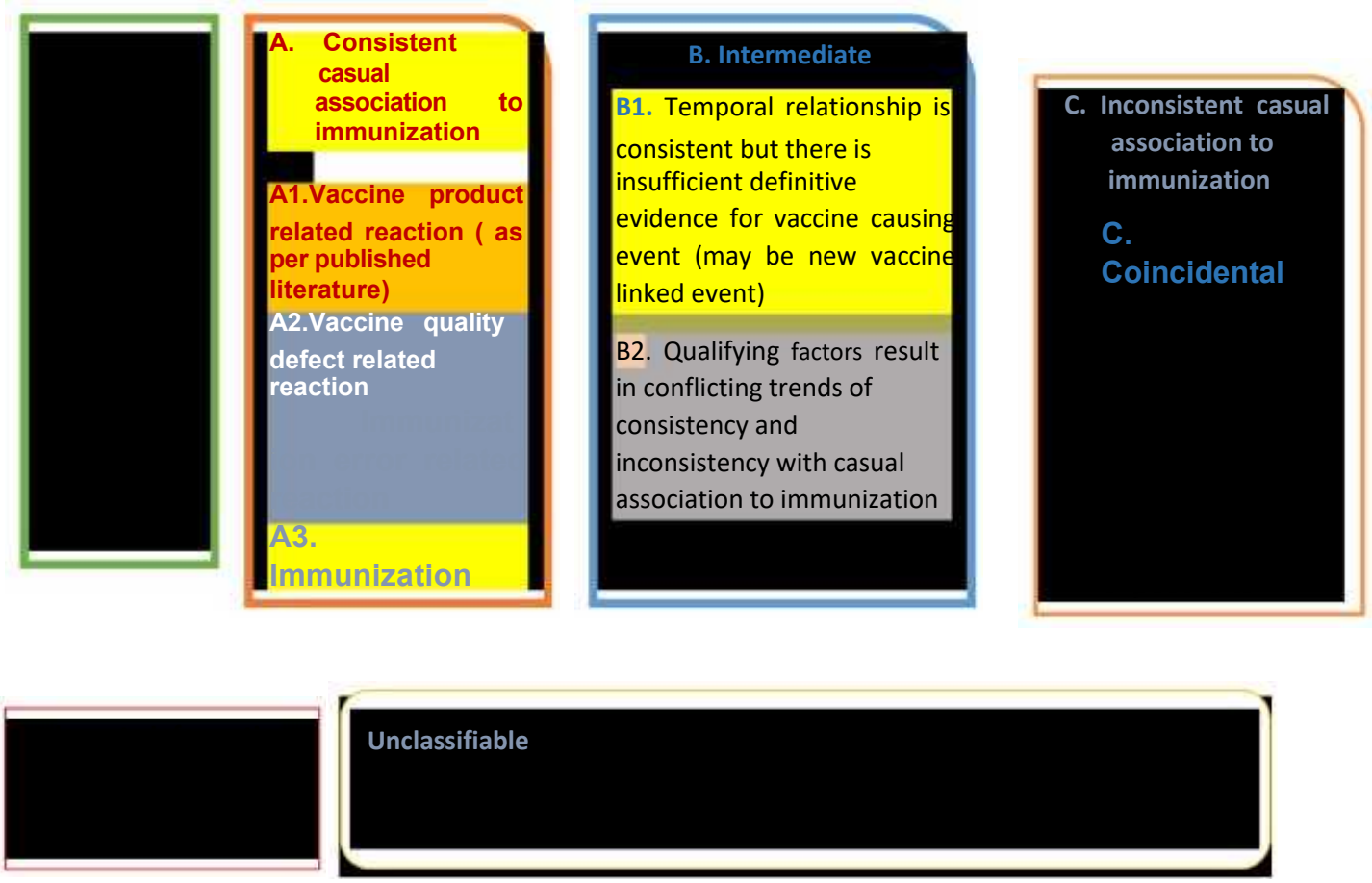


Figure 5.4: Causality assessment classification

5.2. Pharmacovigilance in Anti-TB Medicines

5.2.1. Introduction

Active pharmacovigilance can be implemented through cohort event monitoring (CEM) or active TB drug-safety monitoring and management (aDSM). In Ethiopia, both the active and passive forms of pharmacovigilance are utilized to monitor the safety of patients on different TB treatments. The passive form is used for patients on treatment of drugs sensitive TB using the first line drugs (R,H,Z and E) and aDSM a form of active pharmacovigilance is mandated in to be utilized for patients who are in treatment for drug resistant TB (DR-TB) using new TB drugs, novel MDR-TB regimens, or XDR-TB regimens, to detect, manage and report suspected or confirmed drug toxicities.

5.2.2. Rationale for Pharmacovigilance of TB medicines

The main reasons for pharmacovigilance of TB medicines include:

- Patients on TB treatment take more than one drug at a same time and regimens last for many months (6-24 months).
- DR-TB treatment requires the use of combination of drugs some of which are new and repurposed for which information on their safety profile is incomplete.
- This increases the likelihood of ADEs, some of which are severe and put the life of patients at risk.
- Development of DR-TB on patients who defaulted or modified their treatment due to the ADE they encountered is another risk posed on the patients and others. So, generation and transmission of DR-TB in the community is a real threat that we face today.

Therefore, monitoring the safety of patients on treatment of TB medicines is of paramount importance to protect patients' life and the community from unwanted effects of these medicines.

Table 5.4: Common Adverse Events of Interest in TB treatment

No.	ADR	Possible Responsible TB drug(s)	Other Possible Responsible drug(s)
1	Peripheral Neuropathy	Lzd, Cs/Trd, H, S, Km, Cm, H, FQ, Pto/Eto, E.	D4T, ddI
2	Myelosuppression: (Anemia, leukopenia, thrombocytopenia)	Lzd	ATZ, Cotrimoxazole
3	Prolonged QT interval	Cfz, Bdq, Mfx, Dlm, Lfx.	erythromycin, clarithromycin, quinidine, Ketoconazo le, fluconazole antipsychotics (haloperidol, risperidone, and chlorpromazine), many anti-nausea drugs
4	Optic nerve disorder (optic neuritis)	Lzd, E, Eto/Pto, rifabutin, H, S.	ddI
5	Elevated liver enzymes (hepatotoxicity)	Z, H, Cfz, PAS, Eto/Pto, Bdq, FQ, Amx/Clv.	viral hepatitis (A, B, C), NVP, many drugs.
6	Hearing impaired	S, Km, Am, Cm	
7	Acute kidney injury	S, Km, Am, Cm.	TDF rare
8	Hypokalemia	Cm, Km, Am, S.	TDF rare
9	Hypothyroidism	Eto/Pto, PAS.	D4T
Adapted from End TB Consortium. Please refer "End TB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 4.0; January 2018" or "Guidelines For Management Of Tb, Dr-Tb And Leprosy In Ethiopia, 6th edition, 2018" for further details on the ADRs and their management.			

Commonly used drugs and abbreviations

Drug Name	**Abbreviations**
Linezolid	Lnz
Cycloserine/ Terizidone	Cs/Trd
Isoniazid	H
Streptomycin	S
Kanamycin	Km
Capreomycin	Cm
Amikacin	Am
Flouroquinolones	FQ
Protlonamide/Ethionamid	Pto
Ethambutol	E

Bedaquiline	Bdq
Clofazimine	Cfz
Moxifloxacin	Mfx
Levofloxacin	Lfx
Delamanid	Dlm
Paminosalicylic acid	PAS
Pyrazinamide	Z
Rifampicin	R
Delamanid	DLM

5.2.3. Active TB drug-safety monitoring and management (aDSM)

aDSM is the active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs (Bedaquiline or Delamanid), novel multi-drug resistant TB (MDR-TB) regimens, or extensively drug-resistant TB (XDR-TB) regimens, to detect, manage and report suspected or confirmed drug toxicities.

The recording and reporting activities of aDSM primarily target the serious adverse events (SAEs) as a priority requirement. MDR-TB treatment sites also monitor other AEs which are of clinical significance or of special interest to the program, as part of comprehensive aDSM.

WHO recommended the use of bedaquiline, delamanid and the shorter MDR-TB regimen upon condition of active drug-safety monitoring. Both these medicines are still relatively new and only a limited number of patients have been treated with them. In both cases the decision to grant conditional marketing approval by stringent drug regulatory authorities prior to the completion of Phase 3 trials took into account the serious nature of MDR-TB and the unsatisfactory outcomes obtained when regimens composed solely of older second-line drugs are used.

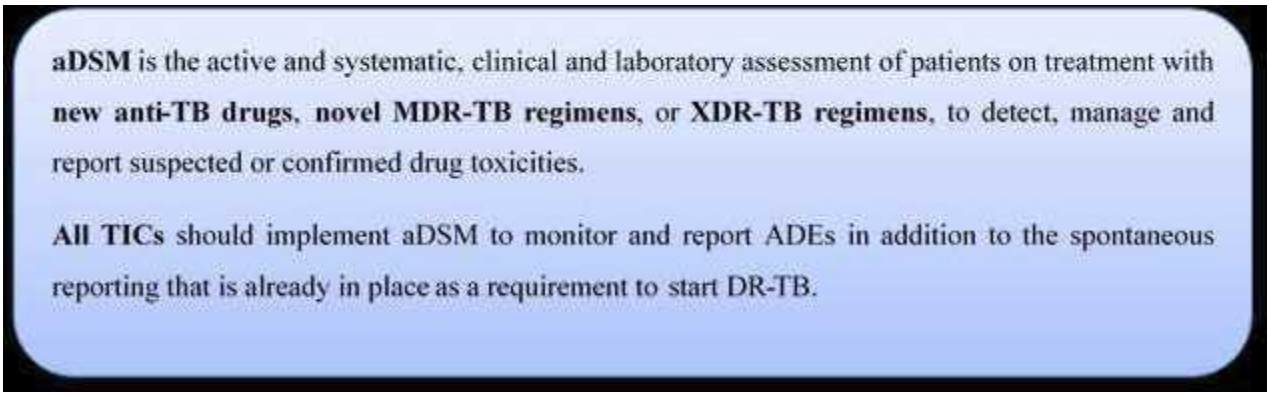
Likewise, the 2016 recommendation for a shorter MDR-TB regimen preceded the results of a randomized controlled trial (RCT) of its use. All reasonable measures are thus needed to ensure that patient safety is monitored alongside the effectiveness of the treatment. In this situation, spontaneous reporting is not expected to represent an appropriate level of care and more active approaches, such as aDSM, are considered necessary to improve the early and systematic detection and proper management of harms. It is also important to collect safety data accurately and undertake causality assessment carefully in order to ensure that all adverse events are properly investigated and that no premature conclusions are drawn regarding the attribution of cause.

aDSM is used to monitor and manage adverse events in patients who receive a particular medication or treatment regimen and to assess causality. It applies the principles of active pharmacovigilance to the specific needs and context of national TB programs and is embedded within the patient monitoring function of TB program. The management of patient safety is an inherent part of aDSM, inseparable from its monitoring component.

In aDSM, besides the spontaneously reported reactions, adverse events are also elicited as part of a patient monitoring plan comprising of a set of questions and oftentimes an array of laboratory/clinical tests at defined periods of time, before, during and after treatment. The records from active TB drug-safety monitoring thus make it possible to determine the exact number of patients monitored and the extent of exposure to a medicine; they also enumerate the events related to an exposure, in a similar way to a longitudinal epidemiological study. Therefore, the main goal of aDSM besides reducing risks from drug-related harms in patients on second line treatment for drug-resistant TB and is to generate standardized aDSM data to inform future policy updates on the use of such medicines.

There are three essential components/activities in the implementation of aDSM. These are:

1. Patients targeted for active PV should undergo active and systematic clinical and laboratory assessment before, during and after treatment to prevent and/or detect drug toxicity and AEs.
2. All AEs detected should be managed in a timely fashion in order to deliver the best possible patient care.
3. Standardized data should be systematically collected and reported for any AE and SAE detected



There are three levels of monitoring (Packages) in aDSM

1. Core package: requiring monitoring for and reporting of all SAEs
2. Intermediate package: includes SAEs as well as AEs of special interest
3. Advanced package: includes all AEs of clinical significance

WHO recommends that nations to implement the core package at a minimum for all centers treating eligible patients with new anti-TB medicines or novel MDR/XDR-TB regimens. These

treatment centers should, as a minimum, also be taking part in spontaneous reporting of ADRs as required by local regulations and expansion of aDSM to the next level should be implemented in a phased approach.

Ethiopia is currently implementing the intermediate package and mandates all DR-TB treatment initiating centers (TIC) to monitor and report and all SAEs and AEs of special interest.

AEs of special interest are AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment. All AEs judged to be of special interest should be reported independent of seriousness, severity or causality.

AE of special interest in Ethiopia:

How to Detect ADEs in aDSM

Patients to be put on TB medicines (SLDs) should be evaluated before, during and after the treatment as part of monitoring patient safety. Pretreatment evaluation is done in order to identify eligible patients to be treated with a regimen including the new TB drugs, identify those patients at a greater risk of adverse effects and poor treatment outcomes, establish a baseline for monitoring and identify and solve potential barriers to treatment adherence including psychosocial and economic issues.

Before initiating of the treatment detailed medical history and physical examination, base line monitoring tests, and patient preparation for treatment should be done and information utilized in selecting the drugs/regimens suitable for an individual patient in order to avoid or minimize risk of occurrence of know ADEs.

During treatment, at each contact with patient systematic symptomatic screening, clinical examination, laboratory monitoring with referral for potential AEs is a mandatory part of scheduled and unscheduled visits under the responsibility of the clinician. In addition, the clinician should systematically assess the evolution and outcome of the previously recorded AEs. Any ADE identified should be classified according to their severity (mild, moderate, severe and life threatening of Grades 1-4) and seriousness (serious or non-serious) and managed properly. All AEs should additionally be evaluated to determine their causal relationship with DR TB treatment (including DR TB drugs and other drugs as appropriate), using the standard terms as certain, probable, possible, etc. This evaluation should take into account all other possible causal factors (e.g. medical history, risk factors, past drug use, concomitant procedures, TB progression).

Post-treatment monitoring should be performed every three months for a period of at least one year (and as clinically indicated) with symptom review, medical evaluation, sputum smear/culture and chest X-ray. Post treatment monitoring is important to assess for relapse, monitor adverse events like cardiotoxicity, liver damage, ototoxicity and assess and manage sequelae of DR TB like bronchiectasis, pneumothorax, lung fibrosis. If there is any evidence of active TB during follow-up, the patient should be reevaluated thoroughly and managed accordingly with full course of treatment. Finally, the manifested ADE need to be recorded and reported according to the national reporting requirements.

Recording and Reporting in aDSM

Generally, any suspected adverse drug event should be reported as soon as possible after all relevant information is compiled. But for convenience and facilitating of recording and reporting of ADEs in DR-TB program special template is designed in addition to the available options. At all sites with TB treatment any occurrence of ADE should be reported using the appropriate form to EFDA. ADEs encountered as a result of first line drugs (FLDs) used in the management of DS-TB, must be reported (voluntarily) as soon as possible using the yellow form or other available mechanisms (Medsafety and e-reporting). For SAEs encountered after use of second line drugs (SLDs) in the management of DR-TB must be reported to EFDA within 24 hrs, using the yellow form or other available options (Medsafety and e-reporting). For AEs of special interest other than the SAEs, it

is recommended to be reported as soon as possible using all available mechanisms. But in case of inconvenience, AE line listing form can be used to report monthly.

The following diagram depicts the mechanism for reporting ADEs occurred during DR-TB treatment.

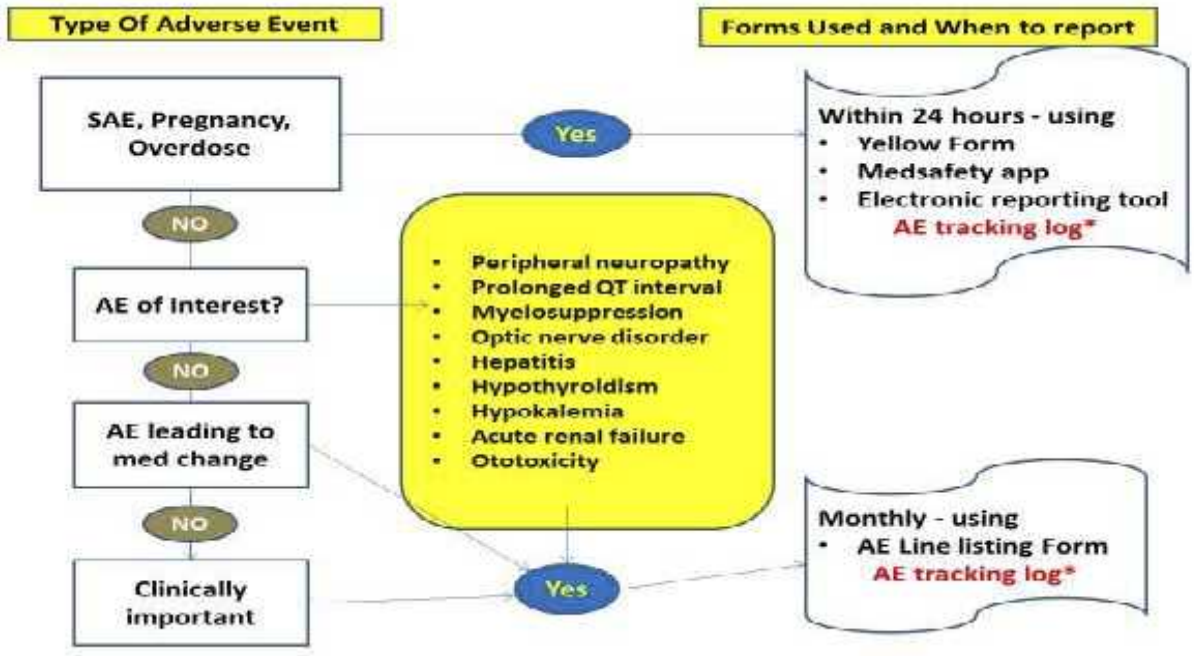


Figure 5.1: Mechanism for reporting ADEs occurred during DR-TB treatment.

*AE tracking log a logbook to record all the ADEs detected at each facility for monitoring purposes.

Monthly AE Line listing form for DR-TB Patients enrolled to new TB Drugs & drugs for shorter MDR TB regimen

Region: _____ Zone: ____ Woreda: _____ Name of Health Facility: _____

Reporter Name: _____ Profession: _____ E-mail Address: _____ Cell phone: _____

Starting date (E.C) End date (E.C)

S.NO	Patient ID No/Unique DR-TB No and name in abbriviation	Age	Weight (kg)	Sex	Regimen	Suspected Drug	Concomitant medications	Date drug Taking was started	Date drug reaction started	Date drug taking was stopped	AE Description	Severity Grading	Causality Result	Measures taken	Relevant medical condition	Outcome	Sequele
1																	
2																	
3																	
4																	
5																	
6																	
7																	
8																	
9																	
10																	
11																	
12																	

Commonly used drugs and abreviations

Drug Name	Abbreviations
Amikacin	Am
Bedaquiline	Bdq
Capreomycin	Cm
Clofazimine	Cfz
Cycloserine	Cs
Delamanid	Dlm
Ethambutol	E
Isoniazid	H
Kanamycin	Km
Levofloxacin	Lfx
Linezolid	Lnz
Moxifloxacin	Mfx
Paminosalicylic acid	PAS
Profionamide	Pto
Pyrazinamide	Z
Rifampicin	R

Causality
Certain
Probable/Likely
Possible
Unlikely
Conditional/
Unclassified

Severity Grading	
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening

Outcome
Fatal
Not resolved
Resolved
Resolved with sequelae
Resolving
Unknown

Case study on filling of AE Line listing form

The following two cases of ADEs are reported from X hospital of Y region, zone 3 by Dr Alem Kassa, (Phone : 0911XXXXXX,Email: Xxxx@gmail.com.The report is for the month of Miazia 2013.

1. AB is 27 year old man of 55kg who began a Bdq-containing regimen on 25/10/2011 E.C due to XDR-TB and failure to respond to a standard MDR regimen. Initially he tolerated the regimen well, but at the three months follow-up evaluation (25/1/2011), the ECG reveals QTc of 543 ms with bradycardia. The patient was asymptomatic.

MDR-TB treatment:

- Bdq (400 mg daily orally)
- Lzd (600 mg daily orally)
- Cfz (200 mg daily orally)
- Mfx (400 mg daily orally)
- Cs (750 mg daily orally)
- Z (2000 mg daily orally)
- Pyridoxine (150 mg daily)

Laboratory tests:

- At three months, hemogram, liver function tests, serum electrolytes, urea and creatinine showed no significant changes from baseline.
- Baseline ECG indicated sinus rhythm, 67 bpm, QTc 434 ms.
- ECG indicated sinus bradycardia at 47 bpm, QTc 543 ms.

CRC was consulted, and recommended to stop Bdq, Clz and Mfx. Monitor ECG three times per week, and update progress. After 10 days of interruption, QTc normalized to 438 ms, electrolytes were normal. Panel team re-initiated Bdq and Clz, but Mfx was suspended permanently. Patient tolerated well the treatment.

2. BG is a 39 year old and 40 kg female patient confirmed MDR-TB/HIV, started on regimen with Bdq due to nephrotoxicity and ototoxicity 3rd month of MDR-treatment. Her treatment start date was 2/1/2013. Bdq containing regimen was started on 17/3/2013. DR TB Ward nurse visited patient at her home after a family member came to the site reporting the patient had been keeping to herself and acting differently for one week since 25/3/2013. The nurse found patient talking to herself and having visual hallucinations; she was unable to carry on ADLs (activities of daily living). She was taken to the hospital to be admitted and evaluated.

MDR-TB treatment:

·Cs (750 mg daily orally)
·Bdq (200 mg 3x week orally)
·Lfx (750 mg orally)
·Pto (750 mg daily orally)
·PAS (8 gm orally)
·Z (1800 mg orally)

ART:
· Abacavir (300 mg BID)
· Lamivudine (150 mg BID)
- Nevirapine (200 mg twice daily orally)

Cs was withdrawn; patient was put on haloperidol 1 mg po bid, pyridoxine 200 mg po, Patient was stabilized and discharged after one month.

Session Summary

- National TB programs that actively pursue drug-safety monitoring and management are better prepared to ensure patient safety while introducing new TB drugs and novel regimens.
- Patients to be put on TB medicines (SLDs) should be evaluated before, during and after the treatment as part of monitoring patient safety.
- TB patients take multiple drugs for long duration and some of which are new and repurposed for which complete safety profile has not established. This increases the likelihood of ADEs which in turn contributes to treatment interruption and development of drug resistance, **aDSM** is of paramount importance to protect patients' life and the community from unwanted effects of these medicines.
- Any suspected adverse drug event should be reported as soon as possible after all relevant information is compiled. But for convenience and facilitating of recording and reporting of ADEs in DR-TB program special template (monthly line listing form) is designed in addition to the available options.

5.3. Pharmacovigilance of medicines used in HIV, malaria, mass drug administration, non-communicable diseases and RMNCH

1.3.1. Pharmacovigilance of Antiretroviral Drugs

1.3.1.1. Introduction

Antiretroviral (ARV) therapy has changed human immunodeficiency virus (HIV) infection from a near-certainly, fatal illness to one that can be managed chronically. Patients take ARVs for long periods of time, which naturally results in more observed toxicity.

There are different combinations and classes of ARV drugs. All classes of ARVs have the potential to cause toxicities with different levels of severity including serious adverse reactions (ADRs)to medicines, with both short- and long-term effects. The reactions include altered body

fat distribution (lipodystrophy), hypersensitivity reactions, hepatic disorders, acute pancreatitis, muscle damage (myopathy) of the newborn and lactic acidosis. These and other reactions may complicate the treatment, causes difficulty in causality assessment, require treatment withdrawal in serious life-threatening reactions, and damage confidence in the national ARV program and affect patient adherence.

Drug-related adverse reactions while on ART can occur immediately (soon after a drug has been administered), early (within the first days or weeks of treatment) or late (after months or more of treatment). Adverse reactions can vary in severity from mild to severe to life-threatening and may be specific to the drug or generic to the class of drugs in use.

1.3.1.2.Rationale

	**Individual reflection**
	What is the rationale of Pharmacovigilance in ARV drugs? **Time:** 5 minutes

- ARV treatment is the only option for persons infected with HIV
- ARV treatment is lifelong
- Combination of three or more active drugs from at least two different classes are needed to suppress viral replication
- There is continuous introduction of new ARVs and regimen changes in the ART program
- Poly pharmacy is common among people living with HIV (PLHIV) and a frequent cause of stopping or changing HIV therapy.
- Every ARV medicine has different levels of adverse drug reactions/side effects
- Adverse drug reactions of ARVs affect the adherence to ARV treatment which has negative impact on treatment outcome.

1.3.1.3.Classification of ARVs

There are four classes of antiretroviral agents currently available for use in Ethiopia. This includes:

1. **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)**: Lamivudine, Abacavir, Tenofovir
2. **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** Efavirenz, Nevirapine,

3. **Protease inhibitors (PIs):** Ritonavir, Lopinavir, Atazanavir, Darunavir
4. **Integrase Inhibitors (INSTIs):** Dolutegravir (DTG)**,** Raltegravir (RAL)

1.3.1.4.Types of ARV drugs Toxicities

	**Small group discussion and Presentation**
	Read and discuss on the types of ARV drug toxicities and present for large group. **Time:** 10 minutes

The ARV drug toxicities are classified in to three types based on their onset, prevalence, and severity

1. **Early Side Effects that are Uncomfortable for the Patient, But Not Dangerous**
   a. **Common side effects, but do not cause danger to the health of the patient.** These include nausea, headache, dizziness, diarrhea, feeling tired and muscle pain. Usually they occur when treatment begins and then improve within two to four weeks. The patient should be reassured that this will go away after some weeks. For example, Efavirenz induced CNS toxicities will often resolve within the first 2 weeks after initiation of treatment.
   b. **Less common and not serious side effects:** It is not necessary (or advisable) to warn patients about these side effects. For example: AZT may cause blue nails.
2. **Early and Potentially Serious Side Effects:** These require emergency consultation. The patient needs to be warned about these potential side effects. For some, the patients need to seek care urgently if they occur. Examples are pallor (anemia can occur with AZT), yellow eyes due to sick liver (hepatitis can occur with EFV or NVP), severe abdominal pain and rash.
3. **Side Effects Occurring Later During Treatment:** These occur after the patient has been taking ARV drugs for several months or even years. Examples include abnormal distribution of body fat (lipodystrophy) and lactic acidosis.

1.3.1.5.Monitoring and Detection of ADEs in ARV drugs

Toxicity can be monitored clinically, based on child/guardian reporting and physical examination, and can also be assessed by a limited number of laboratory tests, depending on the

ART regimen being used and the capacity of the health-care setting. There are two types of ADR monitoring:

- **Routine ADR monitoring:** This is the monitoring of treatment limiting ARV adverse drug reactions integrated into monitoring and evaluation of national HIV treatment programs using patient monitoring tools and reporting systems.
- **Active ADR monitoring**: A system in which active measures are taken to detect the presence or absence of adverse drug reactions through follow-up after treatment. The adverse drug reactions may be detected by interviewing patients, preforming specific investigation or by screening patient records. Cohort event monitoring (CEM) has been tried to ARVs in Ethiopia by EFDA in collaboration with ART sites and AHRI.

1.3.1.6.Guiding principles for the management of ARV drug toxicity

	**Think pair share**
	Read and discuss in pair the guiding principles for the management of ARV drug toxicity. **Time:** 5 minutes

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity may be attributable to an ARV drug or drugs, or to a non-ARV medication taken at the same time.
3. Consider other disease processes (e.g. viral hepatitis in a child on ARV drugs who develops jaundice). Not all problems that arise during treatment are caused by ARV drugs.
4. Manage the adverse reaction according to its severity.
   In general:

   a. *Severe life-threatening reactions:* Immediately discontinue all ARV drugs, manage the medical event (i.e. provide symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized.

   b. *Severe reactions:* Substitute the offending drug without stopping ART.

c. *Moderate reactions:* Consider continuation of ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitution.

d. *Mild reactions:* Reassure child and caregiver that while the reaction may be bothersome, it does not require a change in therapy; provide counseling and support to mitigate adverse reactions.

5. Stress the maintenance of adherence despite toxicity for mild and moderate reactions.

1.3.1.7.Clinical and Laboratory Grading of ARV Toxicities

Table 5.5: Clinical Grading of ARV toxicities

Item	Grade 1 Mild toxicity	Grade 2 Moderate toxicity	Grade 3 Severe toxicity	Se
Cutaneous/ Rash/ Dermatitis	Erythema, pruritus Eryth	Diffuse, maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration	suspe
Diarrhea	3-4 loose stools a day or mild diarrhea lasting less than one week	5-7 loose stool a day or diarrhea lasting more than one week	Bloody diarrhea or over 7 loose stools a day or needing IV treatment or feeling dizzy when standing	Hosp (poss
Fatigue	Normal activity reduced by less than 25%	Normal activity reduced by reduced by 25-50%	Normal activity reduced by over 50%. Cannot work	Unab
Nausea	Mild or transient reasonable food intake	Moderate discomfort or intake decreased for less than 3 days	Severe discomfort or intake decreased for minimal food intake for more than 3 days	Hosp
Vomiting	2-3 episodes a day or mild vomiting for less than one week	4-5 episodes a day or mild vomiting for more than one week	Severe vomiting of all food and fluids over 24 hours or needing IV treatment or feeling dizzy when standing	Hosp treatm grade
Mood disturbance	Mild anxiety, able to continue daily tasks	Moderate anxiety/disturbance, interfering with ability to work, etc	Severe mood changes requiring medical treatment. Unable to work	Acute thoug
Management	**Continue ARV** **Provide careful clinical monitoring** **Consider change of a single drug if condition worsens**		**Substitute responsible drug**	**Stop expe r**

Table 5.6: Laboratory Grading of ARV Toxicities

Laboratory test abnormalities item	**Reference Range**	**Grade 1 toxicity**	**Grade 2 toxicity**	**Grade 3 toxicity**
Hemoglobin	14 - 18 g/dL 12 - 16 g/Dl	8.0-9.4 g/dL	7.0-7.9 g/dL	6.5-6.9 g/dL
Absolute Neutrophil Count	1,500-8,000mm3	1,000-1,500 mm3	750-990 mm3	500-749 mm3
Platelets	130,000 - 400,000	75,000- 99,000	50,000-74,999	20,000-49,999

				mm3
ALT	0 - 35 Unit	1.25-2.5 X ULN	2.5-5 X ULN	5.0-10 X ULN
Bilirubin	0.3 - 1.1m g/dl.	1-1.5XULN	1.5-2.5 X ULN	2.5-5 x ULN
Amylase/lipase	35 - 120 Unit	1-1.5XULN	1.5-2 X ULN	2-5 x ULN
Triglycerides	<160 mg/dL	200-399mg/dL	400-750 mg/dL	751-1200mg/dL
Cholesterol (total)	<200 mg/dL	1.0-1.3 X ULN	1.3-1.6 X ULN	1.6-2.0 X ULN
Management		**Continue ARV** **Repeat test 2 weeks after initial test and reassess**		**substitute responsible drug**
		Lipid imbalances could be managed with diet, exercise and pharmacologically with the use of fibrates. **ALWAYS SEEK EXPERT ADVICE IN CASE OF DOUBT**		

Grade 1 (Mild reaction): are bothersome but do not require changes in therapy

Grade 2 (Moderate reaction): consider continuation of ART if feasible. If the patient does not improve in symptomatic therapy, conside

Grade 3 (Severe reaction): Substitute offending drug without stopping ART. Closely monitor using laboratory and clinical parameters.

Grade 4 (Severe life-threatening reaction): Immediately discontinue all ARV drugs, manage the medical event with symptomatic and s reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized includes severe hepatitis, pancreatitis, lactic acidosis or Steven-Johnson syndrome.

* For a patient on nevirapine, rash with mucosal involvement or associated with fever and/or systemic symptoms, and/or derangement treated as Grade 4 toxicity.

1.3.1.8.

1.3.1.9.Clinical management of major ADRs associated with ARVs

	Group discussion and Presentation
	Read and discuss all ARV medicine toxicity, risk factor and its management and select one class of ARV medicine to present for large group. Time:

Table: 5.7: Clinical management of major ADRs associated with ARVs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 allele	Do not use ABC in the presence of HLA-B*5701 allele. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1A1*28 (UGT1A1*28) allele	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors.
AZT	Severe anaemia, neutropaenia	CD4 cell count of ≤200 cells/ mm3	Substitute with TDF or ABC. Consider use of low-dose zidovudine *(405).*
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG	Hepatotoxicity Hypersensitivity reactions	Hepatitis B or C coinfection Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another

		Concomitant use of hepatotoxic drugs	therapeutic class.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline)	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/ day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	
	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. ATV can be used for children older than 6 years.

			If LPV/r is used in second-line ART for adults, and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol misuse	
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea		Substitute with ATV/r, DRV/r or integrase inhibitors.
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factors unknown	
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age BMI <18.5 or low body weight (<50 kg) notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC. Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	

	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

1.3.1.10. Recording and Reporting ADEs of ARVs

Group discussion

What, When, Why, How, by whom, and to whom should adverse drug events be reported?

Time: 5 minutes

To promote medication safety, any suspected ADRs, medication errors or quality defect should be reported as soon as possible after all relevant information is compiled. Report can be sent either via the yellow prepaid report form (annexed), telephone or email.

Pharmacy professionals working at ART pharmacy are expected to record and document ADRs of ARVs they dispense using patient information sheet (PIS). The PIS can be used as a source of information for ADE reports.

Session of PV of ARV drugs

- All classes of ARVs have the potential to cause toxicities with different levels of severity • Drug-related adverse reactions while on ART can occur immediately, early or late
- ARV drug side effects are classified in to three: 1) early side effects that are uncomfortable for the patient, but not dangerous. 2) early and potentially serious side effect 3) side effects occurring later during treatment.
- Toxicity can be monitored clinically, based on child/guardian reporting and physical examination, and can also be assessed by a limited number of laboratory tests.
- Adverse drug event are voluntarily reported by health professionals and pharmaceutical manufacturers to the national regulatory authority/ Pharmacovigilance center at EFDA.

5.4. Pharmacovigilance for Anti-malarial medicines

5.4.1. Introduction

Malaria is a global public health problem that causes massive morbidity and mortality and poses a higher burden of disease and it is the greatest killer disease of all time. In Ethiopia, three quarters of its territory is considered endemic for malaria putting more than 60 million (60% of the total population) people at risk for infection. After a period of relatively good control in many countries with the use of insecticides and antimalarials such as chloroquine, there has been a resurgence of this disease due to the development of resistance of mosquitoes to insecticides and resistance of parasites to the antimalarials, thus producing an increase in malaria morbidity and mortality

WHO is promoting the use of artemisinin combination therapies (ACTs) as a therapeutic tool to treat uncomplicated acute falciparum malaria. It is known to be effective, but its safety under large-scale operational use has not been fully assessed. Children and pregnant women are the most vulnerable to falciparum malaria and least is known about safety in these populations. A range of ACTs is becoming available and it is important that these are carefully monitored.

In most malaria-endemic countries, pharmacovigilance (PV) activities are either nonexistent or in their preliminary stages. In most of the countries in which PV programs do exist, they are almost solely comprised of spontaneous reporting activities managed by the national regulatory authorities.

Adverse drug reactions (ADRs), particularly serious reactions or those significantly affecting tolerability, that are unknown or poorly understood have the potential to cause significant harm to patients and also to lead to community concerns, which could undermine the efforts of malaria control programs to build community confidence in, and adherence to, these treatments.

5.4.2. Rationale for pharmacovigilance of antimalarial drugs

	**Individual reflection**
	What is the rational for PV of Anti-malarial drug? **Time**: 10 minute

- PV helps in optimizing the management of resources, especially in the national health programs of developing countries.
- PV for ACTs and other combination treatments in Africa is essential.
- Malaria transmission intensity is high and antimalarial medicines are used frequently
- Presumptive treatment of fever with antimalarials is common, often in the absence of a confirmed diagnosis, using drugs obtained without a prescription.
- Informal use of antimalarial drugs may increase the risk of incorrect dosing, inappropriate treatment, and drug interactions, which may impact negatively on drug safety.
- The administration of antimalarial treatments in patients with a concomitant illness, including HIV/AIDs, tuberculosis and malnutrition, is a concern.
- Antimalarials are often purchased from drug shops or pharmacies without consulting a health care worker and such informal use of antimalarial could increase the risk of incorrect dosing, inappropriate treatment and interactions of different medicines, which could have a negative impact on antimalarial treatment safety.
- The safety of antimalarial treatment in vulnerable populations including pregnant women, and in patients with coexisting illnesses (such as HIV/AIDs, tuberculosis and malnutrition) has not yet been established.

.5.4.3. Adverse drug reaction of Antimalarial medicine and its Management

	**Group reading and discussion** • ***Read and discuss on Adverse drug reaction of Anti-malarial Medicines and its management*** **Time: 10 Minutes**

WHO recommends ACTs for the treatment of uncomplicated malaria caused by the P. falciparum parasite. By combining 2 active ingredients with different mechanisms of action, ACTs are the most effective anti-malarial medicines available today. WHO currently recommends 5 ACTs for use against P. falciparum malaria. The choice of ACT should be based on the results of therapeutic efficacy studies against local strains of P. falciparum malaria.

Table 5.8: Classification of Antimalarial Medicines and their Common Side effects

S/N	Antimalarial Medicines	Adverse effect	Management
1	Artemisinin derivatives	• Dizziness, fatigue, anorexia, nausea, vomiting, and diarrhoea. • Others include abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache, and rash	
2	Quinine	• Cinchonism, visual and auditory abnormalities, vomiting, diarrhea, and abdominal pain. • Hypersensitivity reactions and Hematologic abnormalities	• Discontinue if signs of severe cinchonism, hemolysis, or hypersensitivity occur. • Avoided (if possible) in patients with underlying visual or auditory problems • Used with great caution in those with underlying cardiac abnormalities. • Dosage should be reduced in renal insufficiency.
3	Chloroquine	• Pruritus is common, Nausea, vomiting, abdominal pain, headache, • Aanorexia, malaise, blurring of vision, and urticaria are uncommon.	• Should not be used in those with retinal or visual field abnormalities or myopathy. • Should be used with caution in patients with a history of liver disease or neurologic or hematologic disorders • Dosage must be reduced in renal insufficiency
4	Primaquine	The most important adverse effects are hemolyticanemia in patients with G6PD. abdominal pain, deficiency, Methemoglobinemia, mild anemia and leucocytosis	• Should be avoided in patients with a history of granulocytopenia or methemoglobinemia, • Never given parenterally because it may induce marked hypotension. • Patients should be tested for G6PD deficiency before primaquine is prescribed • should be discontinued if there is evidence of hemolysis or anemia • Avoided in pregnancy because the fetus is relatively G6PD-deficient and thus at risk of hemolysis. • Medicines liable to increase the risk of hemolysis or bone marrow suppression should be avoided.
5	Mefloquine	• Nausea, vomiting, dizziness, sleep, notably insomnia and abnormal dreams and behavioural disturbances,	• Contraindicated if there is a history of epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects, or sensitivity to related medicines.

		• Epigastric pain, diarrhoea, abdominal pain, headache, rash, dizziness, neuropsychiatric toxicities and leukocytosis, thrombocytopenia, and aminotransferase elevations	• Should be discontinued if significant neuropsychiatric symptoms develop.
6	Atovaquone-Proguanil	• Abdominal pain, nausea, vomiting, diarrhea, headache, and rash,	• The safety of atovaquone in pregnancy is unknown. Reversible elevations in liver enzymes have been reported.

Session Summary

- With limited resources, it is possible to conduct surveillance of ADRs for malaria patients in the community, with minimal loss to follow-up
- Health service delivery in both the private sector and in rural areas ought to be reviewed and improved so as to optimize therapy, especially in the treatment of malaria in children.

5.5 . Pharmacovigilance in Mass Drug Administration (MDA)

5.5.1. Introduction

Neglected tropical diseases (NTDs) such as lymphatic filariasis, onchocerciasis, trachoma, Schistosomiasis and soil-transmitted helminthiases (STHs) remain major public health problems in many parts of the world; which are especially endemic in low-income populations in developing regions of Africa, Asia and south Americas. The main strategy for control and elimination of these parasites which is recommended by World Health Organization (WHO) is preventive chemotherapy (PC) with the form of mass drug administration (MDA). PC is a public health intervention based on the large-scale administration of safe drugs, either alone or in combination, against selected Neglected Tropical Diseases (NTD). An expansion of preventive chemotherapy programmes will lead to more AE, including more ADR, more coincidental AE and, possibly, more operational errors. It will also lead to more SAE, which are of particular concern because they may cause unjustified opposition to preventive chemotherapy. Thus, the intervention needs systematic monitoring .Surveillance of AE is an effective means of monitoring preventive chemotherapy programmes safety and contributes to their credibility. It

allows for proper management of SAE and avoids inappropriate responses that can create a sense of crisis.

5.5.2. Classification of ADEs following MDA

ADEs following MDA classified in to five categories based on their cause:

1. Adverse reaction to the medicine: ADR caused directly by the medicine(s) used in the intervention;
2. Adverse reaction due to the destruction of parasites killed by the medicine: AEs(often considered ADR) that are the consequence of the death of parasites up on the action of the medicine(s);
3. Operational error: errors and accidents in treatment procedures, logistics, or medicine manufacturing, handling, or administration;
4. Coincidental event: event unrelated to the medicines or preventive chemotherapy procedures but has a temporal association with the intervention;
5. Unknown cause: cases in which the cause of an AE cannot be determined.

5.5.3. ADEs of commonly used drugs in MDA and their management

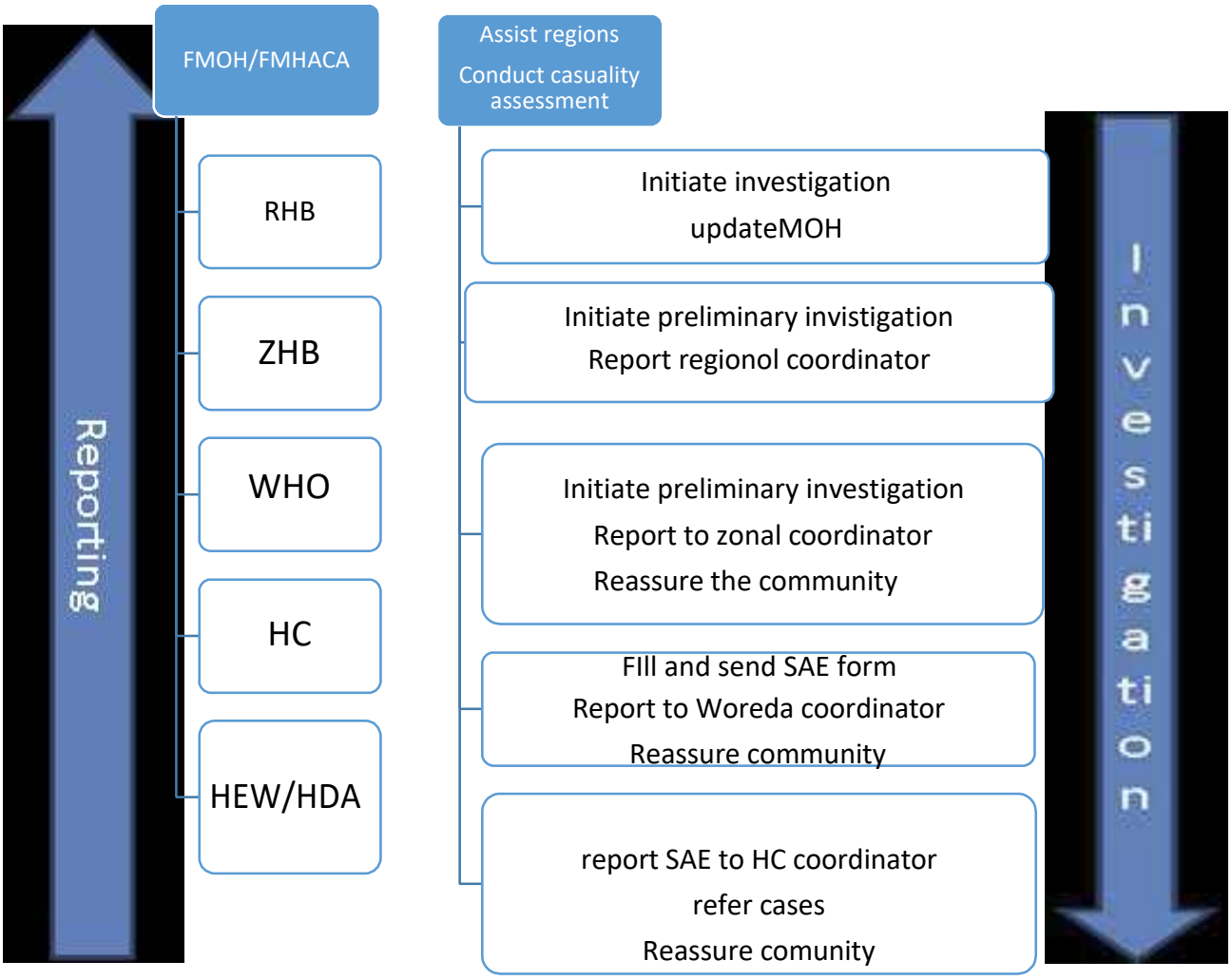
- Mild adverse events are common and expected. They are temporary and can be managed at the distribution site. However, if the adverse event persists for more than two hours, the drug distributer (HEWs or HDAs) should refer the case.
- Serious adverse events (if mild AE persists more than two hours, seizure, convulsion, unconsciousness, shock) are out rare and are not expected to be seen during PC-NTD MDA hence the HEWs should immediately report to the nearest health center.
- All SAE should be filled and reported as soon as possible.
- Prior to MDA start date the MDA coordinator and supervisors should alert health center and hospital staff on how to treat and refer the victim. It is important to establish a referral system including preparation of ambulance.
- Proper and early treatment should be provided to patients regardless of the diagnosis

The following table describes the common ADEs following MDAs and their management.

Table 5.9: ADEs of commonly used Medicines in MDA and their management

Drug	Adverse event	Management
Azithromycin, Ivermectin, Praziquantel, Albendazole and Mebendazole	Abdominal pain, vomiting, diarrhea or weakness (Minor adverse events)	• Keep patient under shade and provide drinking water (juice) • Watch for signs of dehydration
Azithromycin, Ivermectin, praziquantel	Dizziness, rashes, fever, itching and wheezing	• Make sure there is no chocking • Give anti pain like paracetamol • If the AE persists for more than two hours refer to health facility
Azithromycin, Ivermectin, Praziquantel, Albendazole and Mebendazole	Long lasting symptoms, seizure, convulsion, shock, unconsciousness	• Refer immediately the patient
Azithromycin, Ivermectin, Praziquantel, Albendazole and Mebendazole	Choking	For choking individual that is coughing, encourage continued coughing. If the victim is unable to cough, speak, or breathe, complete the following: • Lean person forward and give 5 back blows with heel of your hand. • Give 5 quick abdominal thrusts by placing the thumb side of your fist against the middle of the victim's abdomen, just above the navel. Grab your fist with the other hand. • Repeat until the object the person is choking on is forced out and person breathes or coughs on his or her own. • Refer the patient

5.5.4. Reporting routes and time line



- ***N.B. All SAEs are subjected to detail investigation and causality assessment***

Figure: 5.5.1- ADE reporting timeline and flow for MDA

Session Summary

- Neglected tropical diseases (NTDs) remain major public health problems in many parts of the world
- The main strategy for control and elimination of NTDs is preventive chemotherapy (PC) with the form of mass drug administration (MDA).
- An expansion of preventive chemotherapy programs will lead to more AEs, thus needing surveillance of AE which is an effective means of monitoring preventive chemotherapy programs safety and contributes to their credibility

5.6. Pharmacovigilance in non-communicable disease (NCD) medicines

5.6.1. Introduction

Non-communicable diseases (NCDs) have become the major killers of humankind in recent years. An estimated 36 million deaths, or 63% of the 57 million deaths that occurred globally in 2008, were due to non-communicable diseases, comprising mainly cardiovascular diseases (48%), cancers (21%), chronic respiratory diseases (12%) and diabetes (3.5%)(WHO, 2010a). Nearly 80% (29 million) of these deaths were in low- and middle-income countries and more than 90% of premature deaths (death before the age of 60 years) occurred in these countries.

The African region is not spared from this global epidemic of NCDs and, in fact, continues to suffer from a double burden of diseases (communicable and non-communicable diseases). The WHO predicted that deaths from NCDs will increase globally by 17% over the next ten years, with the greatest inscrease in the African region (by 27% or 28 million deaths from NCDs) (WHO, 2010a). In Africa, projections indicate that deaths from NCDs will exceed the combined mortality from communicable, maternal, perinatal, and nutritional diseases to become the most common causes of death by 2030. It is clear that non-communicable diseases (NCDs) present a leading threat to human health and human development in Africa.

Estimates from the WHO (from 2008) indicated an NCDs-related annual death rate of 34% in Ethiopia (WHO, 2010a). In this report, cardiovascular diseases accounted for 15%, cancers for 4% and respiratory disease for 4% of all causes of death. Furthermore, diabetes accounted for 2%, injuries for 9% and other NCDs for 9% of causes of deaths in the same year.

5.6.2. Rational of Pharmacovigilance for no-communicable disease (NCD)

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;
- Improve public health and safety in relation to the use of medicines;
- detect problems related to the use of medicines and communicate the findings in a timely manner;
- contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;
- encourage the safe, rational and more effective (including cost-effective) use of medicines
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.
- Better assess and communicate information on the effectiveness and risks of medicines and to educate and inform patients.
- An insurance against the undetected use of ineffective, substandard or counterfeit medicines, thus minimizing the possibility of wastage of resources.
- The cost of a pharmacovigilance system, compared with the cost of ADRs to a nation and to the total national expenditure on medicines, is small
- essential for the rational, safe and cost-effective use of medicines by patient

PV for Cardiovascular drugs

	**Activity: Group discussion**
	Discuss on Adverse drug reaction of cardiovascular drugs and Monitoring **Time**: 10 Minutes

Patients with cardiovascular diseases are prescribed multiple drugs, hence poly pharmacy may attribute to higher incidence of adverse drug reactions in these patients.

The most frequently reported ADRs were dry cough and gastritis and the most commonly implicated cardiovascular drugs causing these ADRs were found to be enalapril, atorvastatin and aspirin.

Table 5.9: Classification of Cardiovascular drugs and adverse effect

Class of drug	Drug	Adverse effect
ACEI (Angiotensin converting enzyme inhibitors)	Captopril Enalapril	dizziness, headache, drowsiness, diarrhea, low blood pressure, weakness, cough, and rash
CCBs (Calcium Channel Blockers)	Nifedipine (sustained release formulations)	headache, constipation, rash, nausea, flushing, edema (fluid accumulation in tissues), drowsiness, low blood pressure, and dizziness
Thiazide diuretics	Hypdrocholorothiazide Bendrofluazide	dizziness and lightheadedness, blurred vision, loss of appetite, itching, stomach upset, headache, and weakness
Beta-blockers	Propranolol Atenolol Metoprolol	Diarrhea, Stomach cramps, Nausea Vomiting, Rash, Blurred vision, Disorientation, Insomnia, Hair loss, Weakness, Muscle cramps, Fatigue
Lipid lowering therapy	Simvastatin, Atrovastatin	Muscle injury, new-onset diabetes mellitus and hepatotoxicity.
Antiplatelet therapy	Aspirin	Upset stomach, heartburn, easy bruising/bleeding, difficulty hearing, ringing in the ears, signs of kidney problems (such as change in the amount of urine), persistent or severe nausea/vomiting, unexplained tiredness, dizziness, dark urine, yellowing eyes/skin, serious bleeding from the stomach

Monitoring adverse drug reaction of cardiovascular drug

Monitoring adverse drug reactions in patients using cardiovascular drugs is a matter of importance since this class of medicine is usually used by elderly patients with critical conditions and underlying diseases.

The frequency of ADRs occurrence can be reduced by decreasing the number of drugs prescribed. ADRs of Cardiovascular drugs mostly occur in first days of treatment, therefore monitoring patients in first days of using cardiovascular drugs could help in preventing ADRs. To determine the rate and nature of adverse events induced by different subclasses of cardiovascular drugs, more studies are recommended in various populations.

Antidiabetic drugs

	Activity: 5.9.1. Group discussion
	Discuss on Adverse drug reaction of Diabetic drugs and Monitoring **Time:** 10 Minutes

The prevalence of Diabetes and various comorbid conditions is a frequent observation that compels the clinicians to prescribe multiple drugs. Use of multiple drugs enhances the chance of adverse reactions. Various other factors like age, gender, lifestyle of the patients are also responsible for the development of adverse reactions. These adverse consequences are therefore a limitation for the therapeutic success. Thus, it becomes essential to identify the responsible drugs to avoid adverse effects to ensure safe and efficient therapeutics. Detection and prevention of these adverse reactions is essential to reduce patient suffering. Future studies on adverse drug events will help the therapy and ensure the use of safe medicine.

The research findings cited above has shown clearly that ADRs of these antidiabetic drugs cannot be completely avoided but adequately managed through prompt identification and reporting. Lack of adherence to diabetic therapy contributes to inadequate glycemic control; this often results from self-medication and overdosing, and complicates ADR monitoring.

Table 10: Classification **of Diabetic drugs and adverse effect**

TYPE 2 DIABETES DRUGS		
Class of drug	**Drug**	**Adverse effect**
Sulfonylureas	Chlorpropamide, Tolazamide, Glyburide, Glipizide, Gliclazide, Glimepiride, Tolbutamide, Acetohexamide, Gliquidone, Glisoxepide, Glibenclamide	• low blood sugar, upset stomach, skin rash or itching, weight gain
Biguanides/Metformin	Metformin IR (immediate release Metformin SR (slow release)	• sickness with alcohol, kidney complications, upset stomach, tiredness or dizziness, metal taste
Alpha-glucosidase inhibitors	Acarbose (Precose) Miglitol (Glyset)	• gas, bloating and diarrhoea

Thiazolidinedione's	Rosiglitazone, Pioglitazone, Ciglitazone, Lobeglitazone, Rivoglitazone, Netoglitazone, Balaglitazone, Troglitazone	• weight gain, risk of liver disease, anaemia risk, swelling of legs or ankles
Meglitinides	Prandin (repaglinide), Starlix (nateglinide).	• weight gain, low blood sugar
TYPE 1 DIABETES DRUGS		
Insulin		**Common** • Hypoglycemia, Headache, Flu-like symptoms, Weight gain, Lipoatrophy, Itching **Serious** • Severe hypoglycemia, Allergic reactions, Anaphylaxis, Hypokalemia

Monitoring adverse drug reaction of Diabetic drugs

- Need for effective counselling and diabetic education of patients to enhance their awareness and knowledge of the condition for improved adherence.
- Appropriate medication, alongside a healthy diet and exercise routine will help people living with diabetes to maintain stable blood glucose levels.
- Depending on reactions to prescribed drugs, physicians should be promptly informed for advice or changes where necessary and the ADRs reported to NAFDAC.

5.6.4. Pharmacovigilance in Reproductive, Maternal, Neonatal and Child Health medicines

5.6.2.1. Introduction

In Ethiopia, Reproductive, Maternal, Neonatal and Child Health (RMNCH) program is given a priority focus for both governments and civil society and is being implemented in across all levels of health service delivery. There is the problem of inappropriate use of RMNCH medicines resulting in serious consequences of poor health outcomes. This may affect the country's efforts to end preventable child and maternal deaths.

RMNCH medicines and medical devices covers all medicines and medical devices which are used for the care and management of the health concerns and interventions across the life course involving women before and during pregnancy; newborns, that is, the first 28 days of life; and children to their fifth birthday.

Since RMNCH program is a government health priority agenda, PV of RMNCH medicines and medical devices also ensures the use of safe, effective and quality assured medicines for preventing child and maternal deaths.

5.6.2.2. Rationale

The information collected during the pre-marketing phases or before registration (clinical study phase of medicines) is inevitably incomplete and not sufficient especially in special vulnerable populations (such as: fetus, children, elders, pregnant and breast feeding women's) since due to the ethical and regulatory laws conducting the clinical trial in these vulnerable populations shall be prohibited unless there is a necessary ground and scientific evidence is produced providing that the medicinal product is intended to these group have unique benefits on which extrapolation of data from clinical studies on group of population is useless and impossible.

In addition, RMNCH program is a government health priority agenda, ensuring that every women and child can survive and thrive is a priority for Ethiopia health system, and central to the goal of saving women's lives and improving child health.

Some RMNCH medicine which are used for maternal health (eg: oxytocin) require a special cold chain storage condition and transport equipment (refrigerator) that enables medicines to be stable and maintains its safety, quality and potency from the point of manufacture to the point of use

Therefore, implementing PV program in RMNCH medicines and medical devices ensures the use of safe, effective and quality assured RMNCH medicine & medical devices for preventing child and maternal deaths which has crucial and key role to achieve these national and global priorities.

5.6.3. RMNCH priority medicines and common Adverse Events (AEs)

Globally in 2010, the UN commission identified 13 pharmaceuticals as a priority for the RMNCH services. These 13 overlooked life-saving pharmaceuticals across, if more widely accessed and properly used, could save the lives of more than 6 million women and children.

Table 5.11:UN commission 13 life-saving medicines and medical devices for RMNCH.

RMNCH Type	Medicines or Medical device	Common ADR
Reproductive health	Female condom	Generally safe, but sometimes has allergic reaction to the latex rubber
	Implants	
	Emergency contraceptives	
Maternal health	Oxytocin	fast or irregular heartbeat, nausea or vomiting
	Misoprostol	
	Magnesium sulphate	sweating, flushing, headache, and nausea
New-born health	Injectable antibiotics	GIT disturbances (NVD), allergic reactions
	Antenatal corticosteroids	
	Dexamethasone injection	
	Chlorhexidine	
	Resuscitation equipments	
Child **H**ealth	Amoxicilline	diarrhea, nausea, rash, urticarial and allergy
	Oral Rehydration salt	
	Zinc	Stomach upset, heart burn, nausea, metallic taste

Note that:

- The Adverse Drug Events (ADE) reporting form used for the RMNCH medicines and medical devices are the usual and regular ADEs (Yellow form) paper based form and electronic (e-reporting and med safety mobile apps) reporting tools. And it has no separate and independent reporting system.

- Though special emphasis and focus is given for PV of RMNCH products, all medicines and medical devices also requires implementing PV activities.

Session Summary

- With limited resources, it is possible to conduct surveillance of ADRs for malaria patients in the community, with minimal loss to follow-up
- Health service delivery in both the private sector and in rural areas ought to be reviewed and improved so as to optimize therapy, especially in the treatment of malaria in children • PV of RMNCH medicines and medical devices ensures the use of safe, effective and quality assured RMNCH medicine & medical devices for preventing child and maternal deaths which has crucial and key role to achieve these national and global priorities.
- Monitoring the safety, quality and efficacy of a priority list of medicines and medical devices used for RMNCH care and management should be continuously available in the health system to properly implement RMNCH programs.
- As most RMNCH medicines and medical devices targets in vulnerable population to medicine related harm, implementing PV in RMNCH programs protect them from any medicine-related harms and risk.

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Annex

Annex 1: Suspected Adverse Drug Event (ADE) Reporting Form

Ethiopian Food and Drug Authority (EFDA)
Suspected Adverse Drug Event (ADE) reporting form

Patient Name (Initial)	Card no/MRN	Age, Date of birth	Sex	Weight	Height

Report type □ Initial □ Follow up

Substance of abuse

Information on suspected drug/vaccine

Drug name(write all information including brand name, batch no and manufacturer)	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)

Information on concomitant drug/vaccine, including herbal medicines

Drug name(write all information including brand name, batch no and manufacturer)	Dose/dosage form, route, frequency	Date drug taking was 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)

Was the reaction serious? □ YES □ No
Reason for seriousness
□ Death □ Hospitalization/prolonged □ Disabling
□ Congenital anomaly □ Life threatening
□ Other medically important conditions

Reaction subside after D/C of suspected drug
□ YES, Date □ No □ Unknown
Reaction reappear after restart of suspected drug
□ YES □ No □ Information not available

Treatment of reaction

Outcome: □ Died due to the adverse event □ Died, drug may be contributory □ Not yet recovered
□ Recovered without sequelae □ Recovered with sequelae* □ Unknown

*Sequelae

Relevant medical conditions such as allergies, renal disease, liver disease, other chronic diseases, pregnancy etc

Reported by: Name	Profession:	Email address:	Telephone

Name of health institution	Date

Product quality problem: Color change, separating of components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling, etc (Write if anything different than given above)

Drug name	Batch No	Manufacturer	Dosage form and strength	Size /type of package

For office use only	
Received on:	Registration no:
Key: D/M/Y ; Date /Month/Year D/C; Discontinue treatment Y;YES N;NO	

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What to report?

All suspected reactions to drugs
Unknown or unexpected reactions
Unexpected therapeutic effects
All suspected drug interactions
Product quality problems
Treatment failures
Medication errors

This ADE reporting form was prepared & printed by EFDA in collaboration with .....

NB. Drugs includes

Conventional drugs
Herbal drugs
Traditional medicines
Biologicals
Medical supplies
Medicated cosmetics

የመላይ መስጫ አገልግሎት ፈቃድ ቁጥር: HQ2
Business Reply Service License No HQ2

From:----------

Postage Prepaid

P.O. Box 5681-Tel.0115-523142
Addis Ababa, Ethiopia

Other means of Reporting

Electronic Reporting form on our website: www.efda.gov.et
Med safety Mobile application download from play store or IOM
Email address: pharmacovigilance@efda.gov.et
Toll free telephone: 8482

Annex 2: Allergy card

የመድኃኒት አለርጂ መታወቂያ ካርድ

የባለመታወቂያው ስም_____ያታ_____
እድሚያተወለዱበት ቀን_____
አድራሻ_____ወረዳ_____ተበሌ_____ቤ.ቁ_____
ካርዱ የተሰጠበት ቀን_____
አለርጂውን ያስከተለው መድኃኒት ስም
1_____
2_____
3_____
በአለርጂው ምክንያት የደረሰው ችግር ዝርዝር
_____
_____
_____.
ተጨማሪ አስተያየት
_____.
እባክዎ ከካርዱ ጀርባ ያለውን መመሪያ ይመልከቱ

USAID msh SPS

መመሪያ

ለግንኛውም ጤና ባለሙያ

- እባክዎ ሕክምና በሚሰጡ ወይም መድኃኒት በሚያድሉበት ወቅት ታካሚዎ ለየትኛው መድኃኒት አለርጂ እንዳለባቸው ይጠይቁ ። ከዚያም በዚህ መታወቂያ ካርድ ላይ ይመዝግቡላቸው ።
- ታካሚው ከዚህ በፊትያጋጠማቸውን አለርጂ አመዝግበውም ከሆነ ካርዳቸውን እንዲያሳዩዎት ይጠይቁ ። ለአለርጂው ምክንያት የሆነው መድኃኒት በድጋሚ እንዳይታዘዝ ወይም እንዳይሰጥ ይከላከላል።

ለግንኛውም ታካሚ

- እባክዎ ወደያትኛውም የሕክምና መገልገያ ተቋም ማለትም ሆስፒታል፣ ጤናጣቢያ ፣ጤና ኬላ፣ክሊኒክ ለመታከም ወይም መድኃኒት ቤት መድኃኒት ለመግዛት ሲሄዱ አለርጂ ካጋጠመዎት አለርጂውን ያስከተለው መድኃኒት ስም በዚህ መታወቂያ ካርድ ላይ እንዲመዘገብልዎት ይጠይቁ ።
- በሌላ ጊዜም ለመታከም ወይም መድኃኒት ለመግዛት ሲሄዱ ለጤና ባለሙያ ካርዱን ማሳየትን አይርሱ ። ለአለርጂው ምክንያት የሆነው መድኃኒት በድጋሚ እንዳይታዘዝለዎት ወይም እንዳይሰጥዎት ይከላከልዎታል።