Ministry of Health and Family Welfare

Directorate General of Drug Administration

NATIONAL GUIDELINE ON THE **PHARMACOVIGILANCE SYSTEM** IN BANGLADESH

USAID FROM THE AMERICAN PEOPLE

SIAPS Systems for Improved Access to Pharmaceuticals and Services

Ministry of Health and Family Welfare

Directorate General of Drug Administration

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About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to ensure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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বিষয়ঃ National Guideline on the Pharmacovigilance System in Bangladesh এর অনুমোদন।

সূত্র- ডিজিডিএ/এডিআরএসি-১২০/১৩/১৬৮৫২ তারিখ- ১৩/১১/২০১৭খ্রিঃ ঔষধ প্রশাসন অধিদপ্তর থেকে প্রাপ্ত।

উপর্যুক্ত বিষয় ও সূত্রের প্রেক্ষিতে National Guideline on the Pharmacovigilance System in Bangladesh নির্দেশক্রমে অনুমোদন করা হল।

১৭/১/১৮

(মাকসুদা ইয়াসমিন)
সিনিয়র সহকারি সচিব
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অনুলিপি সদয় অবগতি ও প্রয়োজনীয় ব্যবস্থা গ্রহণের জন্য(জ্যেষ্ঠতার ভিত্তিতে নয়):

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২. মাননীয় প্রতিমন্ত্রী মহোদয়ের একান্ত সচিব, স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়,
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FOREWORD

Pharmacovigilance (PV) promotes public health by ensuring the safety, efficacy, and quality of medicines and other health products. In 2013, the Ministry of Health and Family Welfare (MOHFW) declared the ADRM Cell of the Directorate General of Drug Administration (DGDA) as the National Pharmacovigilance Center (NPC) for Bangladesh. The MOHFW also formed an Adverse Drug Reaction Advisory Committee (ADRAC) to work in conjunction with the ADRM Cell to provide technical guidance for implementing PV activities, evaluating adverse drug event (ADE) reports, and recommending regulatory decisions and actions to ensure medicine safety. In December 2014, Bangladesh became the 120th member of the World Health Organization's International Drug Monitoring Center, known as the Uppsala Monitoring Center (WHO-UMC). Through this membership, Bangladesh has gained international recognition and access to early worldwide information about potential safety risks. To this effect, the DGDA has developed guidelines and strategies to implement PV activities across the country with the cooperation of all stakeholders.

This guidance document, *National Guideline on the Pharmacovigilance System in Bangladesh,* is the first of its kind in Bangladesh and has been developed to build awareness of medicine safety and establish proper PV systems. On behalf of the DGDA, I express my sincere thanks and gratitude to the US Agency for International Development (USAID)-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program, implemented by Management Sciences for Health (MSH), for its assistance in developing this guideline. I also express my gratitude to the stakeholders whose support enriched the guideline.

I hope this guideline will provide the necessary direction for health care professionals and others involved in the PV program to effectively support the DGDA to ensure the safety, quality, and efficacy of medicines and thereby secure public health.

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ACRONYMS

ADE	adverse drug event
ADR	adverse drug reaction
ADRAC	Adverse Drug Reaction Advisory Committee
ADRM	adverse drug reaction monitoring
AEFI	adverse event following immunization
BCPNN	Bayesian Confidence Propagation Neural Network
DGDA	Directorate General of Drug Administration
DGHS	Directorate General of Health Services
HCP	health care provider
IC	information component
ICSR	individual case safety report
MAH	marketing authorization holder
MOHFW	Ministry of Health and Family Welfare
MSH	Management Sciences For Health
NPC	National Pharmacovigilance Center
PSUR	periodic safety update report
PV	pharmacovigilance
RMP	risk management plan
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TSC	technical subcommittee
UMC	Uppsala Monitoring Centre- International Drug Monitoring Center
USAID	US Agency for International Development
WHO	World Health Organization

CHAPTER 1: PHARMACOVIGILANCE SYSTEM OF BANGLADESH

1.1 Introduction

As more pharmaceutical products come on the market and more people gain access to those products, it has become imperative for countries to monitor the safety of medicines and protect the public from medicine-related harm. PV is the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem[1]. More recently, the definition has been expanded to include problems related to any pharmaceutical product, including vaccines, medical devices, biologics, blood products, herbal medicines and traditional and complementary medicines. PV promotes public health by ensuring the safety, efficacy, and quality of medicines and other health products.

PV was introduced in Bangladesh in 1996. However, due to a shortage of manpower and a lack of financial support, the program became dormant. It was revived in 2013 when the DGDA established the ADRM Cell with technical assistance from SIAPS. The MOHFW declared the ADRM Cell of the DGDA as the NPC for Bangladesh. The MOHFW also revived ADRAC to work in conjunction with the ADRM Cell to provide technical guidance for implementing PV activities; evaluate ADE reports; and make recommendations for regulatory decisions to the DGDA, the country's licensing authority for drugs.

This guideline provides a basic framework for the implementation of the national PV system in Bangladesh and its related activities in a comprehensive, systems-oriented manner and serves as a blueprint for operationalizing the system. It outlines what, why, when, where, and how to report information on the safety, efficacy, and quality of pharmaceuticals and other health products. It is expected that the guidelines will ensure uniformity in the execution of safety and effectiveness monitoring activities of pharmaceuticals and other health products in Bangladesh.

1.2 Overview of the System

A functional PV system is characterized by its structure, processes, and outcomes. To run an effective PV system, the DGDA established a protocol for reporting adverse drug reactions (ADRs) associated with drug use and developed a guidance document to help ensure the systematic and effective functioning of PV activities through regular reporting of ADEs.

The objective of the *National Guideline on the Pharmacovigilance System in Bangladesh* is to guide health care providers (HCPs) and other key actors in the health and pharmaceutical sectors on the operations of the PV system. This document gives an overview of what PV is, how to detect and classify ADRs, and the structural organization of the system in Bangladesh. It also describes the reporting system to the NPC and expected outcomes. The document aims to help expand the roles and responsibilities of stakeholders in the country's PV system to identify, analyze, and minimize the risks associated with pharmaceutical products. It also promotes better and broader use of PV data for patient safety.

[1] http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

The document was developed to support:

- Professional staff at the NPC of Bangladesh
- ADRAC and technical subcommittee (TSC) members
- Focal points of hospitals engaged with spontaneous reporting of ADEs
- National public health programs
- DGDA staff
- HCPs (e.g., clinicians, dentists, pharmacists, nurses)
- Academics and academic institutions
- Pharmaceutical manufacturers/marketing authorization holders (MAHs)
- National regulatory authorities of other countries

1.3 The Importance of Pharmacovigilance

All pharmaceutical products have potential adverse effects; however, the consequences vary in severity and frequency and some pose a greater health risk than others. Most information on medicines and other pharmaceutical products is collected through preauthorization clinical trials carried out under controlled conditions in a sample population for a limited time period. These characteristics can result in a situation whereby information from pre-marketing studies may not sufficiently represent real-life conditions or the entire population for whom the product is indicated. As a result, the full scope of potential ADRs of pharmaceutical products may not be detected until after they are authorized for use in the general population. PV offers an opportunity for more complete information on pharmaceutical products and their risks and effects.

PV also helps to document and avert the health risks and challenges posed by the increasing availability and trade in substandard and falsified products, including counterfeits. Through quality surveillance of products on the market, defective, deteriorated, adulterated, or poorly manufactured pharmaceutical products can be identified and recalled. In addition, PV aids in the identification of medical products that have lost potency or are decomposing as a result of inappropriate storage conditions. Once identified, these products can be removed from the supply system, and information about the risk they pose can be communicated to health care professionals, patients, and the public.

PV plays an important role in identifying medication errors so that the frequency of such errors and their effects on patients can be reduced. PV systems collect data and monitor processes and conditions that can facilitate or lead to medication errors. These data, once collected and analyzed, can provide critical information that is ultimately used in the education of health care professionals and the development of effective system control measures to curb the occurrence of medication errors. PV is also used to monitor and review the effectiveness of medications and provide evidence to support changes to treatment protocols.

1.4 Legal Basis for Pharmacovigilance Program of Bangladesh

The PV program aims to prevent harm from adverse events in humans arising from the use of authorized or unauthorized medicinal products within or outside the approved indications and promote the safe and effective use of medicinal products, in particular by providing timely information about the safety of medicinal products to patients, HCPs, and the public.

The Drug Control Committee was formed according to the direction of section 4 of the Drugs (Control) Ordinance of 1982. As per section 6, this committee is entrusted to evaluate all medicines registered in Bangladesh to ensure safety, efficacy, and usefulness. The PV system is one source of information that the committee relies on to evaluate safety, efficacy, and usefulness. Pharmacovigilance has been addressed in The National Drug Policy 2016.

1.5 Vision and Mission Statement

Vision: To safeguard the health of the Bangladeshi population by ensuring that the benefits of pharmaceutical products outweigh the risks associated with their use.

Mission: To improve patient safety and the welfare of the Bangladeshi population by monitoring the safety, quality, and efficacy of medicines, thereby reducing the risks associated with their use.

1.6 Scope and Objectives of Pharmacovigilance in Bangladesh

Scope of Pharmacovigilance in Bangladesh

The PV system in Bangladesh is focused on detecting, evaluating, and preventing adverse events related to medicines and other pharmaceutical products by managing and mitigating the risk that such products pose to patients. ADR reporting emphasizes reporting on medication errors as well as product quality issues.

The medicines and other health products monitored by the PV system in Bangladesh include:

- Conventional (allopathic) medicines
- Vaccines
- Medical devices
- Biological
- Blood products
- Alternative medicines (e.g., ayurvedic, unani, herbal, homeopathic, biochemic)

Objectives of the National PV System in Bangladesh

- Monitoring and detecting medicine safety, effectiveness, and quality problems through passive and active surveillance of adverse events

- Assessing the safety, quality, effectiveness, and risk/benefit of pharmaceutical products
- Disseminating information on the safety and appropriate use of pharmaceutical products to the public and health care professionals to mitigate risk
- Monitoring and engaging pharmaceutical manufacturers and other suppliers in the pharmaceutical industry to ensure that marketed drugs are of high quality and are safe for human consumption

1.7 Short-term Goals

- Develop and implement the essential components of a PV system in Bangladesh
- Enroll focal points, initially at selected medical college hospitals (tertiary level public and private) throughout the country
- Encourage health care professionals to report ADEs associated with the use of medicines, vaccines, medical devices, and biological products
- Collect case reports, analyze data, and conduct causality assessments

1.8 Medium-term Goals

- Enroll focal points at all medical college hospitals (primary/secondary/tertiary level public and private) throughout the country
- Set up PV centers to potentiate the PV system in the country
- Analyze data and conduct causality assessments according to international standards
- Generate safety signals and communicate safety issues to the public, HCPs, and other stakeholders
- Ensure regulatory actions, based on evidence, when necessary

1.9 Long-term Goals

- Expand the PV program to all hospitals (public and private) and public health programs across Bangladesh and expand the number of centers in the country
- Develop and implement an electronic reporting system
- Develop a spontaneous reporting culture among health care professionals
- Make ADR reporting mandatory for health care professionals

1.10 Functions of the National Pharmacovigilance System

The functions of the Bangladesh national PV system include:

- Promoting medicine safety in the country by collecting and managing reports of ADRs, medication errors, and suspected substandard/falsified products
- Collaborating and harmonizing with existing ADE reporting and collection activities within the country (e.g., national disease control programs, Ministry of Health) as well as international cohorts monitoring ADEs in defined patients or populations
- Identifying safety signals (e.g., unknown or poorly characterized adverse events) in relation to a medicine or a combination of medicines
- Undertaking a risk assessment and developing options for risk management
- Identifying quality problems with medicines resulting in ADEs and supporting the identification of medicine quality issues in general
- Providing effective communication on aspects of medicine safety, including prompt notification of confirmed safety and quality problems and dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines
- Applying PV information for the benefit of public health programs, individual patients, and national medicine policies and treatment guidelines
- Developing and maintaining drug utilization information
- Identifying issues associated with inappropriate prescribing and dispensing of medicines

1.11 National Pharmacovigilance Center for Adverse Drug Reaction Monitoring in Bangladesh

The ADRM Cell serves as the coordinating body for the national PV system in Bangladesh and the NPC in Bangladesh as per the declaration of the MOHFW. It is the central point for the system's operations.

An organogram illustrating the structure of the ADRM cell is shown in figure 1.

1.12 Organogram of ADRM Cell

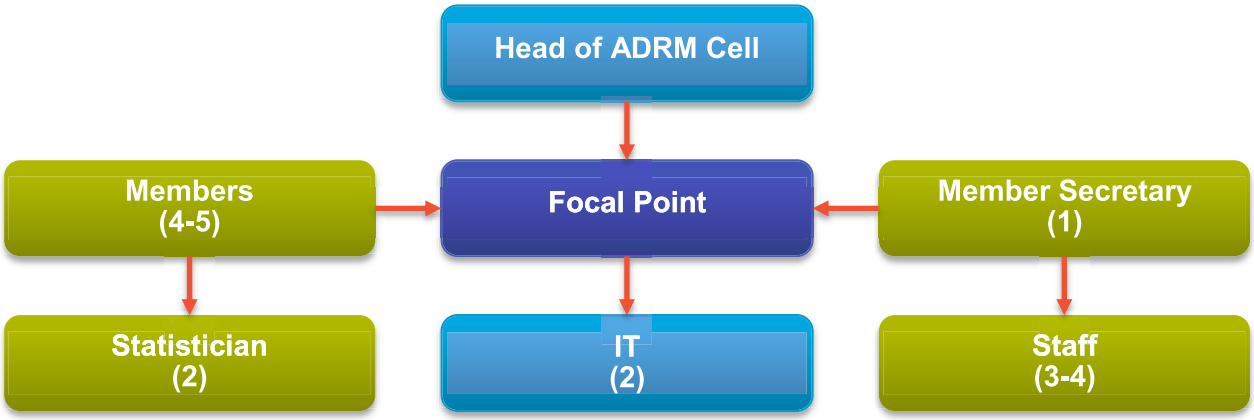

Figure 1. Organogram of ADRM Cell

1.13 Job Responsibilities of ADRM Cell

Head of ADRM cell

- Responsible for managing all key activities of ADRM Cell
- Responsible for updating and revising the standard operating procedures when needed
- Responsible for calling TSC and/or ADRAC meetings when necessary

Member Secretary

- Arranges ADRM cell meetings and coordinates cell members
- In absence of head, performs all activities of head
- Receives and manages ADE reports
- Communicates with report providers for collecting missing information
- Responsible for archiving and maintaining ADRM Cell and ADRAC documents
- Assists focal point as necessary

Focal Point Person

- Responsible for communicating and arranging regular meetings with the stakeholders and committees (e.g., ADRAC, TSC) as QPPV of the Center
- Evaluates ADE reports with other members and/or experts
- Arranges monthly hospital, HCPs and industry visits for ADRM Cell members to raise awareness of PV
- Arranges training and education programs for the focal points of hospitals and pharmaceutical companies, PHPs, and HCPs as needed
- Conducts regular meeting with stakeholders, including the public, and takes steps to build mass awareness
- Coordinates centers, PHPs, clinical trials, bioequivalent studies, and other research programs in the country related to PV
- Responsible for communicating with international stakeholders, such as WHO, and other national regulatory authorities
- Responsible for developing and publishing PV newsletter/bulletin or arwareness and educational materials on a regular basis
- In absence of the member secretary, performs all of his/her activities.

Members

- Evaluate ADE reports with other members
- Search and collect drug safety information from different sources
- Assist head of ADRM Cell, focal point, and member secretary
- Along with focal point, arrange monthly hospital and HCP visits

IT Staff

- Provide support for maintaining in-house data storage system
- Maintain back up data in case of emergency (e.g., fire, earthquake, flood)
- Prepare documents as necessary

Statistician

- Maintain register for all ADE reports each year
- Provide a unique number for each ADE report
- Provide an analysis to assess the number of ADE reports per month according to hospitals and pharmaceutical companies

Supporting Staff

- Provide support as needed
- Perform any activity for assisting officials of the cell

Figure 2. Job responsibilities of ADRM Cell

1.14 Adverse Drug Reaction Advisory Committee

Under the NPC in Bangladesh, ADRAC and its TSC evaluate and review ADE reports. ADRAC is an independent body chaired by the Director General of the DGDA. It comprises clinicians; academics from medical college hospitals; representatives of the Bangladesh Medical Association, Bangladesh Association of Pharmaceutical Industries, and Consumer Association of Bangladesh; and pharmaceutical experts from Bangladesh. The committee works in conjunction with the ADRM Cell to provide technical guidance for PV activities, evaluate ADE reports, and make recommendations on regulatory decisions and actions by the DGDA. A TSC was established within ADRAC in 2015 to assist in the evaluation and expert review of ADE reports and perform causality assessments. ADRAC provides final comments and validates the recommendations (annex A).

The key responsibilities of ADRAC and its subcommittee include:

- Reviewing, evaluating, and analyzing ADE reports, including serious ADE reports, and making recommendations to the DGDA on appropriate regulatory actions and effective ways of communicating information on medicine safety to health care professionals, MAHs, and the public

- Assessing pharmaceutical risks and making recommendations in this regard

- Making recommendations and providing advice to the DGDA and the MOHFW on the implementation of the PV program and approaches on how to promote the safe and effective use of medicines by HCPs and the public

- Reviewing mechanisms for collecting ADEs and advising the ADRM Cell on improvement strategies for processing them

- Assisting the ADRM Cell and the DGDA to develop and implement risk minimization strategies to address drug safety concerns

1.15 Funding for the NPC

To keep the NPC functional, a continuous funding provision from the government and technical assistance from development partners are needed. Sustainable funding is a criterion of a functional PV center, according to WHO. The ADRM Cell of the DGDA is currently operating with technical support from USAID. The DGDA has proposed a funding provision in the Strengthening of Drug Administration and Management operational plan under the 4th Health, Population & Nutrition Sector Development Program. The DGDA also has a plan to arrange sustainable funding from the regular revenue budget and has incorporated funding for routine activities of the NPC into the annual operational plan.

CHAPTER 2: UNDERSTANDING ADVERSE DRUG EVENTS

2.1 Adverse Drug Events

An ADE is defined as any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with this treatment.

Adverse events are directly related to pharmaceutical products and may be due to:

- Known or unknown pharmacological properties resulting in ADRs
- Poor product quality (e.g., spurious, adulterated, misbranded, counterfeit, substandard)
- Medication errors in prescribing, preparing, administering, or taking the medicine

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

- Results in death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is life threatening

2.2 Adverse Drug Reactions

An ADR is a response to a drug that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.

An unexpected adverse reaction is an adverse reaction for which the nature or severity is not consistent with domestic labeling or market authorization or expected from characteristics of the drug. An ADR is distinct from an ADE.

There are two principal types of ADRs.

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

- Will likely occur in most people
- Dose related
- Pharmacodynamic effects
- Common
- Management reduces their incidence

Type B (Bizarre): Not related to the principal action of the medicine/drug

- Will likely occur only in some people
- Not part of the normal pharmacology of the medicine

- Not dose related
- Unpredictable
- Includes idiosyncrasy and drug allergy
- Accounts for most drug fatalities

There are four additional subordinate types:

- Type C (Continues): Reaction due to long-term use
- Type D (Delayed): Effects such as teratogenesis or carcinogenesis
- Type E (Ending of use): Abrupt discontinuation (e.g., rebound adrenocortical insufficiency)
- Type F (Failure of therapy): Treatment failure

More information is provided in annex B.

2.3 Poor Product Quality

An adverse event may be caused by the use of substandard or falsified products, including counterfeits, which does not meet quality standards and therefore are unsafe or ineffective. Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and are consequently ineffective and often dangerous to the patient. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources, or counterfeiting.

Visible signs of poor product quality, which should be checked and reported, include discoloration or color change, separation of components, powdering/crumbling, caking, molding, changes in smell, poor or defective packaging, poor labeling and mislabeling, changes in physical shape, defective components, and expiration of shelf life.

In some cases, there may not be visible evidence of poor product quality even though a quality problem exists and is causing an adverse event in a patient. Therefore, it is especially important that all suspected quality problems are reported so that the product in question can be properly tested in the laboratory and removed from the supply system if necessary.

2.4 Medication Errors

A medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."[2]

[2] National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). Available at: http://www.nccmerp.org/consumer-information

2.5 Therapeutic Ineffectiveness

Therapeutic ineffectiveness is a type of adverse event that may be related to poor treatment adherence, antimicrobial resistance, product quality problems, inappropriate use, or a drug-drug or other interaction.

2.6 Recognizing an Adverse Drug Event

Distinguishing between the natural progression of a disease and an adverse event is challenging. When an adverse event occurs in a patient taking a medicine or using any other pharmaceutical product, the possibility that it is caused by the product must be considered.

The following steps can help determine whether an event is caused by a pharmaceutical product.

A) Collect complete information on the event and assess potential other causes:

- Take a proper history and try to exclude all other possible causes that could explain the event, such as co-morbid conditions, foods, and other medicines used concomitantly that might be interacting.

- Note the time relationship between the event and the use of the medicine. Some reactions occur immediately following the use of a medicine, while others take time to develop.

- Examine the patient thoroughly and do relevant laboratory investigations. Some laboratory tests are useful for the early detection of sub-clinical reactions; others are used to measure severity and/or monitor patient management.

B) De-challenge and re-challenge, if justified:

- Positive de-challenge is an improvement of the reaction after discontinuation of the medicine. It is a strong indicator of a possible association between the medicine and the adverse event. In some cases, there may not be an alternative medicine for the one suspected to have caused the reaction.

- In such cases, when the benefit of using the medicine outweighs the risk of the reaction, it is justifiable to try to treat the patient with the same medicine with extra precautions. This is called re-challenge.

- Positive re-challenge is a recurrence of the reaction that had subsided with the prior de-challenge.

C) Check the pharmacology of the medicine:

- It is important to check whether the reaction observed in the patient is known and documented on the package insert or product monograph submitted during registration. An ADR should be considered when there is no other sufficient explanation.

When in doubt, any suspected adverse event should be reported so that further investigation can be conducted.

2.7 Factors that Predispose Patients to ADRs

When seeking to recognize an adverse event, it is important to note that patients receiving the same medicine or treatment regimen can respond differently based on their individual characteristics. Certain factors tend to predispose some patients to ADRs, including:

A) **Age and gender**: The elderly and the very young are more susceptible to ADRs, and gender also has an effect. Medicines that commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal anti-inflammatory medicines, antihypertensives, psychotropics, and digoxin. All children, and particularly neonates, differ from adults in the way they respond to medicines. Some medicines are likely to cause problems in neonates but are generally tolerated in children.

B) **Concurrent illness**: In addition to the condition being treated, the patient may also suffer from another disease, such as kidney, liver, or heart disease. Special precautions are necessary to prevent ADRs when patients have such concurrent illnesses.

C) **Medicine interactions**: Medicine interactions are among the most common causes of adverse effects. When two or more medicines are administered to a patient, they may either act independently or interact with one another. The interaction may increase or decrease the effects of the medicines and may cause unexpected toxicity. As newer and more potent medicines become available, the number of serious medicine interactions is likely to increase. Interactions may occur between medicines when:

- Medicines compete for the same receptor or act on the same physiological system.
- One medicine alters the absorption, distribution, or elimination of another medicine so that the amount that reaches the site of action changes.
- A medicine-induced disease or a change in fluid or electrolyte balance (physiologic change) indirectly alters the response to another medicine.

D) **Other chemical interactions**: Interactions may also involve nonmedicinal chemical agents, social drugs such as alcohol, traditional remedies, and certain foods.

E) **Genetics:** It is well known that the genetic make-up of individual patients may predispose them to ADRs.

2.8 Pharmaceutical Product Information

The PV system uses multiple sources of information on the safety of medicines and other pharmaceutical products to detect, investigate, manage, and prevent adverse events and mitigate risks. These include:

- Spontaneous reporting of adverse events by HCPs and community pharmacists
- Stimulated reporting of adverse events
- Pre-marketing studies in humans and clinical trials
- Pre-clinical studies
- Active surveillance
- Medical literature, including pharmacy journals
- Alerts from other regulatory agencies and WHO
- Media
- Academia
- Post-marketing surveillance
- The Bangladesh National Formulary
- Medicine newsletters, bulletins, mass media, posters, banners, leaflets, seminar, symposia, workshops, and alerts generated and disseminated by the DGDA
- The DGDA website

CHAPTER 3: ROLES AND RESPONSIBILITIES OF STAKEHOLDERS IN THE NATIONAL PHARMACOVIGILANCE SYSTEM

3.1 Stakeholders

- MOHFW
- DGDA
- Directorate General of Health Services (DGHS)
- Directorate General of Family Planning
- Directorate General of Nursing and Midwifery (DGNM)
- Public health programs under different ministries in Bangladesh
- MAHs/pharmaceutical companies
- WHO-UMC
- HCPs (e.g., doctors, pharmacists, nurses) and professional associations
- Retailers/community pharmacists/pharmacist assistants
- Patients/consumers
- Media
- PV centers in other countries

Ministry of Health and Family Welfare

- Formulate the policies and clinical guidance regarding PV and drug safety in conjunction with the NPC

- Allocate funding to perform PV activities effectively and, when needed, communicate with development partners for stable sources of funding

- Ensure the implementation and roll out of PV activities across the country

Directorate General of Drug Administration

- Receive and review reports from ADRAC and the ADRM Cell

- Maintain confidentiality of the reports

- Make regulatory decisions based on the recommendations from ADRAC and the ADRM Cell

- Communicate regulatory decisions to the MAH and all other relevant bodies through official letters and other means of communication

- Communicate ADRs, medicine safety information, and regulatory decisions to patients and consumers, health care workers, public health programs, and relevant directorates within the MOHFW rapidly and systematically

- Coordinate with other health-related departments and institutions
- Take advice and guidance from the MOHFW with respect to ADE activities
- Collaborate with academic institutions and other countries' PV centers
- Collaborate with WHO-UMC
- Ensure funding from the MOHFW and other organizations (e.g., USAID, European Union, WHO)

Directorate General of Health Services

- Help to ensure the implementation and roll out of PV activities across the country in collaboration with the NPC
- Promote ADE reporting among HCPs and provide training as appropriate
- Communicate active surveillance priorities to the ADRM Cell

Directorate General of Family Planning

- Help to ensure the implementation and roll out of PV activities across the country in collaboration with the NPC
- Promote ADE reporting among HCPs and provide training as appropriate
- Communicate active surveillance priorities to the ADRM Cell

Public Health Programs

- Collaborate and coordinate closely with the ADRM Cell/NPC on PV activities
- Establish a letter of agreement/memorandum of understanding with the ADRM Cell with respect to the collection and processing of ADE reports generated and collected through the program
- Ensure that all ADE reporting forms are submitted to the ADRM Cell
- Set research priorities for active surveillance studies based on the products used in their programs and specific safety concerns
- Train health workers in the appropriate use of the pharmaceutical products in their programs' treatment guidelines and adverse event reporting

Pharmaceutical Manufacturers and Marketing Authorization Holders

- Inform the DGDA (ADRM Cell) of any serious ADR arising from the use of its registered products immediately and no later than one week after the reporting of such adverse reactions
- Ensure that an appropriate PV system is in place within the company to accept responsibility and liability for its product on the market

- All pharmaceutical companies will provide periodic safety update reports (PSURs) to the DGDA every six months for the first two years after marketing an introduced new medicine, and then annually for the next two years.

- Respond promptly and fully to requests for risk/benefit information from the ADRM Cell

WHO-UMC

- Receive and store ADE reports from the ADRM Cell in VigiBase

- Provide guidance, technical support, and training for ADRM Cell staff

- Provide tools, trainings, and access to information systems to enable the ADRM Cell to search the global WHO database

- Monitor signals from the global WHO database (a signal refers to reported information on a possible causal relationship between an adverse event and a drug when the relationship is unknown or documentation is incomplete)

- Communicate signal analyses to the DGDA and conduct a clinical review of the expert analyses

- Facilitate communication among countries

- Develop and maintain WHO Adverse Reaction Terminology and the use of the Medical Dictionary for Regulatory Activities within WHO-UMC to train ADRM Cell staff

- Provide regular feedback and specific services on request

Other Stakeholders

The effectiveness of the national PV system depends on the participation of all actors within the system and their fulfillment of the following roles and responsibilities:

Patients/Consumers

- Report any adverse event that may be associated with the use of pharmaceutical products immediately to their health care provider or directly to the ADRM Cell using the standard ADE reporting form

Health Care Workers

- Detect and appropriately manage adverse events associated with the use of medicines
- Document and immediately report all serious and non-serious suspected adverse events, including unknown or unexpected ADRs, unexpected therapeutic effects, all suspected drug interactions, product quality problems, treatment failures, and medication errors
- Advise patients on drug interactions and possible ADRs
- Prevent the occurrence of medication errors and other avoidable adverse events by using medicines rationally

Retail/Community Pharmacists and Pharmacist Assistants

- Fill out an ADE reporting form when patients/consumers report a suspected adverse event
- Immediately report any suspected ADRs, drug interactions, unusual effects, or product quality concerns to the ADRM Cell by submitting the ADE notification form per the standard reporting procedures
- Advise patients on possible ADRs and drug interactions at the time of dispensing based on the most current information available

PV Focal Points at Health Care Facilities (Government and Private)/Public Health Programs

- Train health care professionals within their respective hospitals on how to recognize and report on adverse events
- Collect all adverse event notification forms from health care professionals in the facility and ensure that these are filled out accurately and completely
- Submit ADE reports to the ADRM Cell as per the standard reporting procedure
- Ensure that all ADE reports are kept confidential and that the identities of patients and reporters and the trade names of the suspected drug are not disclosed
- Take corrective action, as appropriate, in consultation with facility authorities
- Implement recommendations from the DGDA to mitigate risk and prevent adverse events
- Promote rational use of medicines and other health products

CHAPTER 4: METHODS OF PHARMACOVIGILANCE IN BANGLADESH

4.1 Types of Surveillance

Passive Surveillance

Passive surveillance is the most common method used in PV. It covers the entire population and monitors any adverse events that occur in patients. Although it is one of the easiest methods to implement, its weaknesses include a heavy reliance on voluntary or spontaneous reporting, which may not generate a large volume of reports on a specific product or accurate and complete reports. It also provides limited opportunity for comparisons in terms of the target and subject of the surveillance. It does, however, generate signals or alerts that active surveillance can use for further investigations.

Active Surveillance

Active surveillance uses pharmacoepidemiological methods to overcome the limitations of passive surveillance. Based on the signals/alerts generated by passive surveillance, it can be used to identify the focus of surveillance and apply a more rigorous and appropriate methodology to allow causality assessment of the adverse event. Its main weaknesses are its high cost and the limited number of persons it can cover.

Surveillance Program by Pharmaceutical Industries/Marketing Authorization Holders

Once a product is registered and authorized to be on the market, MAHs are requested to continue to monitor the safety of their product through post-marketing surveillance. This surveillance combines the passive and active surveillance methods. Preapproval of post-marketing surveillance studies should be considered to ensure transparency in the study and avoid potential conflicts of interest. MAHs should share all relevant information with the DGDA/ADRM Cell when it becomes available.

4.2 Spontaneous Reporting

Passive surveillance is the primary method used in Bangladesh. Spontaneous reporting, as the main mechanism for passive surveillance, is used to generate signals/alerts of adverse events, which can then be investigated further.

Spontaneous reporting is based on the submission of unsolicited adverse event reports to the ADRM Cell by health care professionals as well as patients and consumers when an adverse event or product quality issue is suspected. It is useful for identifying safety signals of rare adverse reactions, generating hypotheses, and providing critical information that helps characterize patients who are at risk of an adverse event-related use of a specific medicine. It

also can provide information on "real life" experience with a medicine that goes beyond the data obtained from clinical trials.

Spontaneous reports can be used to report both known and unknown or undocumented adverse events, whether they are deemed serious or not. These events could be the consequence of product quality problems (including medical devices), medication errors, drug interactions, or therapeutic ineffectiveness even if there is no obvious relationship between the event and the suspected product. It is important to send spontaneous reports to the ADRM Cell promptly.

Spontaneous reports should also be submitted when a product quality concern is identified on the basis of visual inspection of a product, even if no adverse event has been detected in a patient who has used the product. This is a routine and cost-effective way to monitor product quality. The information on suspected product quality problems is submitted to the ADRM Cell for monitoring safety and is also passed along to other departments within the DGDA so that appropriate actions can be taken with respect to registration, inspection, and quality control (laboratory) testing.

4.3 Benefits to Health Care Professionals, Patients, and the Public of Spontaneous Reporting

HCPs, patients, and the public benefit from reporting through:

- Improved quality of care offered to patients
- Reduced medicine-related problems and better treatment outcomes
- Improved patient confidence in professional practice and potential for increased use of professional health care services
- Improved knowledge
- Access to information on medicine-related problems reported within the country and internationally
- Satisfaction in fulfilling a moral and professional obligation

The submission of spontaneous reports of suspected adverse events should be guided by:

- Prompt reporting
- Immediately reporting any suspected ADR
- Accuracy and completeness

- Completing each notification form accurately and legibly and including as much information as can be collected about the patient, the event, and the product. All of the information requested on the form is important for the causality assessment.

- The minimum information required is:
  - Patient identification
  - Suspected adverse event information
  - Product information
  - Contact information for the reporter

Note that all reporting information is confidential. The name, designation, age, gender, and addresses of both the patient and the physician will not be disclosed.

In some cases—for example, if it is considered an emergency situation or forms are not readily available—a reporter can also contact the ADRM Cell directly by phone or email to inform them about an adverse event. The ADRM Cell will then complete a notification form on the reporter's behalf. Reporters are encouraged to have available all information on the adverse event when they contact the ADRM Cell.

4.4 Protection of Health Care Professionals Who Report Adverse Events

Reporting an adverse event does not necessarily mean that the health care professional who prescribed or dispensed the medicine or who is treating the patient for the adverse event has contributed to or caused the event.

The personal identification information given in the notification form is strictly confidential. The information obtained from reports will not be used for commercial purposes. It is intended to protect patients and improve the rational use of pharmaceutical products.

CHAPTER 5: REPORTING INSTRUCTIONS FOR ADVERSE DRUG REACTIONS

5.1 Suspected Adverse Drug Reaction Reporting Form

See annex C.

5.2 Who Can Report?

Spontaneous reports can be completed by:

- All health care professionals, including doctors, nurses, and pharmacists
- Community health workers
- Patients, consumers, and the general public

5.3 Where and How to Report?

- Patients should report any unexpected deterioration in physical, chemical, or neurological status following the use of a medicine or other health product and any quality concerns about a product to an HCP at a health facility. The provider or facility can properly examine the product, collect all relevant information, and take appropriate action to ensure the patient's safety and well-being.

- If a patient/consumer does not have immediate access to an HCP or facility, he or she can report to a community health worker or directly to the ADRM Cell.

- HCPs should fill out the adverse event notification form for any suspected adverse event or suspected product quality issue and submit it to the PV focal point at their facility.

- If a facility does not have a designated PV focal point or other appointee to receive ADE forms, the HCPs at that facility can report directly to the ADRM Cell.

- PV focal points should collect and collate all notification forms and submit the forms to the ADRM Cell.

- ADE reports can be submitted to the ADRM cell by email, mail, or fax. In emergency cases and when forms are not available, reports can also be made to the ADRM Cell by phone.

5.4 What to Report?

All suspected adverse events and related information (as indicated in the notification form) should be reported through the appropriate channels.

Suspected adverse events include all events related to:

- ADRs (severe and non-severe)
- Product quality
- Medication errors
- Therapeutic ineffectiveness
- Abuse

Suspected product quality issues, which may or may not have resulted in an observable or reported adverse event, include all products that show signs of:

- Discoloration or color change
- Separation of components
- Powdering/crumbling
- Caking
- Molding
- Changes in smell
- Poor packaging
- Poor labeling or mislabeling
- Suspected contamination
- Questionable stability
- Defective components
- Expired shelf life

5.5 When to Report?

Serious adverse events (those that result in death, life-threatening conditions, disability, congenital anomaly, hospitalization, or modification of therapy due to toxicity) should be reported to the ADRM Cell, or PV focal point where available, as soon as they occur or the reporter is notified of them. When those reports are sent to a PV focal point, that person is requested to transmit them to the ADRM Cell without delay. The reporting form for serious adverse events must be filled out and sent to the ADRM Cell within 24 to 48 hours.

Non-serious adverse event reports should be submitted to the ADRM Cell ***no later than one month*** after they were reported to the health facility.

Poor product quality issues should be reported as soon as possible, following the same scheme as that for adverse events.

5.6 What Happens to a Report?

When the ADRM Cell receives an adverse event report, the report is processed according to the following steps:

1. The form is assigned with a unique identification number.

2. The form is reviewed to ensure that all necessary information is included; if any information is incomplete, the ADRM Cell communicates with the report sender directly to obtain the missing information.

3. The ADRM Cell evaluates and investigates serious adverse events (e.g., death) and prepares a case history as soon as possible. It is then sent to ADRAC for review and assessment.

4. The reports are analyzed by ADRAC quarterly, and the causality assessment method is employed for each case. The recommendation is then documented in a standard ADE follow-up form.

ADRs

The reports are analyzed using the WHO methods and classification system to determine causality between the drug and the adverse event that occurred and determine whether it is an ADR.

Suspected Medication Errors

ADRAC will use the US National Coordinating Council for Medication Error Reporting and Prevention Index to categorize medication errors. In addition, the ADRM Cell should monitor the reports and assess the root causes of the problem to identify opportunities to improve medicine use and patient care.

Poor Quality Medicines

The reports should be analyzed by ADRAC and by a team that includes representatives of the DGDA inspection unit, product registration staff, and quality control laboratory.

The reviewed reports and resulting recommendation should then be entered into the WHO VigiFlow database, which is the Bangladesh national database for adverse event management. This database enables the ADRM Cell to keep track of all adverse event reports nationwide.

The information and recommendations obtained from these analyzed reports are submitted to the DGDA to take necessary regulatory action. The ADRM Cell presents the recommendations/analyses of the reports to the Drug Control Committee of the MOHFW as supporting data for any recommendation for withdrawal/suspension or to impose a warning.

Confirmed adverse events may result in the following actions:

- Additional investigations into the use of the product in Bangladesh
- Changes to the package and product information
- Changes in the recommended use of the pharmaceutical product
- Educational initiatives to improve the safe use of the product
- Other regulatory and health promotion interventions that may be warranted, including product withdrawal/recall/suspension from market

The outcome of the notified adverse event will also be communicated directly to the HCP who reported the case. In addition, the DGDA should communicate any potential risk to the public and health care facilities through the media, newsletters, and other channels.

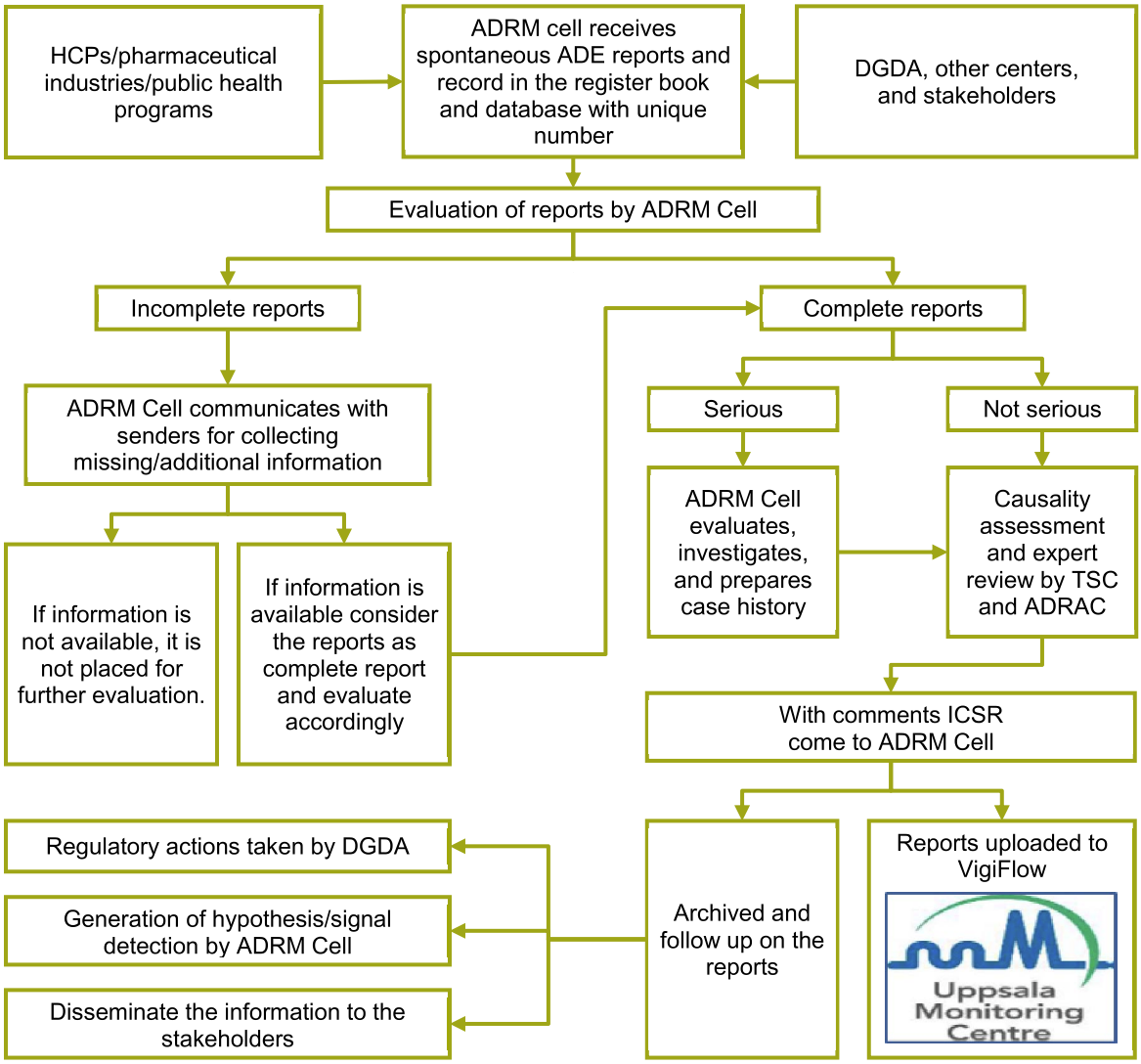

Figure 3. Flow diagram of ADE reporting

5.7 Guidance for Reporting Adverse Event Following Immunization

Immunization is one of the most effective public health interventions to protect individuals and the public from vaccine-preventive diseases and has saved millions of lives. Modern vaccines are safe and effectively protect individuals and public. However, vaccines like other medicinal products, are not free from occasional adverse reactions.

An adverse event following immunization (AEFI) can range from mild to rare and serious. Vaccines rarely cause serious adverse reactions, and common reactions are minor and self-limited. In the majority of serious cases, these are merely coincidental and have no relationship to the vaccine. In others, they are caused by an error in transportation, storage, preparation, or administration of the vaccine.

AEFI Reporting Form

An AEFI reporting form is provided in annex D.

CHAPTER 6: SIGNAL DETECTION AND EVALUATION

The detection and clinical assessment of signals is an important domain of PV. More than one report is generally required to generate a signal, depending upon the seriousness of the event and the quality of the information. In a broader approach, a signal is an alert from any available data source that a drug may be associated with a previously unrecognized hazard or that a known hazard may be quantitatively (more frequent) or qualitatively (more serious) different from existing knowledge. A signal does not imply causation. It can provide preliminary information only for postulating a hypothesis and not for testing it. Analysis of the national PV database can be used for signal detection to be reviewed by the Signal Review Panel to determine any conclusions and make decisions on that report. In the context of spontaneous ADR reporting, a signal is normally a series of cases of similar suspected ADRs reported in relation to a particular drug. Generally, a minimum of three cases is needed.

Various methods have been used to detect signals using spontaneous reporting data. Based on different statistical methodologies—either the Bayesian or Frequentist approach—the basic concept behind these methods is measurement of disproportionality that determines to what extent the number of observed cases differs from the number of expected cases. When all drugs are considered together, large ADR databases tend to have fairly stable proportions of particular reactions over time. A proportion is used as a baseline for comparison to determine what would be expected if there was no signal.

WHO-UMC uses the Bayesian Confidence Propagation Neural Network (BCPNN), while the US Food and Drug Administration uses the Multi-item Gamma Poisson Shrinker methodology. Other disproportionality analysis methods, such as Reporting Odds Ratio and Proportional Reporting Ratio, are employed by some national reporting centers and drug safety research units.

In the BCPNN methodology, computation of the information component (IC) is based on prior and posterior probabilities. According to WHO-UMC, the IC measures the disproportionality in the reporting of a drug-ADR pair in an Individual Case Study Report (ICSR) database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected. However, a review of signals generated with this methodology must be analyzed by clinicians and drug safety experts before a conclusion can be reached.

Each method used for signal detection has its advantages and disadvantages, and no one method can be considered the gold standard. The Signal Review Panel of the NPC identifies and reviews signals from the national database.

CHAPTER 7: RISK MANAGEMENT AND COMMUNICATION

7.1 Risk Management

Risk management is the identification, assessment, and prioritization of risks associated with the use of a pharmaceutical product, followed by the coordinated and economical application of resources to minimize, monitor, and control the probability and impact of adverse events.

Risk management has three inter-related stages:

- Characterizing the safety profile of the medicinal product, including what is known or not known
- Planning of PV activities to characterize and identify new risks and increase knowledge about the safety profile of the medicinal product
- Planning and implementing risk minimization and mitigation activities and assessing the effectiveness of these activities

The overall aim of risk management is to ensure that the benefits of a particular medicinal product exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

The ADRM Cell, ADRAC, and DGDA are responsible for developing and implementing risk minimization strategies based on the information they receive from all available sources, including spontaneous reporting, active surveillance, MAH post-marketing surveillance, and other regulatory authorities and international bodies (e.g., WHO-UMC), on confirmed or potential risks related to the use of certain products. It is through the implementation of these strategies that they protect the population from harm due to use of unsafe, ineffective, or poor quality products.

7.2 Benefit/Risk Assessment

Benefit/risk assessment is an important part of the approval process for registering pharmaceutical products and is a factor in the review process for registration in Bangladesh. However, risks that are identified after authorization through PV activities, including unintended or misuse of products, may alter the original benefit/risk assessment and require another assessment to determine whether the benefits of a product still outweigh the risks.

Based on the incidence of adverse events following the use of a product in Bangladesh and other information available on the product from outside sources, ADRAC and the ADRM Cell may re-assess whether the benefits of the product outweigh the risks given current risk mitigation strategies.

7.3 Risk Management Plans

Risk management plans (RMPs), which outline a set of activities designed to identify, characterize, prevent, or minimize risk related to a product; assess the effectiveness of those interventions; and communicate risk information to HCPs and patients, may be developed and implemented for medicines that have serious confirmed or potential risks, as determined by the ADRM Cell. Public health programs may develop RMPs for specific, high-risk products in use in their programs and are requested to share those plans and their outcomes with the ADRM Cell.

Activities and strategies in the RMP may include:

- Distributing educational materials on the product's safety and use (such as a medication guide for patients and prescribing and dispensing guides/checklists for physicians and pharmacists)
- Distributing a communication guide for HCPs
- Implementing special training programs or certifications for health care professionals
- Restricting the use of the medicine in certain settings (such as dispensing the medicine only in hospitals)

7.4 Product Recall/Withdrawal Based on Benefit/Risk Assessment

If ADRAC determines through its benefit/risk assessment that a product is not safe because the risk it poses to patients outweighs the benefits and the risk cannot be sufficiently mitigated, the committee may recommend to the DGDA that the product be recalled or withdrawn from the market. In such cases, the DGDA will share the decision with the Drug Control Committee, and standard procedures will be followed to remove the product from circulation.

7.5 Risk Communication to Health Care Professionals and Consumers

The ADRM Cell and the DGDA are responsible for communicating information on the safety of medicines and other pharmaceutical products to health care workers and consumers on a regular basis, as well as on an emergency basis when serious risks arise. When an ADR signal is generated, the ADRM cell is expected to communicate this to health care workers and consumers within three weeks and ensure that any required changes to product information, such as labeling, packaging, and package inserts, are made.

The following types of materials are issued by the DGDA via the ADRM Cell, as appropriate:

- Medicine safety alerts when serious or previously unknown safety concerns or information emerges; these may come in the form of a "Dear Health Care Provider" notification

- Medicine bulletins and semi-annual newsletters
- The Bangladesh National Drug Formulary is revised and updated to reflect new information on medicines, including indications, risks, and recommended use, every two to three years
- The registry of approved pharmaceutical products on the market should be revised and updated as soon as possible after a previously registered product is recalled or withdrawn

All alerts, bulletins/newsletters, and lists are available on the DGDA's website (www.dgda.gov.bd)and in hard copy upon request.

The ADRM Cell may also implement public or community education activities to widely distribute new or important information on pharmaceutical products if situations arise that warrant such activities. In addition to actively distributing important information on medicines and medicinal products to mitigate risk and promote appropriate use, the ADRM Cell is responsible for responding to individual requests for information that it receives from health care workers and consumers. Upon receipt of the medicine information request, the ADRM Cell will respond within 15 days.

7.6 Responsibilities of Manufacturers/Marketing Authorization Holders Regarding Risk Management

MAHs for pharmaceutical products in Bangladesh are strongly encouraged to conduct post-marketing surveillance activities and to notify the ADRM Cell of adverse events, particularly serious adverse events, and other product quality issues that come to their attention about their licensed product(s) in Bangladesh. Reports should be submitted with greater frequency during the first two years following authorization because less is known about the safety of newer products on the market.

It is recommended that MAHs follow international standards for serious adverse event notification and report such events to the ADRM cell within 15 days. MAHs are also requested to supply the ADRM cell with any additional information related to suspected serious adverse events that is needed for the purposes of causality assessment and the evaluation of benefits and risks associated with their product.

Based on international standards, manufacturers that are supplying medicines in Bangladesh, both national and multinational, are generally encouraged to have PV structures, systems, and activities in place, including:

- A PV unit and/or designated staff person responsible for PV activities
- PV guidelines, standard operating procedures, and reporting forms

- Ongoing post-marketing surveillance activities, including post-marketing safety studies and risk minimization activities for high-risk medicines and products with unresolved safety profiles
- Risk management plans
- Periodic safety update reports
- A quality monitoring system that includes audits and inspections

In all matters of PV, MAHs are expected to comply with the regulatory decisions of the DGDA that pertain to their products and to take appropriate action.

In cases of products granted conditional marketing authorization in their country of origin, where the benefit-risk balance is such that the immediate availability outweighs the limitations of data availability, specific obligations may be imposed in relation to the collection of PV data, as more intense monitoring of the safety of the product may be needed.

7.7 Medicine Promotion and Advertising

The DGDA regulates promotion and advertising. MAHs are expected to maintain complete and accurate information on their licensed products in Bangladesh and to update it as necessary. MAHs should also comply with good ethical practices and emerging regulations surrounding the promotion and advertising of their products in Bangladesh. Post-marketing surveillance studies related to registered products should be pre-approved by the DGDA and clearly separated from any promotional activities.

7.8 Communication

Communicating safety information to patients and health care professionals is a public health responsibility and is essential for achieving the objectives of PV in terms of promoting the rational, safe, and effective use of medicine; preventing harm from adverse reactions; and contributing to the protection of public health. Communication in a PV program improves patient care and understanding and promotes transparency and accountability. All communications with WHO-UMC will be managed by the NPC, which is also responsible for publishing/communicating any findings from the database to media outlets. Other stakeholders are required to get prior approval from the NPC to publish/communicate any data or information related to the PV program.

Modes of communications used in the PV program include:

Media: This includes press releases and press briefings primarily intended for journalists, who will then relay the information to the public. The head of the ADRM Cell or a designated person is the only person authorized to correspond with the media about the PV program.

Websites: A website is a key tool of communication to reach all stakeholders, including patients and health professionals. The ADRM Cell and DGDA should ensure that all important safety information is available on the websites under their control.

Newsletters: To communicate the findings and regulatory status of medicine in Bangladesh as well as globally to stakeholders, the ADRM Cell publishes the quarterly *Pharmacovigilance Newsletter*. The newsletter is for everyone concerned with the issues of PV and provides practical information and advice on drug safety and information about emerging safety issues.

7.9 Research and Publications

The ADRM Cell is responsible for publishing guidance documents to promote drug safety and working with other directorates, units, and programs within the MOHFW to incorporate drug safety information into their guidance documents.

CHAPTER 8: CAPACITY BUILDING

8.1 Training and Education

The ADRM Cell is responsible for building the capacity of all contributors to the PV system in Bangladesh, including the designated focal points at health care facilities and pharmaceutical companies who are responsible for promoting and managing ADE reporting at their sites and health care professionals who are responsible for reporting. Trainings and workshops are provided to ensure that stakeholders understand adverse event monitoring, identification, management, and reporting. Once trained, the focal persons at health facilities are responsible for providing periodic training for health care professionals at their sites.

Stakeholders need to have confidence and be motivated to report so they can assist the DGDA in its PV mission. Common concerns and barriers to reporting by health care personnel are addressed through capacity building activities. In addition, ongoing clinical guidance to recognize adverse reactions is required. By providing continuous training and consistent communication, HCPs can contribute more effectively to the identification of ADEs, the generation of safety signals, the mitigation of medicine-related risks, and the protection of patient safety.

The ADRM Cell routinely coordinates capacity building activities at national and subnational facilities, such as hospitals, including face-to-face meetings with the physicians, pharmacists, nurses, and other staff to create awareness of ADE reporting procedures. These meetings also ensure the quality of reporting to make the system more efficient.

The Bangladesh National PV Guidelines help equip contributors across the health care delivery system with the necessary skills, knowledge, and attitudes that will enable them to effectively identify, assess, and report ADEs and take appropriate actions to improve medicine safety.

8.2 Information, Education, and Communication Materials

The DGDA and the ADRM Cell provide materials containing critical information to health care professionals, patients/consumers, drug sellers, and manufacturers. These materials on medicine use and safety help people understand the importance of PV and adverse event reporting. Posters, pamphlets, electronic billboards, and radio and television campaigns are some of the ways that the ADRM Cell communicates critical messages and spreads awareness.

CHAPTER 9: TOOLS FOR PHARMACOVIGILANCE

PV activities involve the use of several validated tools to generate and analyze data to guide decisions. In an effort to standardize all PV and medicine information system processes in Bangladesh, the following tools have been developed and adopted for key activities of the ADRM Cell. These tools can be revised as needed.

9.1 Suspected Adverse Event Reporting Form

The Suspected Adverse Event Reporting Form is the official tool for reporting all types of adverse events in Bangladesh, including ADRs, product quality problems, and medication errors (annex C).

9.2 WHO Causality Assessment Scale

Causality assessment is the evaluation of the likelihood that a medicine was the causative agent of an observed adverse event.

An inherent problem in PV is that most case reports concern suspected ADRs. Adverse reactions are rarely specific to the drug, specific diagnostic tests for ADRs are usually absent, and a re-challenge is rarely justified ethically. In practice, few adverse reactions are certain or unlikely; most are somewhere in between these extremes. In an attempt to solve this problem, many systems have been developed for a structured and harmonized assessment of causality, but none of these systems have been shown to produce a precise and reliable quantitative estimation of the relationship. Nevertheless, a causality assessment has become a common routine procedure in PV.

ADRAC and its subcommittee are primarily responsible for performing causality assessments of reports, which will be stored at the ADRM Cell for future activities.

Causality in a report is assessed by using the WHO Causality Assessment Scale, which is a structured tool for determining the likelihood of a causal relationship between drug exposure and adverse events. The four main considerations incorporated in the scale are:

- The association in time between drug administration and event
- Pharmacology, including current knowledge of the nature and frequency of adverse reactions
- Medical or pharmacological plausibility, such as signs and symptoms, laboratory tests, pathological findings, or mechanisms
- Likelihood or exclusion of other causes

Thus, with a causality assessment, we can assess various levels of certainty as to whether a suspected drug has indeed caused a specific ADR.

After adverse event reports are received, the ADRM Cell works closely with ADRAC to determine causality between the reported event and the drug products the patient or consumer has been exposed to (annex E).

9.3 Naranjo Algorithm for Assessing Probability of an ADR

The Naranjo Algorithm, Naranjo Scale, or Naranjo Nomogram is a questionnaire designed by Naranjo et al. to determine the likelihood of whether an ADR is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible, or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of an author's conclusions regarding ADRs (annex F).

9.4 ADR Severity Grading Scale

The severity of a reaction is judged according to the ADR Severity Assessment Scale. The severity of the event will be determined through an evaluation of the ADE reports, medical records, and further discussions with the reporter. Understanding the severity of an adverse event will guide decisions about adverse events that are of importance for further studies. It will also provide information for the education of health care workers on adverse events and their management. In Bangladesh, the WHO toxicity grading scale for determining the severity of adverse events is the official reference for grading the severity of adverse events. This scale categorizes each ADR broadly as mild, moderate, severe, or fatal (annex G).

9.5 Medication Error Assessment Tool

A medication error is defined as an unintended failure in the treatment process that causes, or has the potential to cause, harm to the patient.

Unintended means not intentional; failure means the process has fallen below some attainable benchmark; treatment means all treatments and not just drugs; and treatment process starts with the manufacture of the medicine and includes prescription, transcription, dispensing, administration, and monitoring.

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

Medication errors include:

- Wrong or improper drug
- Inappropriate drug selection (previous history of allergy; medication inappropriate for the patient due to age, clinical status, or underlying pathology)
- Unnecessary medication
- Wrong or improper dose
- Insufficient monitoring of treatment (lack of analytic controls, drug-drug interaction, drug-food interaction)
- Wrong duration of treatment
- Deteriorated drug error
- Wrong administration timing
- Wrong rate of administration
- Wrong dosage form
- Wrong frequency of administration
- Wrong administration technique
- Wrong preparation or manipulation

The National Coordinating Council for Medication Error Reporting and Prevention adopted a medication error index that classifies an error according to the severity of the outcome. It is hoped that the index will help health care practitioners and institutions track medication errors in a consistent, systematic manner.

The index considers factors such as whether the error reached the patient, if the patient was harmed, and to what degree. The medication error index should be used by the ADRM Cell and ADRAC to categorize medication errors detected through spontaneous reporting.

CHAPTER 10: NATIONAL PHARMACOVIGILANCE CENTER AND WHO-UMC COLLABORATION

To participate in the WHO Program for International Drug Monitoring, the NPC collaborates with WHO-UMC. The following software tools are provided by WHO-UMC to achieve the objectives of the PV program in a more efficient way.

VigiFlow

VigiFlow is web-based ICSR management system that is designed for use in national centers in the WHO Program for International Drug Monitoring. VigiFlow is based on and compliant with the ICH E2B standard and is a trademark of the UMC and maintained by the UMC in Uppsala, Sweden. It is a simple, fast, and secures web-based solution that improves all aspects of ADR reporting. ICSR data can be manually entered into VigiFlow with support from the latest versions of terminologies, such as WHO-DD, WHO-ART, and MedDRA. Once a report is complete and committed, the first version of the ICSR is generated and automatically saved in VigiBase (the WHO global ICSR database). It is easy to retrieve reports to amend the content or add follow-up information.

VigiBase

VigiBase is the WHO global ICSR database and consists of reports of adverse reactions submitted by member countries since 1968. The VigiBase data resource is the largest and most comprehensive in the world and it is developed and maintained by the UMC on behalf of WHO. VigiBase includes linked databases (WHO-ART/MedDRA, WHO ICD, and WHO-DD) that contain medical and drug classifications. It is a computerized PV system in which information is recorded in a structured, hierarchical form to allow for easy and flexible data retrieval and analysis. Its purpose is to provide evidence from which potential medicine safety hazards may be detected.

VigiSearch

VigiSearch is a powerful search tool that provides access to all case reports in VigiBase. VigiSearch allows for report searching across multiple drugs and ADRs simultaneously and incorporates a range of filters. Drugs can be searched on a generic substance level or by a specific trade name. VigiSearch also supports browsing the ATC structure. The results can be accessed on an overview level and viewed from a number of aspects (e.g., country, year, reaction term) or at the level of individual case report. For members of the WHO program, VigiSearch enables an international comparison of national spontaneous reporting data and gives access to ADR information on drugs not yet on the national market.

VigiMine

VigiMine was launched in 2008 as a new component of VigiSearch. VigiMine gives access to statistical data on all drug-ADR pairs reported to VigiBase. VigiMine allows results to be filtered based on a number of statistical criteria and stratified by age, gender, country, and year of reporting. VigiMine also shows the change in the statistical values over time.

VigiMine data can be compared with statistics in a national database and are also an independent aid in the detection of new signals of drug safety issues.

VigiMed

VigiMed is a web-based forum for those working at national centers in the WHO program to have easy access to safety concerns in other countries, check regulatory status, and expedite the sharing of drug information. VigiMed is part of the UMC collaboration portal.

VigiLyze

VigiLyze is a powerful search and analysis tool that provides access to more than 8 million ICSRs from more than 100 countries in VigiBase. VigiLyze includes data on conventional medicines, traditional medicines, and biological medicines, including vaccines. VigiLyze can provide a global, regional, or national view of an ADR to identify or monitor international patient safety data. It can be useful to find supporting evidence while assessing Bangladeshi case reports or to see how Bangladeshi data support global PV. VigiLyze enables international comparisons with national spontaneous reporting data and gives access to ADR information on drugs that are not yet on the national market. Results from VigiLyze are instantly available as graphics and in tabular format.

CHAPTER 11: MONITORING AND EVALUATION

The effectiveness of the national PV system and all related activities need to be continually assessed through an established monitoring and evaluation strategy. The ADRM cell has selected key performance indicators to regularly calculate, analyze, and evaluate reports and use them to improve the system and ensure patient safety.

The selected indicators include:

- Number of ADR reports received in the past year
- Percentage of reports received that were entered in the national database within the stipulated time
- Percentage of reports subjected to causality assessment in the past year
- Percentage of local pharmaceutical manufacturers with a functional PV system
- Number of focal points designated and trained
- Number of health care professionals trained on PV
- Number of medication errors detected
- Number of treatment failures detected
- Number of product quality problems detected
- Number of products withdrawn from the market as a result of ADE reporting (passive and active surveillance)
- Percentage of health facilities that have submitted ADE reports
- Percentage of health care workers who have submitted ADR reports

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ANNEX A. FORMATION OF ADVISORY COMMITTEE

1	Director General, DGDA, Dhaka	Chair
2	Director (MIS), DGHS, Dhaka	Member
3	Director (Hospital), DGHS, Dhaka	Member
4	Director (Primary Health Care), DGHS, Dhaka	Member
5	Dean, Pharmacy Department, Dhaka University, Dhaka	Member
6	Professor, Medicine Department, Dhaka Medical College, Dhaka	Member
7	Professor, Pharmacology Department, Bangabandhu Sheikh Mujib Medical University, Dhaka	Member
8	Professor, Skin and VD Department, Sir Salimullah Medical College, Dhaka	Member
9	Professor, Pathology Department, Dhaka Medical College, Dhaka	Member
10	Member, Ministry of Health and Family Welfare, Dhaka (not below the rank of deputy-secretary)	Member
11	Child Specialist, Shihu Hospital, Dhaka	Member
12	Representative, Bangladesh Medical Association , Dhaka	Member
13	Representative, Bangladesh Pharmaceuticals Society, Dhaka	Member
14	Representative, Institute of Epidemiology Disease Control and Research, DGHS, Mohakhali, Dhaka	Member
15	Representative, Bangladesh Aushad Shilpa Samity, Dhaka	Member
16	Representative, Bangladesh Consumers Association, Dhaka	Member
17	Deputy Director, DGDA, Mohakhali, Dhaka	Member-Secretary

ANNEX B. CLASSIFICATION OFL

Error/Harm	Category	Definition
No Error	Category A	Circumstances or events that have the capacity to cause error
Error, No Harm	Category B	An error occurred but the error did not reach the patient (an "error of omission" does reach the patient)
	Category C	An error occurred that reached the patient but did not cause patient harm
	Category D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
Error, Harm	Category E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
	Category F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
	Category G	An error occurred that may have contributed to or resulted in permanent patient harm
	Category H	An error occurred that required intervention necessary to sustain life
Error, Death	Category I	An error occurred that may have contributed to or resulted in the patient's death

Definitions
Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom
Monitoring: To observe or record relevant physiological or psychological signs
Intervention: May include change in therapy or active medical/surgical treatment
Intervention Necessary to Sustain Life: Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

Subclassification of ADRs

Sl no	Classification	Sub classification	Details
1.	Principal types of ADRs	Type A (Augmented): Related to the principal action of the medicine	• Will likely occur in most people • Dose related • Pharmacodynamic effects • Common • Management reduces incidence
		Type B (Bizarre): Not related to the principal action of the medicine/drug	• Will likely occur only in some people • Not part of the normal pharmacology of medicine • Not dose related • Unpredictable • Includes idiosyncrasy and drug allergy • Accounts for most drug fatalities
2.	Subordinate type	Type C (Continues)	• Reaction due to long-term use
		Type D (Delayed)	• Abrupt discontinuation (e.g., rebound adrenocortical insufficiency)
		Type E (Ending of use)	• Treatment failure

ANNEX C. SUSPECTED ADVERSE EVENT REPORTING FORM

Suspected Adverse Event Reporting Form

Identities of reporter, patient, institution, and product trade name(s) will remain confidential

ADR report number_____ (For office use only)
Date received_____

A. PATIENT AND HOSPITAL INFORMATION

Name of health facility (if applicable) _____

Patient name_____Registration #_____

Patient address

_____

_____

Contact number_____

Age_____ Weight (kg)_____ Height (cm)_____ Gender ☐Male ☐Female

Pregnant ☐Yes ☐No ☐Unknown ☐Not applicable

B. SUSPECTED ADVERSE EVENT INFORMATION

Type of event	Suspected product
☐Adverse drug reaction ☐Product quality problem ☐Medication error	Brand name_____Generic name_____ Indication_____ Start Date _____End Date _____ Dose [strength, unit]_____Dosage Form_____ Frequency _____ Batch/Lot number_____Manufacturer_____

Describe event including relevant tests and laboratory results:

Date the event started	Date the event was reported	Date the event stopped
_____	_____	_____

Was the adverse event treated? ☐Yes ☐No
If yes, please specify

Action taken after the reaction	Did reaction subside after stopping/reducing the dose of the suspected product?
☐Dose stopped ☐Dose reduced ☐No action taken	☐Yes ☐No ☐Not applicable Did reaction appear after reintroducing the suspected product? ☐Yes ☐No ☐Not applicable

Seriousness of the adverse event:	**Outcomes attributed to the adverse event:**
☐ Not serious ☐ Hospitalization or prolongation of hospitalization ☐ Disability or permanent damage ☐ Congenital anomaly/birth defect ☐ Life threatening ☐ Other serious ☐ Death	☐ Recovered ☐ Recovered/resolved with sequela ☐ Not recovered ☐ Unknown ☐ Fatal (date of death: _____)
Other relevant history (including pre-existing medical conditions, allergies, pregnancy, smoking, alcohol use, liver or kidney problems, hypersensitivity, history of ADRs, etc.):	

C. OTHER CONCOMITANT PRODUCT INFORMATION

	Product 1	Product 2	Product 3	Product 4
Brand name				
Generic name				
Indication				
Dosage form				
Route				
Dose				
Frequency				
Date started				
Date stopped				

D. REPORTER INFORMATION

Name_____**Designation**_____

Address

_____

_____

Email address_____

Mobile phone_____**Land phone**_____

Signature_____**Date of submission**_____

General instructions for completing the form

- Detailed information about each field can be found in the instructions.
- Fill in as much information as possible. Do not leave anything blank. If unknown, write "unknown" or "n/a" if not applicable.

- What to report:
  - Serious adverse drug reactions
  - Unknown or unexpected ADRs
  - All suspected reactions to new drugs
  - Unexpected therapeutic effects
  - All suspected drug interactions
  - Product quality problems
  - Treatment failures
  - Medication errors

Send all completed forms to:
Directorate General of Drug Administration
Aushad Bhavan, Mohakhali, Dhaka-1212, Bangladesh
Tel : 8802 9880803, 9880864, 9880897, 9880924, Fax : 8802 9880854,
E-mail : dgda.gov@gmail.com

ANNEX D. AEFI REPORTING FORM

(Translation of AEFI Report Form)

AEFI Report Form

Name of the Child/Women : ..... Male/female (for child).....

Date of Birth: ....(dd/mm/yy) or Age: .....Years

Name of Mother:.....Name of Father: .....

Name of Husband (if applicable): .....Gaurdian's phone no.....

Address: House/ GR No. .....Mahalla/ Village:.....Ward.....

Union.....Upazila/Municipality/Zone.....District/CC.....

Type of AEFI (√ mark)

1. ____Abscess at the injection site	6. ____BCG Lymphadenitis
2. ____High Temperature > 101° F	7. _____Unconsciousness
3. _____ Severe local reaction	8._____ Fainting
4._____ rash	9. _____Others (specify) _____
5. ____Convulsion	

Put √ mark where applicable and write date

☐ Hospitalized; date---------- ☐ Death: date ----------

Immunization Information:

Suspected vaccine for occurring AEFI (√ mark/write) BCG / Pentavalent / OPV / PCV / MR / Measles 2nd dose / TT / other (specify).....
Date of vaccine received:.....(dd/mm/yy)
Date of onset of AEFI: .....(dd/mm/yy)
Name and address of vaccination centre: .....

AEFI is reported from: ☐ Community ☐ Health Facility

Name of Reporter:.....Signature .....

Designation & Organization :.....Date.....

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ANNEX E. WHO CAUSALITY ASSESSMENT CRITERIA

Sl No.	Causality Assessment Criteria	Details
1	Certain	• Clinical event or lab test abnormality with plausible time relationship to drug intake • Cannot be explained by concurrent disease or other drugs/chemicals • Response to de-challenge plausible • Event must be definitive pharmacologically/immunologically • Positive re-challenge, if performed
2	Probable/Likely	• Clinical event or lab test abnormality with reasonable time relationship to drug intake • Unlikely to be to concurrent disease, drugs/chemicals • Clinically reasonable response to withdrawal (de-challenge) • Re-challenge not required
3	Possible	• Clinical event or lab test abnormality with reasonable time relationship to drug intake • Could also be explained by concurrent disease or other drugs or chemicals • Information on drug withdrawal may be lacking or unclear
4	Unlikely	• Clinical event or lab test with improbable time relationship to drug intake • Other drugs, chemicals, or underlying disease provide plausible explanations
5	Inaccessible/Unclassifiable	• Insufficient/contradictory evidence that cannot be supplemented or verified
6	Conditional/Unclassified	• More data are essential for proper assessment or additional data are under examination

ANNEX F. NARANJO ALGORITHM FOR ASSESSING PROBABILITY OF AN ADR

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

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

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

ANNEX G. ADR SEVERITY GRADING SCALE

Sl No.	Severity Grading Scale	Details
1	MILD	• The ADR requires no change in treatment with the suspected drug • The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed and no antidote or other treatment is required • No increase in length of stay.
2	MODERATE	• The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed and/or an antidote or other treatment is required • Increases length of in-patient stay by at least one day • The ADR is the reason for in-patient admission
3	SEVERE	• The ADR requires intensive medical care • The ADR causes permanent harm to the patient
4	FATAL	• The ADR either directly or indirectly leads to the death of the patient

NATIONAL GUIDELINE PHARMACOVIGILANCE SYSTEM IN BANGLADESH