Authorized Personnel Only

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Revision History

Revision	Date	Modified by	Reason for change
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1. Introduction

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem” (WHO Pharmacovigilance). More recently, the definition has been expanded to include adverse effects and problems related not only to drugs but also to vaccines, medical devices, biologicals, blood products, herbal drugs, and traditional and complementary drugs. PV secures the health of the public by ensuring the safety, effectiveness, and quality of drugs and other health products.

Because of the need to monitor the safety of drugs, particularly in resource-constrained countries like Bangladesh, the Directorate General of Drug Administration (DGDA), under the Ministry of Health and Family Welfare (MOHFW), introduced a program to monitor adverse drug events. As a result, the DGDA has been declared the National PV Center for Bangladesh. The responsibility for implementation and oversight of the center has been given to the Adverse Drug Reaction Monitoring Cell (ADRMC), which was officially established in 2013. In the same year, the Adverse Drug Reaction Advisory Committee (ADRAC) was also established by the MOHFW as an independent advisory body.

ADRAC is an independent body that comprises clinicians, academicians from medical college hospitals, representatives from the Bangladesh Medical Association, Bangladesh Association of Pharmaceutical Industries, Consumer Association of Bangladesh, and pharmaceutical experts from Bangladesh. ADRAC works in conjunction with ADRMC to provide technical guidance for PV activities, evaluate adverse drug event (ADE) reports, and make recommendations for regulatory decisions and actions by the DGDA. In addition, a technical subcommittee has been established within ADRAC to assist in the evaluation of ADE reports and perform causality assessments. ADRAC provides final comments on the recommendations.

Because of a functioning ADRMC and ADRAC, Bangladesh has become the 120th full-member country of WHO’s Uppsala Monitoring Centre (WHO-UMC). Bangladesh is now part of this vital network promoting PV throughout the world. This membership will enable Bangladesh to continue to monitor ADEs, maintain international standards of

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reporting, and increase in-country PV awareness through data sharing with other member countries.

2. Purpose

The purpose of this SOP is to describe the procedures and activities of ADRAC in the review and evaluation of ADE reports received by ADRMC. It is applicable to all ADE reports received for medicinal products, including Unani, Ayurvedic, herbal, homeopathic and biochemical systems of drugs, vaccines, and biological products.

3. Scope

This procedure is applicable to all ADRAC members. It describes the processes used by members to review and evaluate ADE reports received from health care providers and ADRMC.

4. Definitions

- **Adverse drug event (ADE):** Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction (ADR):** A response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function.

- **Serious adverse drug event (SADE)**: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- **Causality assessment**: The evaluation of the likelihood that a drug was the causative agent of an observed adverse reaction. Causality assessment is usually made according to established algorithms.

- **Vigiflow**: A complete, web-based, individual case-safety report management system created and maintained by WHO-UMC. It can be used as the national database for countries in the WHO program because it incorporates tools for report analysis and facilitates sending reports to VigiBase, the WHO drug database. The DGDA has adopted VigiFlow as their national database.

5. Roles and Responsibilities of ADRAC and its Technical Subcommittee

1) Assess the causal relationship between a given medicine or health product and reported ADEs.
2) Evaluate, analyze, and make recommendations to the DGDA on appropriate regulatory actions and effective ways of communicating information on medicine risk to health professionals, marketing authorization holders, and the public.
3) Make recommendations and provide advice to the DGDA and MOHFW about implementation of the PV program and approaches on how to promote the safe and effective use of medicines by health care professionals and the public.
4) Review mechanisms for collecting ADE information and advise ADRMC on improvement strategies for processing them.
5) Assist ADRMC and DGDA to develop and implement risk minimization strategies to address drug safety concerns.

It is the responsibility of the Director General (DG) of DGDA to ensure that this procedure is adhered to by ADRAC.

6. Activities and Procedures of ADRAC

No.	Activities	Description
1	Collection of ADE reports and data entry	• ADRMC receives ADE reports from public and private hospitals, including pharmaceutical manufacturers, every month through the PV focal person assigned to the facilities who collects the reports • ADE reports are also received by ADRMC as an in-house database, which is normally shared by the PV focal person of the health care facility that maintains the database

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No.	Activities	Description
		• ADE reports should be sent monthly by health care facilities and pharmaceutical manufacturers; in the case of fatal/serious cases, reports should be sent within 48 hours • ADRMC requests that health care facilities notify them even if there are no ADE reports (NIL) for the month • In an emergency situation or if the ADE form (annex 1) is not readily available to the reporter, ADRMC can be contacted directly by phone or email to inform them of the ADE; ADRMC can then complete the form on their behalf • Standard ADE report is available in a fillable pdf format for download at the DGDA website at www.dgda.gov.bd Alternative reporting methods: • Telephone: A specific member of ADRMC serves as the contact person who can be called directly and take the report on the ADE form • E-mail: Consumers can directly send ADE reports to DGDA at dgda.gov@gmail.com • Fax: ADE reports may be sent by fax to + 8802 9568166 Data entry • ADRMC/data entry operator maintains in-house Excel spreadsheet that contains all relevant information from ADE reports received, which allows for easy summarizing and sorting of the data
2	Meetings and evaluation of ADE reports by subcommittee and ADRAC	• Subcommittee meetings should be held every two months to perform causality assessment (SOP page 9) on ADE reports and to record their recommendations using the standard follow-up form (annex 2) • ADRAC meetings should take place every four months to review and validate recommendations made by the subcommittee
3	ADRMC actions on ADRAC recommendations	• ADRMC revisits and follows up on comments and recommendations made by the subcommittee and ADRAC • If needed, ADRMC may collect further information/references

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No.	Activities	Description
		from the reporter and, if necessary, inform and discuss with the focal persons of hospitals and pharmaceutical manufacturers to meet with ADRMC for further discussion
4	Data upload and analysis in WHO VigiFlow and submission to Vigibase	• ADRMC uploads all ADE reports evaluated by ADRAC into VigiFlow and completed reports are sent to VigiBase for WHO-UMC analysis within two weeks of ADRAC meeting • ADRMC should perform in-house data analyses of the ADE reports using Excel spreadsheet and WHO VigiLize tool
5	PV newsletter and bulletin publications	• ADRMC should publish a PV newsletter every six months • The newsletter can provide information on PV activities, drug safety data, and RMU • The newsletter should be shared with ADRAC before finalizing
6	DGDA makes data-driven regulatory decisions	• The conclusion drawn from the in-house data analyses should be used to support the causality assessment and recommendations made by ADRAC • Based on the reports and recommendations, DGDA should be able to generate hypothesis or detect a signal with regard to probable ADEs, if any • ADRMC, through the DGDA, should present the recommendations/analyses of the ADE reports to MOHFW's Drug Control Committee as supporting data for any recommendation for withdrawal or to impose any warning in extreme cases of any drug • DGDA should take regulatory action on any specific drug safety issue • DGDA should communicate any potential risk to the public and health care facilities through the media, newsletters, etc.

It should be noted that all reporting information is confidential. The name, designation, age, gender, address of both the patient and physician, and the trade name of the product are not to be disclosed.

The ADRMC, ADRAC, and the DGDA are responsible for developing and implementing risk-minimization strategies based on the information they receive from all available sources, namely all spontaneous and active reporting systems in the country. In

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addition, ADRMC and ADRAC should engage research partners and academic institutions to expand PV in the country and to establish support groups, such as signal detection and assessment group; and perform descriptive studies and clinical review, etc.

7. Reporting Instructions

a. Who should report

Spontaneous reports should be completed by

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

b. Where and how to report

- Patients should report any unexpected deterioration in physical, chemical, or neurological status following the use of a drug or other health product or any quality concern about a product they have received or used to a health care provider at a health facility.
- If a patient or consumer does not have immediate access to a health care provider or facility, they can report to a community health worker and health care providers (physicians, pharmacists, and nurses or directly to the ADRMC).
- Health care providers should fill out the DGDA standard ADE form (annex 1) for any suspected adverse event or suspected product quality issue and submit it to the PV focal point person at their facility.
    - If a facility has not designated a PV focal point person or other appointee to receive ADE reports, health care providers at the facility can report directly to the ADRMC.
- PV focal point persons should collect and collate all ADE reports and submit to the ADRMC.
- ADE reports can be submitted to the ADRMC by email, post, or fax. In an emergency or if forms are not available, reports can also be made to the ADRMC by phone.

c. What to report

- All suspected adverse events
- Product quality issues
- Medication errors
- Therapeutic ineffectiveness, abuse, and related information

d. When to report

- SAEs that result in death, life-threatening conditions, disability, congenital anomaly, hospitalization or modification of therapy due to toxicity should be reported **within 48 hours** to the ADRMC or PV focal point, if available, as soon as they occur or the reporter is notified of them.

    - The notification form for SAEs must be filled out within 24 hours and sent to the ADRMC within 48 hours from the time of notification.

- Non-SAE reports should be submitted to the ADRMC 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 the adverse events mentioned earlier.

8. WHO Causality Assessment

The WHO causality assessment system has been developed in consultation with the national PV center participating in the program for international drug monitoring and is meant as a practical tool for assessment of case reports. It basically takes into account the drug and the adverse reaction, clinical–pharmacological aspects of the case history, and the quality of the documentation of the observation. There is no universal scale for describing or measuring the severity of adverse reactions as assessment is largely subjective, however, ADRMC made a decision to adopt the WHO causality assessment criteria to evaluate Bangladesh ADE reports. Therefore, ADRAC evaluates each ADE report by using the WHO criteria to make recommendations.

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9. Categories of WHO Causality Assessment

No.	Categories	Features
1	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 • Rechallenge satisfactory, if necessary
2	Probable/ likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
3	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
4	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
5	Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper assessment needed • Additional data under examination
6	Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory

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10. References

- SOP 11, Adverse Event Reporting Procedures; http://www.dgda.gov.bd/index.php/2013-03-31-04-35-57/instructions-for-completing-ade-reporting-form/112-ade-form-instructions-revised-10-feb-14
- The use of the WHO-UMC system for standardised case causality assessment; http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf
- Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (August 25, 2007); http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/clinical-safety-data-management-definitions-and-standards-for-expedited-reporting.html
- Essential medicines and health products: Pharmacovigilance (WHO); http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

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Addendum 1. 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	Brand name_____ Generic name_____
☐Product quality problem	Indication_____
☐Medication error	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	☐Yes ☐No ☐Not applicable
☐Dose reduced	**Did reaction appear after reintroducing the suspected product?**
☐No action taken	☐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
105-106, Motijheel Commercial Area, Dhaka-1000, Bangladesh
Tel: 8802 9556126; Fax: 8802 9568166; Email: drugs@citech.net

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Addendum 2. Standard Follow-Up Form

ADR report number_____ (For office use only)
Date received_____

FOLLOW UP

Assessment Date _____

Assessment Outcome

☐Certain ☐Probable ☐Possible ☐Unlikely ☐Unclassifiable

Recommendation by ADRAC Sub-committee

Action recommended by ADRAC

Action(s) Taken

Action Date _____