# Islamic Republic of Afghanistan
# Ministry of Public Health
## National Medicine and Healthcare Products Regulatory Authority

# Standard Operating Procedure for Causality Assessment of Suspected Adverse Drug Reaction Reports

March 2017

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| **Title:** | Standard Operation procedure For Causality Assessment of Suspected Adverse Drug Reaction Reports | | |
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## 1. Purpose

This standard operating procedure (SOP) provides step-by-step instructions for conducting causality assessments for suspected adverse drug reactions (ADR) reported through the Afghanistan national spontaneous reporting system in accordance with the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment System. This SOP helps determine if a drug is causally associated with a reported adverse event.

## 2. Background

Not all adverse events that happen to patients are causally related to drugs (or vaccines). The aim of causality assessment is to determine the likelihood that a particular drug is responsible for an adverse event. Causality assessment is an important, routine component of pharmacovigilance, contributing to better evaluation of the risk-benefit profiles of medicines. The most widely used method for causality assessment is the WHO-UMC Causality Assessment System.[1] This method takes into consideration the pharmacological properties of the suspected drug as well as the quality of the documentation included in the ADR Reporting Form. The WHO-UMC Causality Assessment System groups causality into one of six categories based on a number of assessment criteria. In practice, most adverse reactions are categorized as 'possible' or 'probable' and few are definitely categorized as 'certain' or 'unlikely.' While there are limitations to any approach to performing causality assessment, the WHO-UMC Causality Assessment System is a practical tool that reduces the inconsistency between those who evaluate ADR reports, categorizes the likelihood of a relationship, and improves the scientific evaluation of ADRs.

## 3. Responsible Person

Causality assessment should be completed by clinician members of the Pharmacovigilance Department-Medicine Safety Committee who are trained in causality assessment, i.e., completed the "Adverse Drug Reaction Causality Assessment Training Module."

## 4. Overview of the Causality Assessment Process

The causality assessment process involves reviewing ADR Reporting Forms (Annex 1) to determine possible factors that might link the reported adverse event to the suspected drug as well as to determine factors that might rule out a link to the suspected drug. After causality assessment is determined, this information should be recorded onto The Review Report of Suspected ADR Case Form (Annex 2) that is forwarded to the Medicine Safety Committee (MSC) along with a copy of the ADR Reporting Form.

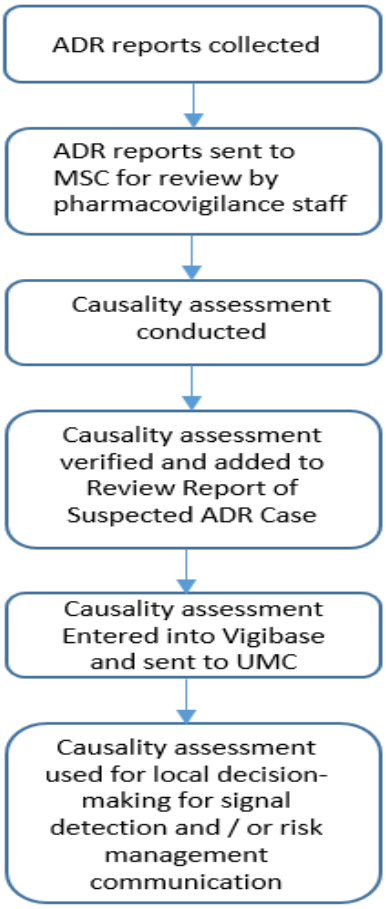
The following is an overview of the process of performing causality assessment:

1. Review the information recorded onto the ADR Reporting Form.
2. Conduct causality assessment either by a member of the Pharmacovigilance Department or by a subcommittee of the MSC.
3. After a causality assessment is completed this information should to be verified by the MSC.
4. Verified causality assessments will be added to the Review Report of Suspected ADR Case Form and recorded as a part of data entry into VigiBase.
5. Use of the results from causality assessment for relevant, local decision-making as it pertains to signal detection and/or risk management and communication, as appropriate.

Causality assessments should follow this general process as outlined in the flow chart below.

[1] Uppsala Monitoring Center. The Use of the WHO-UMC System for Standardised Case Causality Assessment. http://who-umc.org/Graphics/24734.pdf Accessed 29 May 2016.

# Overview of Causality Assessment Process




## 5. Principles for Conducting Causality Assessment

### 5.1. Key Considerations

When conducting a causality assessment, the assessor needs to consider if the drug could in fact caused the adverse drug reaction. The assessor should start by considering:

1. Can the drug cause the adverse drug reaction, based on known pharmacological properties of the drug?
2. Has the drug caused the adverse drug reaction in this person based on the information provided on the ADR Report Form?

These questions are crucial because there could be other factors such as the patient's disease state, other medications, or chance events that may have caused the adverse event.

1. **Can the drug cause the adverse drug reaction?**

   This can be determined by consulting the following to determine the known pharmacological properties of the suspected drug:

   - Medical and pharmacological references books as mentioned below:
     - Afghanistan National Formulary, MoPH/GDPA, 2015
     - National Standard Treatment Guidelines for the Primary Level, MoPH/GDPA, 2015
     - Current Medical Treatment and Diagnosis
     - Harrison's Principles of Internal Medicine
     - Nelson Textbook of Pediatrics
     - Current Treatment and Diagnosis of Obstetrics & Gynecology

- Martindale, the compete drug reference
- British National Formulary (BNF)
- http://www.webmd.com

➢ Product information insert
➢ Current literature (clinical trial reports, research papers, etc.) and drug bulletins.

**2. Has the drug caused the adverse drug reaction in this patient?**

This can be determined by considering information recorded onto the ADR Reporting Form:

➢ Time – the time interval between administration of the drug and the adverse event, e.g., did the drug exposure precede the adverse event?
➢ Medical plausibility – clinical characteristic signs, symptoms, laboratory tests and pathological findings.
➢ Likelihood or exclusion of other causes.

### 5.2. Relevant data from the ADR Reporting Form for conducting causality assessment

**1. Reasonable time relationship**

Assessors should examine the dates and times recorded in the ADR Reporting Form to determine when the drug was administered/taken by the patient and when the suspected ADR occurred. This step helps establish a time relationship with the drug can help causally link if the drug did in fact cause an ADR or if it was due to another factor. For example:

➢ If the suspected ADR occurred prior to the administration of the drug, the probably of the suspected ADR being connected to the drug is lower. Other factors should be investigated.
➢ If the suspected ADR emerged after administration of the drug, the probability of the suspected ADR being connected to the drug is higher.

**2. Type of reaction**

Assessors need to check what type of reactions was noted on the ADR Report Form. From this information they need to determine if there is a relationship to the drug while ruling out other causes. For example:

➢ **Pharmacology -** is the drug known to have adverse effects as described in the ADR Reporting Form?
  - Does the mechanism and pharmacologic effects related to the drug able to cause the types of adverse reactions reported?
  - Does the medical literature or do drug bulletins contain reports of the ADRs?
➢ **Medical plausibility –** is the patient's disease or health status a potential cause of the ADR?
  - Is the current disease state that is being treated known to cause these types of adverse reactions?
  - Are complications related to the disease being treated known to cause these types of adverse reactions?
➢ **Likelihood or exclusion of other causes -** are there other factors that could cause these reactions?

### 5.3. General steps for conducting causality assessment

Conducting a causality assessment generally follows these procedures:

1. Framing a causality question to help assessors focus their efforts while determining causality.
2. Reviewing the ADR Report Form.
3. Utilizing the WHO-UMC Causality Assessment System to classify causality assessment.

➢ Framing a causality question
  - From the ADR Report Form, the signs, symptoms, diseases, and/or laboratory findings should be reviewed.
  - Next a causality question should be framed according to the format:
    Has drug "name of drug" caused "name of adverse event"?
    Example: Has the drug "**Penicillin"** caused "**anaphylaxis**"?
➢ Reviewing the ADR Report Form
  - The staff member should review the ADR reporting form to consider all possible factors that may be associated with the suspected adverse event.

- Important considerations outlined in section 6.1 should be reviewed and analyzed.
- Specific procedures are outlined in section 7.

➢ Utilizing the WHO-UMC Causality Assessment System to classify causality
- As noted in Section 6, the WHO-UMC Causality Assessment System provides a tiered categorical system for determining causality.

# 6. UMC-WHO Causality Assessment System

## 6.1. Overview

The WHO-UMC Causality Assessment System is a tiered categorical classification system for causality assessment. It is based on the availability of certain types of data that can increase or decrease the probability of linking a suspected ADR with a drug or determining that a ADR report is not assessable due to factors such as insufficient information.

Different factors can help increase or decrease the probability of linking suspected ADRs with a drug including:

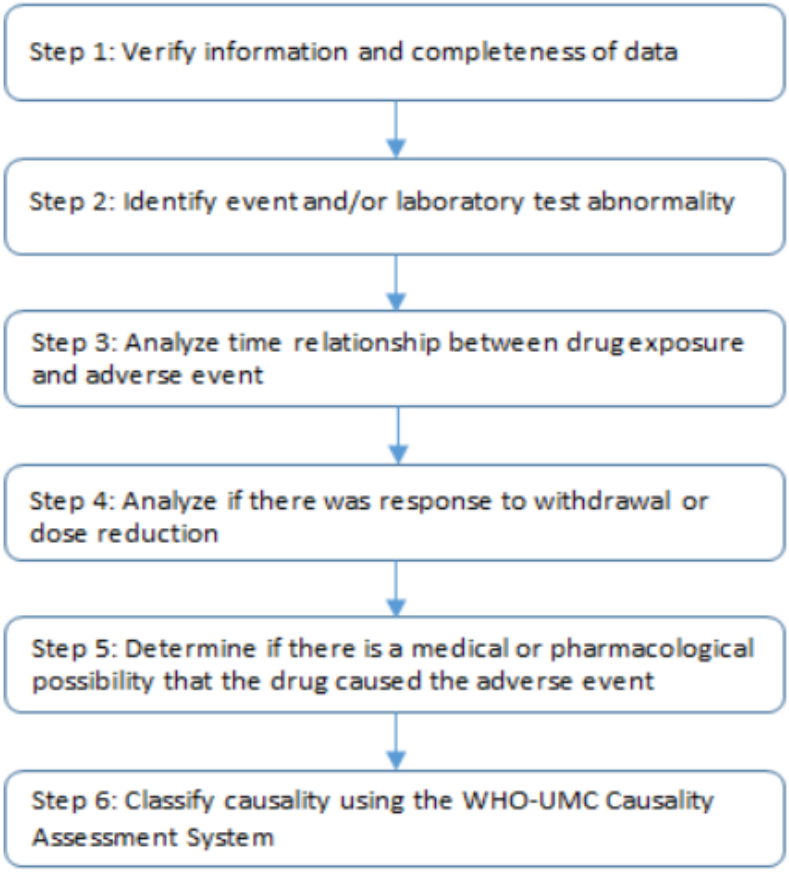
- Characteristics of the adverse event and/or laboratory test abnormality
- Time relationship between the adverse event and exposure to drug
- Response to withdrawal of the drug
- Response to dose adjustment of the drug
- Re-challenge to drug, if appropriate or happened inadvertently
- Medical or pharmacological properties of the drug
- Consideration of other causes of the adverse event
- Completeness of data contained in the ADR Report Form

## 6.2. Causality categories

**Table 2. WHO-UMC Causality Assessment System categories**

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

## 7. Causality Assessment Flowchart




## 8. Procedures for Conducting Causality Assessment

1. Verify patient info, suspected adverse drug reaction along with completeness of data.
    - The assessor reads the ADR Report Form to become familiar with the case.
    - The assessor reviews the ADR Report Form to make sure relevant sections are complete. If critical information is missing, the assessor should contact the health care provider who completed the ADR Report Form to gather more information if possible.
2. Identify the event and/or laboratory test abnormality.
    - The assessor identifies the suspected adverse event on the ADR Report Form and review Section 4. Reaction Details of the Form, examining the recorded signs and symptoms, and laboratory tests.
3. Analyze time relationship for the drug exposure and adverse event.
    - The assessor analyzes the time relationship of the ADR report. Of specific relevance would be determining whether the event occurred before or after the administration of the drug. On the ADR reporting form, consult sections:
        - Date & time event started
        - Date & time event stopped
        - Time interval between administration of suspected reaction and reaction
        - Suspected drug name(s) and the section for therapy dates (if known)
        - Concomitant drug name(s) and the section for therapy dates (if known)
4. The assessor should analyze the situation to determine if the time relationship is plausible, reasonable or improbable.
5. Determine if there was a response to withdrawal or a response to dose reduction.
    - The assessor analyzes whether there was a response to the withdrawal of the drug or dose reduction. For example, when the drug was discontinued did the ADR symptoms decrease

or stop entirely. Also, note if the reaction reappeared upon reintroduction to the drug, if reintroduction of the drug occurred. On the ADR reporting form, consult sections:

- Discontinuation of suspected drug
- Reaction abated after drug stopped or reduced
- Reaction reappeared after reintroduction of suspected drug

6. Determine if there is a medical or pharmacological possibility that the drug caused the adverse event.
    - The assessor checks if the drug or disease state can actually cause the suspected ADR. On the ADR reporting form, consult sections:
        - Reaction details
        - Reaction management details
        - Outcome of reaction
        - Reaction seriousness
        - Relevant laboratory test and results with dates
        - Other relevant history medical conditions
        - Information on the reporter
        - Further information on ADR case
    - The assessor should consult other references to help come to a complete determination:
        - The reference books should be used.
        - Product package insert.
        - Current literature (clinical trial reports, research papers, etc.) and/or drug bulletins, e.g. from WHO.
7. Classify causality using WHO-UMC Causality Assessment System:
   Use the WHO-UMC Causality Assessment categories to determine which category best fits the suspected ADR. Most classifications will be under the ‘probable / likely’ and the ‘possible’ categories, whereas the ‘certain’ and ‘unlikely’ categories may be more difficult to assign. If more information is needed or not enough information is be available, classification may be ‘Conditional/Unclassified’ or the ‘Un-assessable/Unclassifiable’ categories may be appropriate.

## Annexes:

**Ministry of Public Health**
**National Medicine and Healthcare Products Regulatory Authority Pharmacovigilance Department**
**Adverse Drug Reactions (ADR) Reporting Form**

**A. PATIENT INFORMATION**

| 1. Patient Initial | Age | Sex | | Weight (Kg) | Pregnancy | Breastfeeding | Name of hospital or health center: |
|---|---|---|---|---|---|---|---|
| | | Male ◯ | Female ◯ | | Yes ◯ No ◯ | Yes ◯ No ◯ | Medical record no: |
| Patient Address: | House # | Street # | Village | Dt/ward | Province | Phone # | Clinical ward or related dept.: |
| | | | | | | | Hospitalized on: |
| | | | | | | | Discharged on: |

**B. SUSPECTED ADVERSE EVENT (ADR & MEDICATION ERROR)**

| 5. Date and time event started: / / (time___:___) AM ◯ PM ◯ | 6. Date and time event stopped: / / (time ____:____) AM ◯ PM ◯ |
|---|---|
| 7. Reaction details*: *(please refer to the backside for further information)* | 8. Reaction management details: |

9. Time interval between administration of suspected medicine and reaction:
10. Discontinuation of suspected drug: Yes ◯ No ◯
11. Reaction abated after drug stopped: Yes ◯ No ◯ Reaction abated after drug reduced: Yes ◯ No ◯
12. Reaction re-appeared after reintroduction of suspected drug: Yes ◯ No ◯
Suspected drug not re-introduced ◯
13. Outcome of reaction: Recovered/Resolved ◯ Recovering/resolving ◯ Not recovered/Not resolved ◯
Recovered/resolved with sequelae ◯ Fatal ◯ Unknown ◯
14. Reaction seriousness: Not serious ◯ Requires hospitalization ◯ Prolonged hospitalization ◯ Disability ◯
Life threatening ◯ Congenital anomaly ◯ Death ◯ *(please write the date: / / )*

12. Other relevant history or medical conditions [e.g. allergy (individual or family), smoking, alcohol use, renal/hepatic dysfunction etc.]

13. Relevant laboratory test & results with date

| Lab tests | Results of lab tests | Date |
|---|---|---|
| | | |
| | | |
| | | |

**C. SUSPECTED DRUG(S) (please refer to the backside for further information)**

| **Suspect(s) drug name (brand/generic)/Dosage Form**** | **Strength** | **Manufacturer** | **Batch Number** | **Expiry Date** | **Doses** | **Route of Use** | **Frequency** | **Indication** | **Therapy Dates (if known)** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Started | Stopped | Duration of Use |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| **Concomitant(s) drug name (brand/generic)/Dosage form***** | **Strength** | **Manufacturer** | **Batch Number** | **Expiry Date** | **Doses** | **Route of Use** | **Frequency** | **Indication** | **Therapy Dates (if known)** | | |
| | | | | | | | | | Started | Stopped | Duration of Use |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**D. REPORTER (TO BE KEPT CONFIDENTIAL)**

| | | |
|---|---|---|
| Name of the reporter:_____ | Phone number:_____ | E-mail address (if available):_____ |
| Profession:_____ | Date of reporting: / / | Signature: |

Report received by *(name and signature of the person who received the form)*

Name: _____ Date report received: / / Signature

**The following guide will aid the reporter in reporting any suspected event and filling the Adverse Drug Reaction Reporting Form**

| | |
|---|---|
| **Adverse Drug Reaction (ADR):**<br>A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.<br>An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e., judged as being at least possibly related to treatment by the reporting or a reviewing health professional.<br>* Reaction details: Describe the adverse reaction, including any signs and symptoms that occurred with available information and also other related information regarding the event.<br>** Suspect drugs: Includes the entire information on name, dosage form, and any other information about the drug which is suspected to cause the event.<br>*** Concomitant drugs: The name, dosage form, and any other information of other drugs which are given to patient at the same time.<br>What to report? In order to improve patient safety, all health providers should report any suspected adverse reaction due to any medications (drugs or biologicals), vaccines, and herbal remedies; if the reaction is weak, mild, or severe. | **Who can report?**<br>Physician, dentist, pharmacist, nurse, midwife, public health manager, other health provider, patient or any person related to him, manufacturer, and dispenser.<br>**What happens after reporting?**<br>MSC reviews and performs causality assessment of the suspected ADRs, provides risk minimization plans, and gives feedback to reporter.<br>The reporter can receive the feedbacks from the pharmacovigilance focal person at the hospital drug and therapeutic committee (DTC) or health center, or directly from MSC members.<br>Confidentiality: The patient's and reporter's identities are held in strict confidence and protected to the fullest extent, and the information provided by the reporter will not be used against him/her.<br>**Where to report?**<br>Please submit the filled ADR Reporting Form to the pharmacovigilance focal person at the hospital DTC or health center, or submit directly to the mentioned address below. |

Further Information on ADR case:

Address: Pharmacovigilance center,
National Medicine and Healthcare Products Regulatory Authority,
Kabul, Afghanistan.
Contact:
E-mail: pvcenterafg@gmail.com, Website: www.nmhra.gov.af

**Thanks for the ADR Report**

**Annex 2: Review Report of Suspected ADR Cases**

**Ministry of Public Health**
**National Medicine and Healthcare Products Regulatory Authority**

| Hospital Name | Clinical Ward of Hospital | Date Event Started | Date Event Stopped | Date of Reporting | Date Report Received |
|---|---|---|---|---|---|
| | | | | | |

**The Review Report of Suspected ADR Case (S/No: )**

Physician, Pharmacist, Nurse, Midwife, Patient or any related person to him

**A. Detail of Reported Case (S/No: )**

1. **Patient Characteristic:**

   Name Age: Weight:

   Residency:

   Contact address Registration number:

2. **Reactions or events:**

   Medicine:
   Event:

3. **Suspected medicine characteristic:**
   - ❖ Name/Dosage form:
   - ❖ Manufacturer:
   - ❖ Manufacture Date:
   - ❖ Expire Date:
   - ❖ Batch No:
   - ❖ Strength:
   - ❖ Dose:
   - ❖ Frequency:
   - ❖ Indication:

4. **Reporter Information**

**B. Discussion in Medicine Safety Committee:**

**Pharmacological Findings of Suspected Medicine**

**Indication:**
**Precautions:**
**Contra-indication:**
**Adverse effects:**
**Half-life:**
**Toxic dose:**

**Clinical Features**

**Sign and symptom:**

**Event Specification**

**Risk specification:**
**Type of event:**
**Seriousness of event:**

**Causality Assessment**

| Causality | Comments |
|---|---|
| 1. Certain | |
| 2. Probable/Likely | |
| 3. Possible | |
| 4. Unlikely | |
| 5. Conditional/Unclassified | |
| 6. Un assessable/Unclassifiable | |

## Registration of Suspected Medicine

**Registration of suspected medicine in NMHRA:**
**The official permission of product from NMHRA:**

## Medicines Safety Committee (MSC) Conclusion & Recommendation

**Decisions taken by MSC:**
**Risk Minimization Plan:**
**Feedback and recommendation to reporter:**
**Report to related departments:**

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