Adverse Drug Reaction

Identifying, Causality & Reporting

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Adverse Drug Reaction – WHO Definition

Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function

Adverse Event (AE) → Serious Adverse Event (SAE)

FDA reports Adverse events as Serious when anAE falls under the following criteria:

- Death
- Life-Threatening (real risk of dying)
- Hospitalization (initial or prolonged)
- Disability (significant, persistent or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Adverse Drug Reactions Classification

Characteristics	Type A	Type B
Dose dependency	Dose Related	Dose Relationship is unclearly defined
Frequency of Occurrence	Common	Uncommon
Severity of Reaction	Variable but usually mild	Variable, but proportionately more severe
Host factors	Genetic factors might be important	Dependent on host factors
Animal models	Usually reproducible in animals	Unknown in animal models
Percentage proportion of adverse drug reaction	80%	20%
Predictable from known pharmacology	Yes	Not usually
First detection (Clinical Trials)	Phase I - III	Phase IV, occasionally phase III
Clinical burden	High morbidity & Low Mortality	High morbidity & High mortality

Adverse drug reaction (ADR) monitoring

- Identifying Adverse Drug Reaction
- Assessing Causality (Relationship between drug and suspected reaction)
- Documentation of ADR
- Reporting Serious ADRs to Pharmacovigilance centres /ADR Regulating Authorities

Identifying Adverse Drug Reaction

Type of Post Marketing Surveillance	Description
Anecdotal Reporting	Individual doctors report when a patient has suffered some peculiar effect
Population Statistics	Registers of Birth defects and cancer can be used if the drug induced event is highly remarkable or very frequent
Intensive Monitoring Studies	Special trained health care professionals devote their full time efforts towards recording all the drugs administered and all the events, which might possibly be drug induced
Meta analysis	Quantitative analysis of two or more independent studies for the purpose of determining an overall effect and of describing reasons for variation in study results

Type of Post Marketing Surveillance	Description
Spontaneous Reporting System	Clinicians encourage reporting any or all reactions that believe may be associated with drug use usually, attention is focused on new drugs and serious ADRs
Cohort studies (Prospective studies)	In these studies, patients taking a particular drug are identified and events are then recorded
Case control studies (retrospective studies)	The prevalence of the drug taken in this group is then compared with the prevalence in a reference population who do not have the symptoms or illness
Case cohort studies	Patients who present with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. The results are then compared with the incidence of the symptoms or illness in a prospective cohort of patients who are taking the drug.
Record linkage	Brings together a variety of patient records like general practice records of illness events and general records of prescriptions. In this way it may be possible to match illness events with the drugs prescribed

Causality Assessment Between Drug and Suspected reaction

Assessment performed by usually 2 methods include:

- Clinical Judgment

➢ An individual who is an expert in the area of ADRs would evaluate the case

- Algorithms

➢ Commonly used algorithm is the Naranjo algorithm

Naranjo's Algorithm

Question	Yes	No	Don't Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0

Question	Yes	No	Don't Know
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total Score			

The total score calculated from this table defines the category an adverse reaction belongs to the categories are defined as follows:

- Definite(Certain) --- > (total score>8)
- Probable --- > (total score 5-8)
- Possible --- > (total score1-4)
- Doubtful(Unlikely) --- > (total score <1)

Documentation of ADRs

Documents used for Reporting ADRs:

- Source Documentation

  eg. Patient's Medical Records, X-Ray or Diagnostic Reports

- AE/SAE Forms

•Paper Case Report Form (CRF)/ Electronic CRF

http://www.oxfordradcliffe.nhs.uk/research/documents/Template-CaseReportForm-ORHv1.doc

Adverse Event Form

STUDY NAME	
Site Number: _____ **Pt_ID:** _____	

Has the participant had any Adverse Events during this study? ☐ Yes ☐ No *(If yes, please list all Adverse Events below)*

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = Resolved, No Sequel 2 = AE still present- no treatment 3 = AE still present-being treated 4 = Residual effects present-not treated 5 = Residual effects present- treated 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (If yes, complete SAE form)

Adverse Event	Start Date	Stop Date	Severity	Relationship to Study Treatment	Action Taken	Outcome of AE	Expected?	Serious Adverse Event?	Initials
1.									
2.									
3.									

Serious Adverse Event (SAE) Report Form

Protocol Title:	
Protocol Number: _____ **Site Number:** _____ **Pt_ID:** _____	

1. SAE Onset Date: _____ (dd/mm/yyyy)
2. SAE Stop Date: _____(dd/mm/yyyy)
3. Location of serious adverse event: _____
4. Was this an unexpected adverse event? Yes ☐ No ☐
5. Brief description of participant(s) with no personal identifiers:
   Sex: F ☐ M ☐ Age: _____
6. Brief description of the nature of the serious adverse event (attach description if more space needed)
   _____
   _____
7. Category of the serious adverse event:
   - ☐ death – date __/__/__(dd/mmm/yyyy)
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability / incapacity
   - ☐ congenital anomaly / birth defect
   - ☐ required intervention to prevent permanent impairment
   - ☐ other:_____
8. Intervention type:
   - ☐ Medication or Nutritional Supplement: specify_____
   - ☐ Device: Specify: _____
   - ☐ Surgery: Specify: _____
   - ☐ Behavioral/Life Style: Specify: _____

Serious Adverse Event (SAE) Report Form

9. Relationship of event to intervention:
   - ☐ Unrelated (clearly not related to the intervention)
   - ☐ Possible (may be related to intervention)
   - ☐ Definite (clearly related to intervention)
10. Was study intervention discontinued due to event? ☐ Yes ☐ No
11. What medications or other steps were taken to treat serious adverse event?
    _____
    _____
12. List any relevant tests, laboratory data, history, including preexisting medical conditions:
    _____
    _____
13. Type of report:
    - ☐ Initial
    - ☐ Follow-up
    - ☐ Final

Signature of Principal Investigator: _____ Date: _____

Reporting Serious ADRs

Information to be Captured for Reporting includes the following:

- **Patient details**

➢ Initials

➢ Gender

➢ Age and date of birth

➢ Weight

➢ Height

- **Suspected drugs**
  - Generic name of the drug
  - Indication(s) for which suspect drug was prescribed or tested
  - Dosage form and strength
  - Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)
  - Route of administration
  - Starting date and time of day
  - Stopping date and time, or duration of treatment

- **Other Treatment(s)**

  Concomitant drugs

- **Details of Suspected Adverse Drug Reaction(s)**

- Full description of reaction(s) including body site and severity, as well as the criteria for regarding the report as serious,whenever possible, describe a specific diagnosis for the reaction
- Start date (and time) of onset of reaction
- Stop date (and time) or duration of reaction

- **Outcome**

- Information on recovery; results of specific tests and/or treatment
- For a fatal outcome, cause of death and its possible relationship to the suspected reaction; any post-mortem findings
- Any Other information relevant to facilitate assessment of the case, such as medical
- history of allergy, drug or alcohol abuse; family history; findings from special investigations etc

- **Details about the Investigator**

➢ Name

➢ Address

➢ Telephone number

➢ Profession (speciality)

➢ Date of reporting the event to Licensing Authority

➢ Date of reporting the event to Ethics Committee overseeing the site

➢ Signature of the Investigator

Reporting Responsibilities

- **Responsibilities of Sponsor**

➢ SAEs should be reported to the licensing authority within 14 calendar days of awareness

➢ Submit status report (Periodic Safety Update Reports) to the licensing authority periodically

- **Responsibilities of Investigator**

➢ SAEs and unexpected AEs should be reported to the sponsor and licensing authority within 24 hrs

➢ To their respective Ethics Committee within 7 working days

Severity Grading for Reporting

Reference for Severity is conducted as per the NCI – CTCAE Grading:

Grade Type	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf


Thank You!