Adverse Event data collection and reporting

AE collection timelines

- PV is a lifelong process for a product
- Even during preclinical stage risk is evaluated
- At clinical stage AEs are reported and analysed
- Once approved we have Post mkting studies as well as spontaneous reporting

Reason for A E Collection and Reporting

- The most important responsibilities of investigators and sponsors of clinical research studies
  - Protection of human subjects
  - Collection of clean and reproducible data
- Regulatory perspective
  - They need to analyze the data and determine
  - Risk/ benefits before giving permission to market

Pharmacovigilance in clinical trials

- All protocols must have a PV section
- Risk to patients varies in the range of clinical trials. Extent of recording and notification of adverse events may vary depending on knowledge of the risks and benefits of drugs under study and aims of the trial.
- Responsibilities and systems to deal with recording, assessment and reporting must be clearly stated.
- Time frames for notification, assessment and reporting are critical
- All the above should be a part of the SOPs of the Site/CRO/Sponsor

Period of Observation

Informed Consent signed

Treatment start

Treatment ends

Run In period = Screening phase

Active treatment period

Follow up period

Routine procedures collect adverse events

Screening Visit

End of Observation For AEs

Period of observation for AE collection is specified in each protocol

ICH – AE (Adverse Event)

- Any untoward medical occurance in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

ICH Definitions

An adverse event (AE) can be

- any unfavorable and unintended sign

(including an abnormal laboratory finding),

- symptom, or
- disease

temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples- Unwanted Effects

– Symptoms (headache, nausea)

– Physical findings (elevated BP, lump, pallor, edema)

– Abnormal lab values (increased liver enzymes, decreased hemoglobin)*

– Overdoses

* In clinical trials it is important to define what % cut offs to be taken as Adverse events

AE can also be

- Unfavorable deviation from baseline health, which includes:–
  - Worsening of conditions present at onset of the study
  - Patient deterioration due to primary disease
  - Intercurrent illness
  - Events related or possibly related to concomitant medications

Example

- Unfavorable deviation from baseline health, which includes:–
    - Worsening of conditions present at onset of the study
    - Headache present at baseline was mild , now become severe.

Example

- Unfavorable deviation from baseline health, which includes:–
  - Patient deterioration due to primary disease
  - BPH study-Patient going into acute retention of urine
  - Antibiotic Study: URTI progressing to LRTI

Example

Unfavorable deviation from baseline health, which includes:–

Intercurrent illness

In a Hypertensive study

Pt presenting with URTI

Example

Unfavorable deviation from baseline health, which includes:–

Due to concomitant medication

In a Hypertension trial, a patient comes with Diarrhea, on questioning it is revealed that he had taken antibiotics because of URTI

ICH - Adverse Drug Reaction (ADR)

- In the ***pre-approval clinical experience***
- *Defined as A*ll noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
- The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

ICH - Adverse Drug Reaction (ADR)

Regarding *marketed medicinal products*,

- Adverse drug reaction in the post-marketing setting
- A 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 modification of physiological function.

WHO Technical Report 498 [1972]

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ICH – Serious Adverse Event

Serious AE is defined as an AE that:

- Results in death;
- Is life-threatening (see below);
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in a persistent or significant disability or incapacity (see below);
- Results in a congenital anomaly or birth defect.
- Results in cancer;

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Definition SAE – Life-threatening

- **Life-threatening** refers to immediate risk of death as the event occurred, per the reporter. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death but as it actually occurred did not create an immediate risk of death.
- For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though hepatitis of a more severe nature can be fatal.
- Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

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Also an SAE

important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious AE's when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples

- allergic bronchospasm requiring intensive treatment in an emergency room or at home;
- blood dyscrasias or convulsions that do not result in hospitalization;

or the development of drug dependency or abuse.

Examples of Life-Threatening AE

- Pacemaker failure
- Gastrointestinal hemorrhage
- Infusion pump failure
  - Excessive IV fluid dosing
  - Toxic drug levels

Examples of Hospitalization AE

- Diarrhoea needing iv treatment
- Hypoglycemia needing iv dextrose treatment

Disability

- Substantial disruption of person's ability to conduct normal life functions
    - 21 CFR 312.32 (a)
- Significant, persistent, or permanent change, impairment, damage or disruption in patient's function, structure, physical activities or quality of life
    - MedWatch
- If there is any doubt whether the information constitutes a serious AE, the information is treated as a serious AE for the purposes of this policy.

Examples of Disability

- Stroke
- Loss of limb
- Toxic drugs levels
  - Hearing loss
  - Blindness

Assessing AEs

- Seriousness
- Intensity
- Relationship to drug
- Expectedness/ unexpectedness

Intensity

- Mild
- Moderate
- Severe

Intensity

Severity of the Adverse Event (WHO Classification)

1.Mild: Awareness of sign, symptom, or event, but easily tolerated.

2.Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention.

3.Severe: Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention

Serious/ Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (**as in mild, moderate, or severe myocardial infarction**); the event itself, however, may be of relatively minor medical significance (**such as severe headache**).

This is *not* the same as "serious," which is based on patient/event *outcome or action* criteria usually associated with events that pose a threat to a patient's life or functioning.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Examples

- Dizziness
- Patient feels the symptom, but can go on with routine activities

- Non Serious AE with Mild intensity

Examples

- Dizziness
- Patient feels the symptom, needs to lie down , finds it difficult to concentrate on work

- Non Serious AE with Moderate intensity

Examples

- Dizziness
- Patient feels the symptom, needs to lie down , finds it difficult to concentrate on anything. Unable to get up without getting the symptom. Needs intervention

- Non Serious AE with Severe intensity

Example

- Dizziness
- Patient falls unconscious. BP, Pulse very low. Needs emergency treatment, hospitalization
- Serious AE with severe intensity

Example

- Myocardial infarction
- Affecting only 10% myocardium
- Serious AE, with mild intensity

Example

- Headache
- Causing a person to take leave, not able to work, needs medication.
- Non Serious AE, with severe intensity

Difficulty Assessing Relationship AEs with drug

- Incomplete information: objective criteria
- Multiple drugs taken
- Variability of clinical responses
- Underlying illness mimic AE

Relationship/Causality

- Various definitions
- WHO Definition

Certain

Probable /Likely

Possible

Unlikely

Conditional /Unclassified

Unassessable/Unclassifiable

WHO-UMC Causality Categories

- **Causality term Assessment criteria* --- Certain**
- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific
- medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory

WHO-UMC Causality Categories

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

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

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WHO-UMC Causality Categories

Unlikely

Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)

- Disease or other drugs provide plausible explanations

Conditional / Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination
- **Unassessable/ unclassifiable**

Report suggesting an adverse reaction

- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

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Commonly used Adverse Event Relationship to Study Products

Definite clear ,cut temporal association, and no other possible cause

Probable clear cut temporal association, and a potential alternative etiology is not apparent

Possible less clear temporal association; other etiologies are also possible

None/Not Related the AE is completely independent of study product administration; and/or evidence exists that the event is definitely related to another **etiology**

***Where an event is assessed as *possibly related, probably related, definitely related* the event is an *adverse reaction*.**

Naranjo Algorithm

- Generally used for all serious trial & spontaneous cases, and non-serious, medically confirmed, unexpected events
- Scores of 5 or more, used for upgrades
- For temporal relationship, rule of 5 half lives is used
- For withdrawal reactions, rechallenge & dechallenge interpretation is reversed
- Scoring
  - 9 =definite
  - 5-8= probable;
  - 1-4= possible
  - 0 =unlikely

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Naranjo 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 after 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
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 drug in **any** previous exposure?	+1	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0

Example

Antihypertensive study

Drug: Antihypertensive drug

AE: Giddiness,

- Stops on stopping drug
- Restarts if re-challenge given
- No concomitant medication

Causality: Definitely related

Example

Drug: Antibiotic drug

AE: Giddiness

- Pt known hypertensive, taking antihypertensives
- Does not stop on stopping drug
- Anti hypertensives concomitant medication

Causality: not related

Example

Drug: Antibiotic drug

AE: Giddiness

- Pt known diabetic
- Stops on stopping drug
- No concomitant medication

Causality: probably related

Example

Drug: antibiotic, URTI

AE: increase in SGOT, SGPT

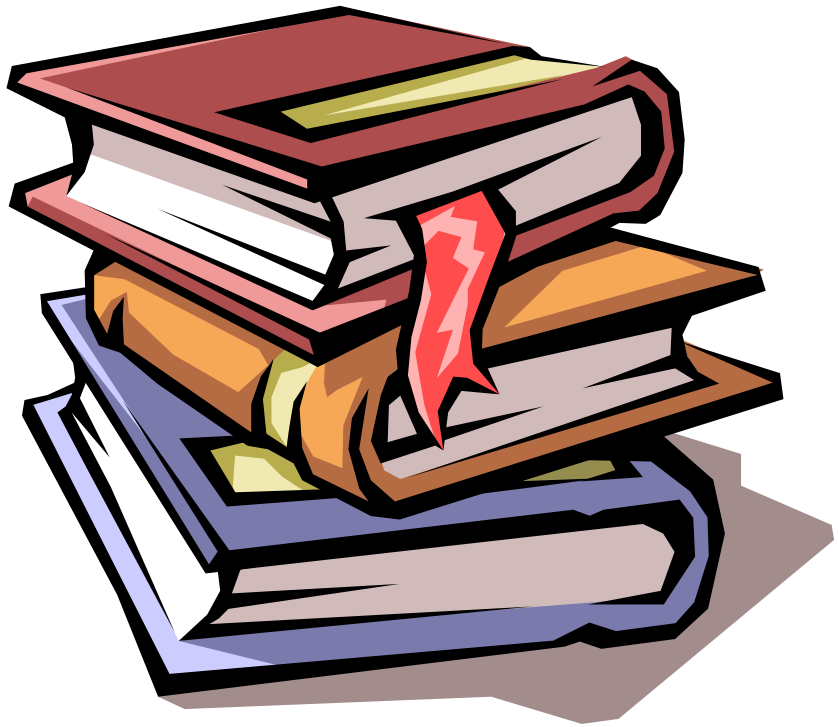
- Pt had normal values at baseline
- Does not stop on stopping drug/ decreasing trend
- NSAIDs were taken ,concomitant medication

Causality: Possibly related

Expected vs Unexpected AE

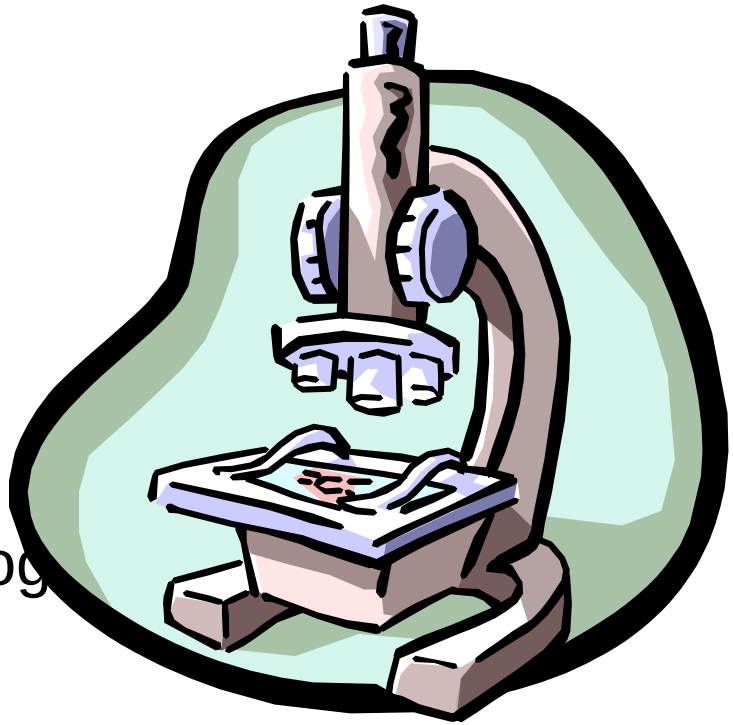
Expectedness

- **An *expected* AE is any adverse reaction whose nature and severity have been previously observed and documented for the study product.**



Expected vs Unexpected AE

An ***unexpected*** AE is any adverse reaction not previously observed, whether or not it has been anticipated because of the pharmacolog properties of the study



Assessing Ex/Unexpectedness

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

package insert for a marketed product

For a medicinal product not yet approved for marketing in a country, a company's **Investigator's Brochure will serve as the source document in that country.**

Unexpected AE

Reports which add significant information on **specificity or severity o**f a known, already documented serious ADR constitute **unexpected events.**

(a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and

(b) hepatitis with a first report of fulminant hepatitis.

SUSAR: Suspected Unexpected Serious Adverse Reaction

- Serious Unexpected adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s).

Reporting

- Expedited – within a week
- Routine - In the normal course

Reporting

STANDARDS FOR EXPEDITED REPORTING

A. What Should be Reported?

1. Single Cases of Serious, Unexpected ADRs

All ADRs that are both serious and unexpected are subject to expedited reporting. (SUSARs)

Not expedited

What Should Not be Reported?

- Expedited reporting of reactions that are serious but ***expected*** will ordinarily be inappropriate.
- Expedited reporting is also inappropriate for serious events from clinical investigations that are considered ***not*** **related** to study product, whether the event is expected or not.
- Similarly, **nonserious** adverse reactions, whether expected or not, will ordinarily not be subject to *expedited* reporting.

Others needing expedited

There are situations in addition to single case reports of "serious"

adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgment should be applied for each situation.

Examples include:

a. For an "**expected," serious ADR, an increase in the rate** of occurrence which is judged to be clinically important.

b. A significant hazard to the patient population, such **as lack of efficacy with a medicinal product used in treating life-threatening disease**.

c. A **major safety finding from a newly completed animal study, (such as carcinogenicity) .**

Reporting Time Frames to:

- Regulatory
- IRB/ ECs
- Participating investigators

Reporting Time Frames- Serious Unexpected

Fatal or Life-Threatening Unexpected ADRs

- Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting.
- **Regulatory agencies** should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by within 8 additional calendar days the complete report
- This report should include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

Reporting Time Frames- Serious Unexpected

All Other Serious, Unexpected ADRs

- Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days
- Case should meet the minimum criteria for expedited reporting.

Reporting to other participating investigators

- USFDA & India

- USFDA
- Sponsor reports all serious, unexpected ADR to other investigators within 15 calendar days

- India
- Sponsor to report all serious, unexpected AEs to participating investigators within 14 calendar days

Minimum Criteria for Reporting

Initial reports should be submitted within the prescribed time as long as the following minimum criteria are met:

- an identifiable patient;
- a suspect medicinal product;
- an identifiable reporting source; and an
- event or outcome that can be identified as serious and unexpected, there is a reasonable suspected causal relationship.

Follow-up information, should be actively sought and submitted as it becomes available.

Managing Blinded Therapy Cases

In a double-blind study

? whether to open (break) the code for the specific patient.

When a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the Sponsor, even if not broken by investigator

Breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data. Blind be maintained for people responsible for analysis eg biometric

Managing Blinded Therapy Cases

Problems arising by retaining the blind

Placebo and comparator (usually a marketed product) cases are filed unnecessarily.

When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory data bases are revised.

If the event is serious, new, and possibly related to the medicinal product, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading.

Managing Blinded Therapy Cases

Primary efficacy endpoint- fatal or other "serious" outcome.

The integrity of the clinical investigation may be compromised if the blind is broken.

Under these and similar circumstances, reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

Special cases

Reactions Associated with Active Comparator or Placebo Treatment

It is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies.

Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, no need for expedited reporting.

Post-study Events

- Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor.
- Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

Sponsor Responsibilities

The sponsor should expedite the reporting of all adverse drug reactions (ADRs) that are both serious and unexpected.

- To investigator(s)/institutions(s),
- to the IRB(s)/IEC(s), where required, and
- to the regulatory authority(ies)

- Train The study personnel (both sponsor's & investigator's)in assessing and reporting AEs
- Updating the Investigator Brochure
- Informing Regulatory the expedited and the periodic reports
- Sending the IND safety reports to sites
- Preparing the annual Reports
- Final reports with all analysis

Monitor Responsibilities

- Train the site personnel in
  - Assessing AEs- site initation
  - Reporting AEs with timelines

- Familarizing them with updated Investigator Brochure wrt expectedness
- Sending the IND safety reports to sites
- Informing Regulatory within timelines

Principal Investigator Responsibilities

- Medical management of the adverse events
- Train the site personnel under him/ her in assessing and reporting AEs
- Sending the IND safety reports to IRB as per their SOP
- To report all ADRs that are both serious and unexpected to IRB and sponsor within 24 hrs.
- New information that may affect adversely the safety of the subjects or the conduct of the trial
- The only exception to this is where the protocol or Investigator's Brochure identifies the event as not requiring immediate reporting

Decision chart