Adverse Event Reporting and IND Safety Reports

The What, Why, Who, When, Where, and How of Reporting Them

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Trivia: Name this Maryland Mountain

What are *Adverse Events*?

- **Per ICH E6 – Good Clinical Practice Guidance,**

  an *Adverse Event* is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

What are *Adverse Events*?

- **Per the US FDA regulation, 21 CFR 312.32a,**

  An *Adverse Event* is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- **NIH IRB Guidebook Definition**
  - An undesirable and unintended, although not necessarily unexpected, result of a therapy or other intervention.

What are *Adverse Reactions*?

- **ICH E6 Good Clinical Practice Guidance defines an Adverse (Drug) Reaction as follows:**

  In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

  Regarding marketed medicinal products: 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 diseases or for phys fx modification

What are *Adverse Reactions*?

- **Per FDA Guidance, Adverse (Drug) Reaction is defined as follows:**

  Any adverse event caused by a drug (intervention). Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug (intervention) caused the event.

What are *Unexpected Adverse Drug Reactions*?

- **ICH E6 Good Clinical Practice Guidance does not define Unexpected *Adverse Event* but does define Unexpected Adverse Drug Reaction as follows:**

  An adverse reaction whose nature or severity is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

What are *Unexpected Adverse Drug Reactions*?

- **Per 21 CFR 312.32a,**

  An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or package insert

  or

  is not listed at the *specificity* or *severity* that has been observed (as states in said IB or pack insert);

What are *Serious Adverse Events*?

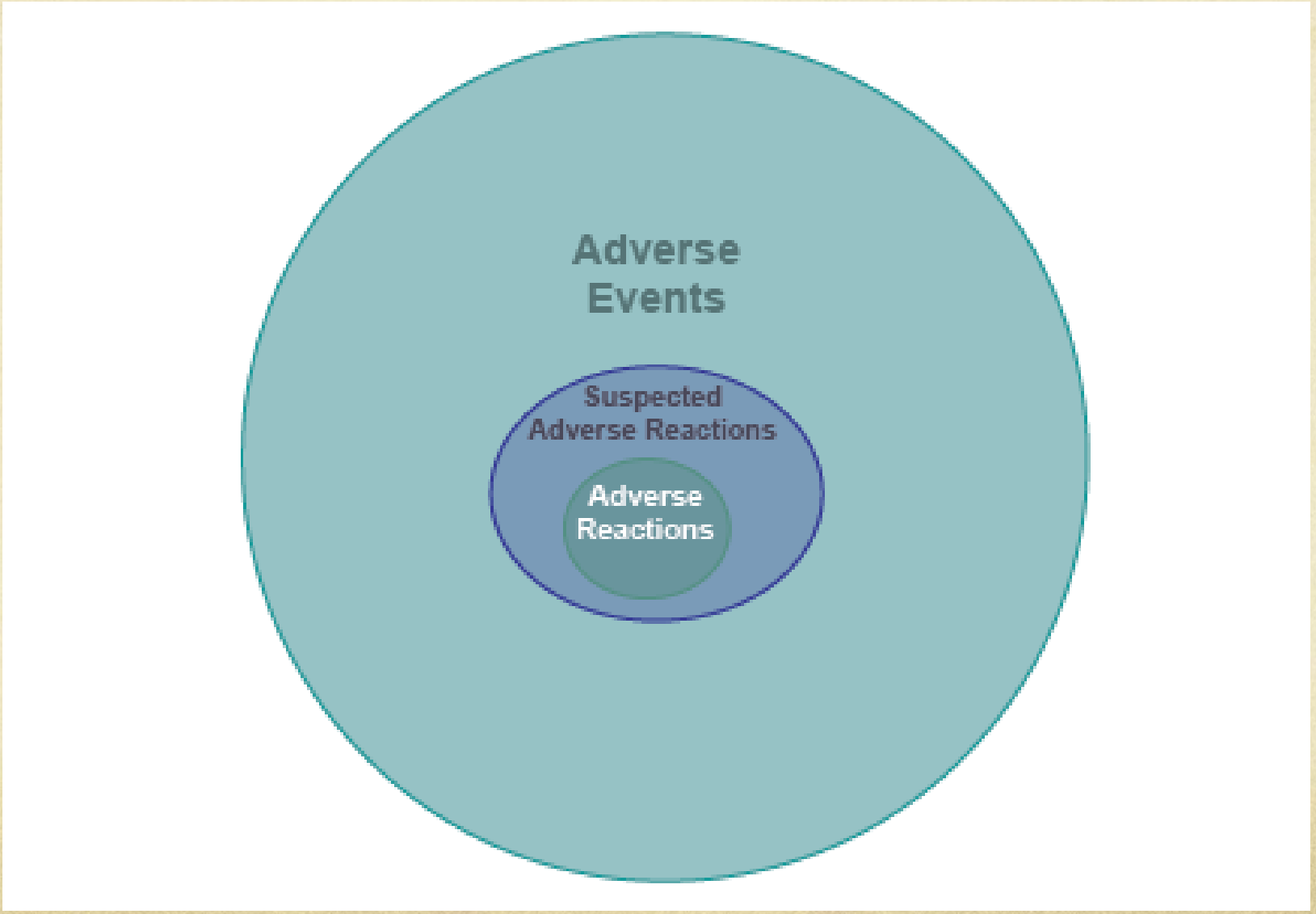
- **Per ICH E6 Good Clinical Practice Guidance, a Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is any untoward medical occurrence that at any dose (*outcome*):**
  - **results in death,**
  - **is life-threatening,**
  - **requires inpatient hospitalization or prolongation of existing hospitalization,**
  - **results in persistent or significant disability/incapacity,**

    or
  - **is a congenital anomaly/birth defect**

What are *Serious Adverse Events*?

- **Per 21 CFR 312.32a, an *Adverse Event* is an AE or suspected adverse reaction that is considered "serious" if, in the view of either the investigator or sponsor, it results (*outcome*) in any of the following outcomes:**
  - **Death,**
  - **A life-threatening adverse event,**
  - **Inpatient hospitalization or prolongation of existing hospitalization,**
  - **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,**
  - **A congenital anomaly/birth defect,**
  - **Other important medical events***

What are the Universe of *Adverse Events?*



BTW, What is a Sponsor?

- **ICH GCP Definition**
  - An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial

- **21 CFR 312.3 (FDA) Definition**
  - Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

    Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

BTW, *What* is an IRB?

- **According to HHS [45CFR46.103] IRBs are responsible for:**
  - "protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution"
  - "ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy…"

BTW, *What* about the Participant?

- **Participants who experience an AE:**
  - Directly affected
  - May require treatment or withdrawal of treatment
  - May affect willingness to continue participate

- **Subject who learns of others experiencing AEs**
  - May affect willingness to continue participating

What are *IND Safety Reports*?

- **Per 21 CFR 312.32c, an IND sponsor must report any *suspected adverse reaction to study treatment* (i.e., including active comparators) that is *both serious and unexpected* (21 CFR 312.32(c)(1)(i)) via an IND Safety Report.**

What are *IND Safety Reports*?

- **The IND sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.**

What are *IND Safety Reports*?

- **In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.**

What are *IND Safety Reports*?

- **Upon receipt of the SAE, the IND sponsor must ascertain whether the event meets 3 criteria:**
  - ***Was the event <u>Related</u>* ?(final relationship to study product decision made by sponsor)**
  - ***Was the event <u>Serious</u>?***
  - ***Was the event <u>Unexpected</u>?***

  If the AE meets all 3 criteria, then the sponsor must submit the event to the FDA as IND Safety Report within 7 (fatal/life-threatening outcome) or 15 days (non-fatal/life-threatening outcome) of being notified of said event via Form 3500A.

  If the event does NOT meet all 3 criteria then the event will be reported to the FDA in the IND sponsor's next IND annual report.

What are *IND Safety Reports*?

- **The IND Sponsor is required to inform all participating investigators of the IND Safety Report ASAP.**
- **Once trial PIs receive said IND safety report they must review & consider whether the event was:**
  - **unanticipated vis-à-vis the current consent/protocol?**
  - **reasonable to believe that it could be possibility related to the study/study intervention?**
  - **suggests that the research poses greater risk of harm than was previously known OR significantly changes the conduct of the study (i.e. requiring a protocol or ICF update)**

When all 3 criteria are met then the study PI must report IND Safety Report to an IRB as an unanticipated problem/event .

Or also submit to IRB when sponsor insists and its contractually reqd in the sponsor-PI CTA.

Why?

- **Proper adverse event assessment, management and reporting is standard GCP and is required per 21 CFR 312, IRB policies, and study protocol.**

Who?

- **The Trial Sponsor, Principal Investigators, Study Team Members**

How to Manage Adverse Events

- **AE information must be collected throughout the study (per protocol and institutional requirements) and must capture all adverse experiences, anticipated or unanticipated.**
- **The Investigator or Study Coordinator will record all AEs on the appropriate CRF (and must be PI-reviewed at least every 30 days).**
- **Any AE considered serious or unanticipated in nature, degree or severity must be reported to the Sponsor's representative within 24 hours of becoming aware of the adverse event (or per protocol).**
  - **Per 21CFR312.64: "An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately**

How to Manage Adverse Events

- **All AEs must be followed until resolution or a stable clinical endpoint is reached. All required treatments and outcomes of the AE must be recorded.**
- **All AEs and SAEs must be followed until:**
  - **AE is resolved and has returned to normal/baseline values or has stabilized**
  - **Subject is lost to follow-up or has withdrawn consent**
  - **AE is judged by the investigator to be no longer clinically significant**
  - **Subject has completed study required follow-up**
  - **Study Closure**

How to Manage Adverse Events
Methods of AE Discovery

- **Lab reports**
- **Standardized questionnaires**
  - Ensures consistency across staff and sites
- **Open-ended questioning**
  - ”Have you had any problems you want me to hear about?”
  - ”How have you been feeling since your last visit? “
  - Leading → “Have you had any headaches since you started the study?”
- **Observation**
  - Examples: Unsteady walking
- **Symptom checklists**

How to Manage Adverse Events
Methods of AE Discovery

- **Develop a systematic way to collect AE information**
  - Diaries, lab reports, questionnaires, symptom checklists, observation
- **Be careful not to lead the participant**
- **Probe for more information and clarification**
- **Remain as objective as possible when questioning**
- **Balance role of participant advocate and responsibility to study**
- **Discuss concerns with the investigator**

How to Manage Adverse Event *Information to Document*

- **Participant's words**
  - When
  - Record exact words as closely as possible
  - Record in source documents, study records, and/or CRF
- **Timing**
  - Date of report, date and duration of event
- **Lab abnormalities**
- **Characterization of event**
  - Severity
  - Cause
  - Expectedness
  - Relationship to study investigational agent or procedures
- **Actions taken**
- **Outcome**
- **Have PI review and sign all AEs (within 30 days or earlier of documented occurrence)**

How to Manage Adverse Events
Grading or Severity

- **Toxicity Grading Scale**

  (Required for Oncology and HIV Studies)

  - Grade 1 – Mild
  - Grade 2 – Moderate
  - Grade 3 – Severe
  - Grade 4 – Life-threatening or disabling
  - Grade 5 – Death

- **Website:** http://ctep.cancer.gov

How to Manage Adverse Events
Relationship Determination

- **Related**
  - Reasonable possibility that the event may have been caused by the investigational intervention
- **Unrelated**
  - No possibility that the event had anything to do with the investigational intervention

How to Manage Adverse Events
Relationship Scale

- **Relationship to the Intervention**

  (Required for Oncology and HIV Studies)

  - Definite: clearly related
  - Probably: likely related
  - Possibly: may be related
  - Unlikely: doubtfully related
  - Unrelated: clearly NOT related

How to Manage Adverse Events
Relationship Assessment

- **Is it an EXPECTED reaction?**
  - Are there previous reports documenting this type of event?
  - Is the event similar to other AEs currently listed?
  - Is the event similar to AEs listed in the same drug/ device class?
- **Was the AE TEMPORALLY RELATED to the intervention?**
  - Consider the half-life and elimination pattern of the agent.
- **Did the AE improve or disappear when the intervention was DISCONTINUED?**
- **Did the AE reappear upon RECAHALLENGE with the intervention?**

How to Manage Adverse Events
Relationship Assessment

- **Was the AE present at BASELINE?**
- **Can the AE be reasonably explained by the participant's MEDICAL HISTORY or DISEASE STATUS?**
- **What CONCURRENT MEDICATIONS is the participant taking?**

How to Manage Adverse Events
Attribution

- **Expected**
  - Expected for the agent based on previous clinical experience
  - Previously reported in Investigator's Brochure or package insert
- **Unexpected**
  - Event reporting is greater in severity or frequency than before
  - Not reported in the current Investigator's Brochure, package insert or described in the protocol's risk information.

  IRB determination of expectedness relates to the IRB-approved participant informed consent document.

How to Manage Adverse Events
Investigator Responsibilities

- ✸ **Investigator must assign the relationship to study drug/intervention at the site**✸

- **Initially assigned at the time of clinical evaluation**
  - May be changed later when AE is put into context with additional data on the participant or others
  - Often attribution can only be determined when analyzing multiple, independent AE reports
  - Master AE log is crucial (see attached)

When and Where to Submit Adverse Events / IND Safety Reports

- **Refer to attached AE Reporting Table**

AE Variable Descriptions

Adverse Event	Identify the event. *[Headache].* Work with sponsor to know whether you identify symptoms *(runny nose, achy, headache*) or disease *(cold).*
Severity/Grade	Mild, moderate, severe, or "graded" numerically according to a toxicity grading scale provided in the protocol
Relationship	Was the event associated with the use of the test agent? Options are usually yes/no or definitely/ probably /possibly/ remotely related. *[Ask, "Did anyone else you came in contact with have a headache? How big was that party?"]*
Treatment	Was treatment required? What was the treatment/action? *[Ask, "Did you take any medication for the headache?" What other symptoms did you have?"]*
Outcome	Did the participant recover from the AE?
Seriousness	*This category relates specifically to reporting requirements to the sponsor and the FDA. NIH uses "Common Toxicity Criteria" (CTC).*
Unexpected	*Relates to reporting requirements to the sponsor and FDA.*

Recommendations

- At the beginning of the study, establish a mechanism for identifying and tracking the occurrence, outcomes and reporting of events (i.e. Master AE log):
  - Definition of adverse events, outline procedures for documenting and reviewing reported adverse events
    - Event coding dictionary (e.g., CTCAE)
    - Laboratory/test abnormalities
    - Source documents: logs, checklists, flowcharts
  - Define reportable adverse events, outline procedures for reporting (per protocol)
    - IRB, FDA, other regulatory bodies
  - Procedure for distribution of reported adverse events to study team members and sites (if Sponsor)

Resources

- **Food and Drug Administration:**
  - **General Website:**

  http://www.fda.gov/
  - **FDA Guidance on IND Safety Reports:**

  http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf
  - **MedWatch Forms:**

  http://www.fda.gov/Safety/MedWatch/
- **Johns Hopkins IRB:**
  - **Unanticipated Problems:**

  http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/103_6b.html
  - **Protocol Deviations:**

  http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/protocol_deviations.html

Trivia Answer: ???