The Fundamentals of International Clinical Research

Understanding Adverse Events

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Reason for Adverse Event 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.
Goals of the Presentation

UNDERSTANDING:

- Definition of Adverse Event
- Expected vs. Unexpected Adverse Event
- Definition of SERIOUS Adverse Events
- Intensity vs. Seriousness of Adverse Events
- Relationship of Adverse Event to Study Product
- Reporting of Adverse Events
What is an Adverse Event (AE)?

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

(ICH-E2A)
What is an Adverse Event (AE)?

- Any unfavorable and unintended sign (including an abnormal lab finding)
- Symptom or disease, temporally associated with use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product

(ICH-E2A)
What is an Adverse Event (AE)?

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
What is an Adverse Event (AE)?

Unwanted Effects

- Symptoms (headache, nausea)
- Syndromes of disease
- Physical findings (elevated BP, lump)
- Abnormal lab values
- Overdoses
- Toxicities
An **expected** AE is any adverse reaction whose nature and intensity have been previously observed and documented for the study product (e.g. in the investigator brochure, product information).
Expected vs Unexpected AE

- An **unexpected** AE is any adverse reaction not observed, whether or not it has been anticipated because of the pharmacologic properties of the study agent.

- **Unexpected adverse drug experience**: Any adverse drug experience, the specificity or severity of which is not previously consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. 21 CFR 312.32
How Would You Describe an AE?

Wherever possible, adverse events should be described in terms of a change in the status of patient’s health, NOT the action taken or outcome.
How Would You Describe an AE?

Example:
A patient experiences a bleeding stomach ulcer that requires hospitalization.

- Question: What event(s) should be listed on the Case Report Form (CRF)?
- Answer: Bleeding ulcer
What Is a **Serious** Adverse Event?

A **SERIOUS** Adverse Event (SAE) is defined as an AE meeting one of the following conditions:

- **Death** during the period of protocol defined surveillance
- **Life threatening** (defined as a subject at immediate risk of death at the time of the event)
What is a **Serious** Adverse Event?

- **Hospital admission** during the period of protocol defined surveillance
- Any event that results in **congenital anomaly or birth defect**
- Any event that results in a **persistent or significant disability/incapacity**
What is a **Serious** Adverse Event?

- **Any other important medical event** that may not result in death, be life threatening, or require hospitalization, **may be considered a serious adverse event** when, based upon appropriate medical judgment, **the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.**
Intensity of the Adverse Event

All adverse events will be assessed by the investigator using the protocol defined grading system.

If the protocol has no defined grading system, then guidelines such as the following will be used to quantify intensity:
Intensity of the Adverse Event

- **Mild**: Transient or mild discomfort (<48 hours); no medical intervention/therapy required

- **Moderate**: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
Intensity of the Adverse Event

- **Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible

- **Life threatening**: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care possible
Serious vs Severe

**Serious**: Serious is defined as a regulatory definition

**Severe**: Severe is defined as an intensity classification (mild, moderate, severe)
Adverse Event Relationship to Study Products

All AEs must have their possible relationship to study product assessed by a system such as the following:
Adverse Event Relationship to Study Products

- **Associated** – The event is temporally related to the administration of the study product and no other etiology explains the event.

- **Not Associated** - The event is temporally independent of study product and/or the event appears to be explained by another etiology.
Reporting Adverse Events

Non-serious AEs

- ROUTINE REPORTING
  (e.g. annual report, AE form, CRF)
Reporting Adverse Events

ANY Serious AE

- Complete DMID SAE form and send to PPD or send to DMID via PPD
  - For fatal/ life-threatening SAEs:
    - Within **24 hours** of site awareness
  - For all other SAEs:
    - Within **72 hours (3 days)** of site awareness

- ROUTINE REPORTING
  (e.g. annual report)
Goals of the Presentation...

- Definition of AE
- Expected vs. Unexpected AE
- Definition of SERIOUS AE
- Intensity vs. Seriousness of AEs
- Relationship of AE to Study Product
- Reporting of AEs

...Achieved?
Breakout Session

- Does the scenario constitute an AE?
  - If yes, is it an SAE?
  - Why or why not?

- For AEs, please discuss the following:
  - Intensity
  - Relatedness
  - Site responsibilities
    - Reporting
    - Clinical follow-up