

Clinical and Translational
Science Institute / **CTSI**
at the University of California, San Francisco



Welcome to Online Training for
Clinical Research Coordinators

Adverse Events in Clinical Trials: Definitions and Documentation



Clinical and Translational Science Institute / CTSI
Accelerating Research to Improve Health

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UCSF

Objectives

- Recognize the difference between a non-serious adverse event and Serious Adverse Events (SAEs).
- Recognize a Suspected Adverse Reaction
- Recognize Unexpected or Unanticipated Adverse Events
- Differentiate between Severity and Serious Adverse Events
- Understand Documentation Best Practice



Before Beginning, Let's Review Principles of Subject Safety

- Protecting safety is a Federal mandate requiring investigators to report certain adverse events (see investigator commitments on FDA form 1572).
- Terminology used in this module are derived from
 - FDA 21 312.32 Code of Federal regulations,
 - Safety Reporting Requirements for INDs and BA/BE Studies FDA Guidance, December 2012
 - International Conference of Harmonization ICH E-6 Good Clinical Practices
- Protecting safety is an institutional mandate from the UCSF CHR/IRB.
- Safety is often one of the protocol objectives when testing new therapies so adverse event data must be collected and reviewed by the Principal Investigator.
- Stopping rules are often clearly identified in terms of types and frequency of SAE's; the risk versus benefit ratio is a key variable on whether enrollment to a study can continue.



Definitions of Adverse Events



- Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

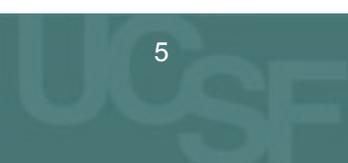
[21 CFR 312.32\(a\)](#)



Definitions of Adverse Events

ICH E6 Section 1.2

- An **adverse event** (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease **temporarily** associated with the use of a drug, **without any judgment about causality** or relationship to the drug.
- An **adverse event** can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.



Definitions of Adverse Events

- Indicates a change in the subject's health status 'since baseline' right before taking the study drug.
- When toxicity of the study drug is a hypothesis, you will see on the calendar, a baseline physical exam to be completed either at Day 0 or Day -5 prior to dosing.



Definitions of Adverse Events

Baseline would include all of the below:

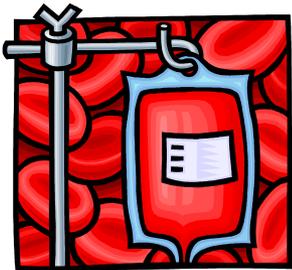
- Pre-existing conditions that are ongoing during the clinical trial
 - Hypertension
 - Diabetes
- Concomitant medications taken prior to participation in the clinical trial
 - Anticoagulants to prevent thrombosis
 - Steroids for autoimmune condition



Definitions of Adverse Events

Examples of Adverse Events which are not related to [or caused by] the study drug but if they occur while the subject is on study, would have to be collected, reviewed by PI and tracked:

- Transfusion reactions
- Accidental injuries
- Surgery



Definitions of Adverse Reaction

- A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.
- ‘Reasonable possibility means there is evidence to suggest a causal relationship between the drug and adverse event.



Definition of a Serious Event or Serious Suspected Adverse Reaction

[21 CFR 312.32 \(a\)](#)

- An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results 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, or a congenital anomaly/birth defect.



A “Life Threatening Adverse Drug Experience” Defined

- Any adverse experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, or it is suspected that the use or continued use of the product would result in the patient’s death.

Examples include:

- hemorrhaging and internal bleeding with rapid drop in blood pressure;
- Loss of consciousness from increase in pressure on the brain



Hospitalization Defined

Admission to the hospital for longer than 24 hours or prolongation of a hospital stay due to adverse event.



“Disability” Defined

- A substantial disruption of a person’s ability to conduct normal life functions.
- Examples include: loss of speech; fatigue so great the subject cannot get out of bed at all; loss of memory; and paralysis.



“Congenital Anomaly” Defined

- Exposure to a medical product prior to conception or during pregnancy resulting in an adverse outcome in the child.

Thalidomide is the best example of a drug causing congenital anomalies with babies born with deformed arms and legs.



Definition of a Serious Event or Serious Suspected Adverse Reaction

[21 CFR 312.32 \(a\)](#)

One final outcome that makes an event or reaction serious:

- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience 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 of Important Medical Events

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home



- Blood dyscrasias



- Convulsions that do not result in inpatient hospitalization,



- Development of drug dependency or drug abuse.



What is Expected versus Unexpected when Defining Adverse Events or Suspected Adverse Reactions

Expected toxicities from the study drug if found in the following:

- Safety information on approved products is reflected in product labeling (Package Insert)
- Up-to-date safety information on the products under investigation is found in the Investigator's Brochure (IB)
- From these sources the protocol and the informed consent is written to explain to describe what risks we currently expect from this study drug.
- Safety profile of other drugs in the same class

Unexpected means that the event experienced by the subject is not listed in any of the documents above.



Definition of an Unexpected Adverse Event

Unexpected: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, 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 (a)



Examples of an Unexpected Adverse Event

- **Hepatic necrosis** would be unexpected (**by virtue of greater severity**) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis.
- **Cerebral thromboembolism** and cerebral vasculitis would be unexpected (**by virtue of greater specificity**) if the investigator brochure only listed cerebral vascular accidents



Definition of Severity vs. Serious

- Refers to the intensity of the event and can be used with any event, without regard to whether or not it meets the federal criteria for 'serious'....is expressed in 'grades' of severity.
- Responsibility of the principal investigator to concur with all intensity assessments added to the database for the events identified in the subject.



Examples of Grading Severity/Intensity Ranges

- **Grade 1:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention 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 ; urgent intervention indicated.
- **Grade 5:** Death related to an AE
- **References:**
 - <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>
 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf



Example of Future use of Grading Adverse Events during the Clinical Trial

- When a drug gets approved to be used in clinical practice, prescribing information will refer to the intensity grading scales to assist physicians managing patient care.
- For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours or greater than or equal to Grade 3 diarrhea, withhold [drug name] until diarrhea resolves to Grade 1 or less, and resume [drug name] with appropriate dose reduction.



IND Safety Reports

- All SAE reports sent from Site Principal Investigators to the Sponsor must be prepared as an 'IND Safety Report' and then tracked as sent to all of the other site investigators with the expectation both the PI and the IRB will review them.
- PI/CRC receives of safety report/letter
- PI determines need to:
- Update informed consent
- Risk/benefit analysis change to subjects
- PI and CRC report to UCSF CHR, in a timely manner
- Follow CHR requirements
- Keep a log of IND Safety Report receipt date, event, date reported to CHR, informed consent updated (yes/no) for the sponsor
- File in study files
- [21 CFR Subpart B section 312.32\(c\)\(1\)IND safety reports](#). The 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...



Where are Adverse Events or Reactions Documented?

ANSWER: During the course of the study, the CRC will find them in the Medical Record, Laboratory reports, Radiology reports, Surgical reports, Infusion Center nursing notes, subject diaries, subject surveys or questionnaires.

Documentation of all adverse events should be written and signed by qualified clinicians in the subjects medical record which will serve as original source. This includes lab and radiology reports often need PI initials to show review.

- Non-serious and serious adverse events
- Unanticipated events
- Report all directly observed events (rash etc)
- Events elicited from the subject
- Events spontaneously volunteered by subject
- Laboratory, EKG or other test results that meet protocol requirements for classification as adverse event



CRC Role in Adverse Event Collection

Best Practice

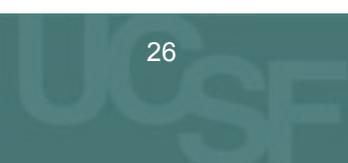
- Review data entry for adverse events and serious adverse events provided by the sponsor or investigator developed data entry. It will clue you in on what needs to be tracked.
- All adverse events and suspected adverse reactions are collected from 'source documentation' and the CRC abstracts the events
- Documentation can be within UCSF medical records, but at times the CRC will also have to have the subject or family send outside source documentation. If you will have to request records on your own, you will need a HIPAA release form signed by the subject for the outside institution.
- Report all SAEs immediately to the Principal Investigator upon identification or notification from family.
- NOTIFY: MD/NP assigned to the study for 'subject's medical care' in the event the study drug needs to be stopped, per protocol. The CRC assists clinical staff to manage the subject. Certain drugs to treat the adverse event can be forbidden by the protocol....it is the CRCs role to know the protocol details to assist the clinicians.



Tips and Tricks

Print AE Tracking Tool from Database

- Oncore and some sponsor databases allow print out of AEs entered, in a table format, so this can be reviewed by the Principal Investigator; then ideally signed or initialed by the PI as having reviewed causality, severity grades, description of the event.
- The CRC must collect and enter this safety data accurately but cannot take responsibility for assessing the events.



Tips and Tricks

Collecting Adverse Events

Events that are NOT linked pathophysiologically, or temporarily, are reported as separate events

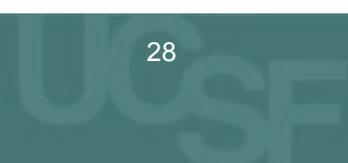
Example

- Subject is admitted to the hospital with Heart Failure
- Subject develops sepsis while in the hospital as a result of the venous catheter and this prolongs the hospitalization.
- **Two SAEs for this subject:** One for Heart Failure and one for Sepsis



Coding of Adverse Events

- Process of converting investigators “verbatim documentation” terms to standardized “Preferred Terms” (PT)
- Standardization allows sorting of AEs and grouping of like events.
- PT used to calculate incidence of AE.
- Currently the most used coding dictionary is: MedDRA (Medical Dictionary for Regulatory Activities) Is available in OnCore and many large pharmaceutical safety databases.



Be Aware of the Need for Accurate Coding as you Abstract Clinician Dictation

Coding problems may lead to missing safety signals; can be a real challenge for the CRC and the monitor from the drug company will want to make sure that data entered is coded correctly

Examples:

- Splitting same AE among similar PTs
 - Hypertension, high blood pressure, etc.
- Lumping different terms to same PT
 - Leg edema, face edema, etc.
- Lack of adequate term/definition
 - Drug hypersensitivity, Metabolic syndrome, Serotonin syndrome



Takeaways...



Documentation of the subject's baseline medical history, physical examination, medications and treatments is critical for evaluating the subject's safety, and adverse events during the study period

- CRC is responsible for abstracting and tracking the adverse events and adverse reactions in manner that helps the Principal Investigator review before entering this into a sponsor database.
- Understand protocol-specific adverse event definitions and what is required to be reported in addition to those meeting the federal definitions.
- MD/NP evaluation of the subject cases and IND Safety Reports for the need to modify the informed consent when changes to risk have been identified.
- Be consistent and use scientific terminology when reporting AEs; get assistance from your investigators!

It is all about subject safety and human subject protection!

