Patient Safety and Adverse Events

Participant Safety & Adverse Events

What is an adverse event?

The Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH) define an adverse event (AE) as: “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment”

The term adverse event is defined in the U.S. Code of Federal Regulations (CFR) Title 21 Section 312.32(a) as follows: "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

ICH guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting uses the ICH GCP definition.

An AE may be “any unfavorable or unintended" sign, symptom, or disease that occurs in a person who has taken a medication. The occurrence does not need to be related to the drug treatment.

An adverse event (AE) may be:

- A physical event (e.g., a rash).
- A psychological event (e.g., depressed mood).
- A laboratory event (e.g., elevated blood sugar).
- An increase in the severity or frequency of a pre-existing symptom or condition (e.g., increased pain in a painful tooth)

An adverse event may also be referred to as an “adverse experience”.

What is an adverse drug reaction?

The terms adverse event and adverse drug reaction are easily confused, but they have distinctly different meanings. As discussed in earlier sections, an adverse event (AE) is any “untoward occurrence” in a patient or clinical study participant that need not be related to treatment.

By contrast, an adverse drug reaction (ADR) implies an adverse event that results from a medicine or treatment (i.e., there is a degree of relatedness between the adverse reaction and the treatment).

FDA regulations define an ADR as

“an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence” (21 CFR 201.57(c)).

Remember: Although every ADR is also an AE, only some AEs will also be ADRs. Therefore, it is very important to collect clear and complete information about every AE.

What is a serious adverse event?

An AE is considered serious if it poses a threat to the patient's life or functioning. The FDA defines a serious adverse event (SAE) as any untoward medical occurrence that:

- Results in death, or
- Is life-threatening (places the patient at risk of death), or
- Requires hospitalization or prolongs an existing hospitalization, or
- Causes persistent or significant disability or incapacity, or
- Is a birth defect, or
- Requires medical intervention to prevent one of the above outcomes (e.g., an asthma attack that requires intensive treatment in an emergency room, a seizure that does not result in hospitalization but requires medical treatment).

An AE needs to meet only one of the above criteria to be considered serious. A change in vital signs, diagnostic tests (e.g., an electrocardiogram), or laboratory test results may be an SAE if the change is of sufficient magnitude to meet one of the above criteria.

An adverse event is judged "serious" on the basis of the threat it poses to a patient's life or functioning. For example, a patient could be diagnosed with pneumonia in his or her doctor's office and given antibiotics to take at home. The pneumonia is an AE, but not an SAE

However, if the patient is hospitalized for the pneumonia, that is considered an SAE. (The SAE is pneumonia resulting in hospitalization.)

It is also imperative to clarify between severe and serious. While the intensity of an event may be severe, it may not meet the criteria for serious (e.g. Severe Migraine).

Elective surgery (i.e. surgery that is planned prior to entry into the study) is not a Serious Adverse Event. For example, removal of bunions on feet, nose reconstruction, planned hysterectomy, etc.

What is an unexpected adverse event?

For clinical studies that involve the use of marketed drugs (as opposed to investigational new drugs), FDA defines an unexpected AE as:

- An AE that is not listed in the drug's current labeling, or
- An AE that is more severe or more specific than indicated in the labeling.

For clinical studies in which investigational new drugs are used, the FDA defines an unexpected AE as: • An AE that is not consistent with the information about the drug's risks that appears in the relevant source document(s) (e.g., protocol, Information sheet, and consent documents), or

- An AE that is not consistent with the risk information, or

- An AE that has occurred within the class of drugs, but not specifically with the Investigational Product.

What is an unanticipated problem?

The Office of Human Research Protections (OHRP) defines unanticipated problems involving risks to study participants and others as an event that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

Suspected unanticipated problems must be promptly reported to the IRB, who will make the subsequent determination to report it to the proper regulatory authority.

Assessing an Adverse Event

Every protocol should list specific AEs that are to be addressed at every visit. Generally, this will be a very short list of lab values and clinical signs and symptoms. The protocol should also specify the duration that information on AEs will be collected.

All AEs that occur in any clinical study participant should be assessed for:

Severity

The severity of an AE is not the same as its seriousness. Severity refers to the intensity of a specific event (e.g., mild, moderate, or severe pain). However, the event itself may be of minor medical significance (e.g., a severe toothache)

By contrast, the seriousness of an AE is assessed by the extent to which it poses a threat to the patient's life or functioning. Thus, an AE may be severe (e.g., severe pain from a toothache) without being serious (threatening the patient's life or functioning).

Determining the severity of an AE is largely a matter of individual clinical judgment. No universally accepted scale exists for describing or measuring the severity of AEs. The severity of an AE should be determined with input from a qualified physician or licensed medical staff.

Relatedness

An AE may or may not be causally related to the study intervention. A causal relationship means that the intervention caused (or is reasonably likely to have caused) the AE. This usually implies a relationship in time between the intervention and the AE (e.g., the AE occurred shortly after the participant received the intervention).

For all AEs, it is the responsibility of the clinician who examines and evaluates the patient to determine the relatedness of the event to the study intervention. Data managers who have no role in patient clinical assessment must not perform this important task.

Acceptance that an AE is related to the intervention usually requires a plausible mechanism of action—that is, a believable sequence of events by which the intervention brought about the AE. It may be helpful to seek the opinion of the Study Medical Monitor on this point. It can also be helpful to ask the participant whether he or she thinks the intervention could have brought about the AE

If an AE is thought to have a causal relationship with the intervention, and the AE raises concern about the safety of the participant, serious consideration must be given to temporarily halting or permanently discontinuing the intervention. Additionally, rechallenging the participant (that is, giving the intervention again to test the causal relationship to see if the AE occurs again) is not often done because of safety concerns. For this reason, it is often impossible to say with certainty that an experimental intervention caused an AE.

The causal relationship between an intervention and an AE may be tested by discontinuing the intervention and then rechallenging the participant (giving the intervention again) to see if the AE occurs again. However, this is rarely done because of safety concerns. For this reason, it is often impossible to say with certainty that an experimental intervention caused an AE.

When an AE is labeled “associated with the use of the intervention,” therefore, this means there is a reasonable possibility that the AE may have been caused by the intervention and is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Early in the development of a drug or other intervention, when little is known of its safety profile, it is especially important to maintain a high level of suspicion for AEs and to report all AEs that may in any way be causally related to an experimental drug or intervention.

Any AE reported by a participant should be followed up at each subsequent study visit until the AE has resolved. It is important to document both the duration (e.g., minutes, hours, days) and severity of an AE. An AE that persists from one study visit to the next should be documented as one event. For AEs that are sustained past the study duration, follow-up may occur until resolution or for a reasonable period of time defined by the protocol.

The initial report of an AE is usually made by the participant; however, an AE may also be reported by a family member, friend, nurse or other caregiver, or someone else. For example, a family member or friend may call to report that a participant has been hospitalized. Or another participant may report hearing from a third party that a participant is seriously ill.

Regardless of who reports an AE, the event should always be documented in the participant’s source documents including progress notes. When an AE is reported by a third party, the Research Assistant should make every effort to contact the participant directly to verify the report. In some

cases, a report of an AE may turn out to be false. As more information about the event is gathered and assessed, the Research Assistant must ensure that source documents and reports are updated with accurate information about the AE.

Adverse Event Reporting

AE reporting is an essential part of participant safety protection during a clinical study. Determining whether an incident is a reportable AE—and if so, what should be reported about it, to whom, and when—depends on many factors, including:

- Previous experience and knowledge of the drug or intervention, • The disease being treated, and
- Regulatory requirements.

In addition to the factors listed above, investigators must consider incident reporting requirements for funded studies, including reportable AEs and unanticipated problems (UPs). All funded studies are required to comply with National Health Research Council (NHRC) for safety event reporting. For OHRP's current guidance on UPs involving participant safety risks, follow the link here.

Not all AEs require reporting, as they might not directly impact participant risk or present significant new findings. Inundating the study IRB with individual, unanalyzed UPs is an uninformative process, and UPs that don't impact participant risk can be covered during the IRB's continuing review. Requirements for the reporting of AEs are defined in each protocol.

The investigator and research team must consider these factors when writing the sections of the protocol and the operations manual that discuss adverse event reporting. The investigators and the study sponsor jointly determine the extent and type of AE data that will be collected for a specific trial.

They may decide that minor complaints of daily living will not be considered AEs. An event such as the worsening of symptoms of a current illness could be captured in the patient's progress notes or on a case report form.

ICH GCP requirements for AE reporting

The investigator must report all Serious Adverse Events to the sponsor immediately. The immediate reports should be followed promptly by detailed, written reports.

In the event of a death, the investigator should supply the sponsor, SGNHC Research Unit and the IRB with any additional requested information.

In addition, the investigator must comply with the applicable regulatory requirements as well as protocol specific requirements related to the reporting of safety issues. In some instances, the local laws or network requirements may request more stringent reporting of emergent or safety events.

Adverse Event Follow-Up

Medical Follow-Up of Participants with an Adverse Event

Unless otherwise specified in the protocol, in some networks it is common practice that all AEs and non-study–related SAEs should be followed-up until they have resolved or stabilized or until 30 days after the participant's involvement in the study has ended, whichever occurs sooner.

All SAEs should be followed until resolution, or until the condition has stabilized with no further change expected. According to FDA guidance, participants should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention that develops during or after the course of their participation in a study, even if the follow-up period extends beyond the end of the study.

When a participant discontinues participation in a study because of an SAE, investigators should:

- Continue to follow up the SAE as noted above.
- Document the SAE and its follow-up in the participant's record.
- Attempt to complete any final evaluations required by the study protocol.
- Attempt to perform other medical evaluations to try to determine the cause of the SAE and its possible relationship to the study intervention. These evaluations would include obtaining an autopsy report, if available, in the event of a participant's death.

For a woman who is discontinued from a study because of pregnancy, attempt to follow up the outcome of the pregnancy to term. If the woman was enrolled in a trial of an investigational drug that is known to present a risk of birth defects, any information regarding birth or congenital abnormality should be obtained.

Loss to follow-up of participants with ongoing SAEs is a serious problem that can affect the validity of a study's results. For this reason, every effort should be made to contact participants who leave a study after experiencing an SAE. Documentation of that effort should be maintained by the PI.