

## Adverse Event Reporting: During the Study

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The reporting of adverse events (AEs) is a standard task for investigative sites involved in clinical trials. This article will focus on the actions and considerations that a site should take to facilitate the proper identification and handling of AEs once it begins enrolling subjects in a clinical trial under an Investigational New Drug Application (IND).

The site will have completed a preparatory phase consisting of the following four steps:<sup>1</sup>

**Step 1.** Become knowledgeable about applicable laws, regulations, guidances and guidelines.

**Step 2.** Become knowledgeable about the sections of the study protocol that concern adverse events.

**Step 3.** Become knowledgeable about applicable reporting requirements for the IRB presiding over the study. Request a copy of the IRB's reporting requirements and maintain it in a location accessible to all staff, e.g., in the regulatory binder.

**Step 4.** Obtain a thorough baseline medical history and conduct a comprehensive physical exam for each study subject.

### Adverse Event Terminology

An understanding of the key definitions and associated terminologies of AEs is required before the reporting process can begin. The following definitions are based on the pertinent definitions in 21 CFR 312.32 (a) and International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidance.

**Adverse Event (AE).** 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. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.<sup>2</sup>

AEs thus include illnesses, injuries, signs and symptoms that appear during the course of a clinical study. AEs also include illnesses, injuries, signs and symptoms present at baseline that worsen during a study. It does not matter whether the event was caused by use of the investigational product (IP) for it to be an AE; it only requires that it occurred during the study (or reporting timeframe specified by the study protocol).

If the signs and symptoms constitute a condition (illness or injury), the condition is the AE. Otherwise, the sign and/or symptom itself is the AE. Each AE should consist of a single event. Thus, an entry such as "nausea & vomiting" should instead be documented as separate events, i.e., "1. nausea" and "2. vomiting." Treatments, such as surgery, are not AEs; the medical condition for which the procedure was performed is the AE.

**Adverse Drug Reaction (ADR).** In a preapproval 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. The phrase "responses to a medicinal product" means that a causal relationship between the medicinal

product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.<sup>3</sup>

An ADR is thus an AE that may have been caused by use of the investigational product. The investigator decides the question of causation.

**Unexpected Adverse Drug Reaction.** An adverse reaction, the nature or severity of which 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).<sup>4</sup>

An unexpected adverse drug reaction is thus an AE that has been judged to be related to the use of the investigational product (IP) AND the investigator's brochure or package insert does not specify the AE as a side effect of the IP. If an investigator's brochure is not available, the decision of whether the AE is unexpected or not is based on the risk information described in the general investigational plan or elsewhere in the current application, as amended.

**Serious Adverse Event (SAE).** Any untoward medical occurrence that 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.<sup>5</sup>

The same parameters as noted above for AEs apply, i.e., that it does not matter whether the event was caused by use of the IP for it to be included as an SAE; it only requires that it occurred during the study or reporting timeframe specified by the study protocol. Other important facets of the SAE definition include the following:

**Disability.** A substantial disruption of a person's ability to conduct normal life functions.<sup>6</sup>

Examples include loss of vision, mobility, dexterity or cognition.

**Life-threatening.** Places the subject, in the view of the investigator, at immediate risk of death as it occurs; it does not include an experience that, had it occurred in a more severe form, might have caused death.<sup>7</sup>

An event with an immediate risk of death requires immediate action.

**Serious adverse drug experience.** Any untoward medical occurrence that, at any dose, 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.<sup>8</sup>

A serious adverse drug reaction/experience is thus an SAE that has been judged to be related to the use of the investigational product. Although there is some ambiguity in the regulations, the investigator is responsible for the subject's health and thus for classifying the seriousness and causality of adverse events in reports to the sponsor.<sup>9</sup> The sponsor may voice its own opinion in its communications to the FDA.

The SAE report with the causality information is forwarded by the investigative site to the Sponsor to comply with their reporting requirements according to 21 CFR 312.32. In some cases, the Sponsor may disagree with the causality assessment provided by the Investigator; however, it is only when a relationship to the study drug is ruled out by both the investigator and the sponsor that filing an IND Safety Report is not required.

## Collecting Adverse Event Data

The protocol specifies when AE reporting begins, typically after the subject signs the informed consent form or is randomized. Use an organized method to collect AE data. A detailed medical history and baseline physical exam identify initial signs and symptoms for comparison to subsequent evaluations for AEs. Summarize the safety reporting process to the subject and explain that data related to his or her health will be collected throughout the study. Some studies use subject diaries to collect AE and other study information. In the absence of an official diary, you may still ask subjects to keep notes on their health so they can provide information at their next study visit or contact.

The following questions will usually identify an adverse event:

- Has your previous AE (if any) continued unchanged, worsened or resolved?
- Have you taken any new medications since the last study visit? There is a good chance that any new medications were used for an AE.
- Have you stopped or changed the dosage or frequency of any of the medications you were taking at the time of the last study visit? Any such changes may correspond to a new AE or the resolution of an existing AE.
- Has your health changed in any way through illness or injury since the last study visit?

Do not cause the subject to either invent or discount possible AEs. When inquiring about adverse events, do not suggest that because the drug is experimental, they should expect side effects. Also, never read a list of AEs to the subject and ask which ones they have. Ask follow-up questions in a neutral manner.

Compare the information you collect to information from previous visits and to the baseline physical and medical history taken at the start of the study.

Document any new condition, recurrence of a previously resolved condition, or worsening of an existing condition as an AE. Collect detailed information about the event(s) to enable the investigator to assess and manage the subject. For example, if the subject had suspected pulmonary congestion, document whether in one lobe or in the bronchia, started at a specific time, and either stopped at a specific time or continues. It may be associated with standing or lying down. It may or may not be associated with labored breathing or reduced blood oxygen.

Record this information in any suitable combination of progress notes, sponsor-provided visit source worksheets, and concomitant medication & AE logs. The study visit note should state that site personnel continue to monitor any ongoing AEs.

Inform the subject of his or her AEs, even if medical care is not needed. If medical care is required, provide it or refer the subject to his or her physician for treatment. (It is preferable, but not required, to inform the subject's primary care physician that the subject is participating in the study when the subject first enrolls.)<sup>10</sup>

## Documenting Adverse Events

As noted above, sites may use various types of source documents to collect AE data. This data is used to enter AEs into the case report form (CRF). Many sites use an AE log to create a complete list of events. Besides including the basic information required for entry on the CRF page, the AE log will often have a column where the investigator initials and dates his or her review of the AE entry and enters the causality assessment. Some sponsors have guidelines for the site to make CRF entries within a certain timeframe, e.g., one week after a study visit is completed. In any case, complete AE CRFs promptly so they can be

monitored and forwarded to the sponsor for review. The CRF for an AE consists of several basic parts (Note: Some sponsors add other sections depending on the study itself or preferences of their data management department):

1. AE name. The succinct description of the event using medical terminology.
2. Start/Stop dates. In a day, month and year format, enter the start date and date the event was resolved. Some CRFs have a box to check if the event was ongoing at the end of the study. In some cases, the start or stop date will be unknown. In these cases, list only what could be confirmed and indicate what information is unknown in an acceptable format such as "UNK." Some CRFs require information about the outcome of the event, such as: recovered, recovered with sequelae, ongoing with sequelae.
3. Severity. Usually designated as mild, moderate or severe.
4. Relationship (causality) to the IP. Usual choices include: not related, possibly related, probably related, or definitely related. Some protocols require the site to further state if the AE was related to use of a concomitant medication, a concurrent illness, etc.
5. Action(s) taken. Examples include discontinuation from the study, medicinal treatment(s), and non-medicinal treatment, such as physical therapy or surgery. Some CRFs will include a section that documents action taken with the IP: none, dose adjusted, discontinued temporarily, etc.
6. Whether the event is classified as serious or not. Most AE CRFs have a yes/no box to check. Some CRFs require the site to check off the factors that qualify the event as an SAE: death, life-threatening, disability, hospitalization, congenital anomaly, medically important.

### **Analyzing Adverse Event Data**

The investigator has primary responsibility for the health of the subjects. This responsibility cannot be delegated to the study coordinator or nurse, although they share the responsibility. Therefore, promptly provide the information to the investigator (or delegated and qualified subinvestigator physician) for his or her review and decisions:

1. Confirm that the visit findings should be documented as an AE based on one of the following criteria:
  - a. The condition has worsened from what was documented in the medical history.
  - b. A sign or symptom has worsened from what was observed and recorded at the baseline study examination.
  - c. The condition, sign, or symptom is new since the AE reporting period began.
2. Using medical terminology, describe the event. (An alternative descriptive terminology system for reporting AEs is the NCI Common Terminology Criteria for Adverse Events (CTCAE).<sup>11</sup> Some protocols may require use of this system to classify AEs observed during the study.) Provide a clear and detailed description. For example, if congestion, specify whether it is nasal, sinus or pulmonary.
3. Determine the relationship of the AE to use of the IP, i.e., whether the event is definitely, probably, possibly or not caused by use of the IP. AEs occur with active controls and even placebos, which is a challenge when assessing causation in a double-blind study. A subject's treatment should not be unblinded unless the information is important for treating an AE with significant health ramifications. The protocol should include requirements for unblinding.
4. Explain the causation determination, including any sources of uncertainty. If an AE appears to be an intercurrent illness rather than a reaction to the IP, note this opinion, but still document the event as an AE. Considerations when determining AE causation include the following:
  - If it occurred following use of the IP.

- If it followed a known pattern of response to the IP.
  - If it reappeared or worsened when the IP was re-administered.
  - If there is a plausible physiological connection between use of the IP and the AE. (However, many proven drug/AE connections have not been explained biologically.)
  - If, instead, it could have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy.
5. When an AE appears to be related to the use of the study drug, the investigator must also determine whether the event was anticipated or unanticipated. Report unanticipated AEs (and other problems) promptly to the sponsor and, in most cases, to the IRB.<sup>12</sup> The FDA recently published a guidance document that discusses reporting of unanticipated problems.<sup>13</sup>
  6. Review laboratory and other test results for relevance to AEs observed during the visit, as well as independent evidence of AEs. An abnormal lab value or other test result is clinically significant if either of the following conditions is met:
    - The abnormality indicates that a disease and/or organ toxicity is new or has worsened from baseline.
    - The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.
 The Investigator then determines if the name of the AE is based on the sign/symptom/condition(s) observed and supported by the lab/other test findings OR the lab value/other test result itself.<sup>14</sup>
  7. If a subsequent diagnosis explains a sign or symptom as the result of a condition, document the condition as an AE, referencing the preceding signs and/or symptoms, and close the AE(s) that consist just of signs and/or symptoms, referencing the condition AE.

### **IRB, Investigator and Sponsor Handling of Safety Information**

The IRB, investigator and sponsor all have responsibilities for handling AE information; some are dependent on the other, as noted in these excerpts from the FDA's January 2009 "Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs — Improving Human Subject Protection":

After the initial review and approval of a clinical study, an IRB must conduct continuing review of the study at intervals appropriate to the degree of risk presented by the study, but at least annually (§ 56.109(f)). The primary purpose of both initial and continuing review of the study is "to assure the protection of the rights and welfare of the human subjects" (§ 56.102(g)). To fulfill its obligations during the conduct of a clinical study, an IRB must have, among other things, information concerning unanticipated problems involving risk to human subjects in the study, including adverse events (AEs) that are considered unanticipated problems (§§ 56.108(a)(3), (4), (b)). Due to increasingly large volumes of individual adverse event reports submitted to them, the IRBs ask sites to carefully review their reporting guidelines and federal guidelines concerning unanticipated problems.

Investigators are required to submit progress reports to the Sponsor for the submission of their annual reports to the FDA (§ 312.64(a)). Investigators are also required to report promptly "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" (§ 312.64(b)). Investigators are required to report promptly "to the IRB...all

*unanticipated problems* involving risks to human subjects or others,” including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report of “any adverse experience associated with the use of the drug that is both serious and unexpected” and “any finding from tests in laboratory animals that suggests a significant risk for human subjects” (§ 312.32(c)(1)(i)(A),(B)). And, more generally, sponsors are required to “keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use” (§ 312.55(b)). In a multicenter study, to satisfy the investigator’s obligation to notify the IRB of unanticipated problems, an investigator may rely on the sponsor’s assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

### **Serious Adverse Events**

SAEs, by definition, require special attention and action by the site. Vigilance is required not only during study visits. Information may arrive obscurely or indirectly. For example, if a subject cancels a visit, it may be due to an illness or injury. A subject’s death or injury may be reported in the local newspaper. Detective work may be required.

When a possible SAE is detected, collecting comprehensive data, analyzing it, and treating the condition become the highest priorities.

When an SAE is recognized, the process for the site is relatively simple, albeit often laborious: notify the study sponsor company in the specified time (usually 24 hours) and follow the sponsor’s reporting process to conclusion. The institutional review board (IRB) probably also has stringent SAE reporting requirements.

While an event resulting in death is obviously an SAE, the other criteria may require some clarification. For example, if a subject goes to a hospital’s outpatient clinic but is admitted as an inpatient solely for the convenience of the hospital, the event probably does not constitute an SAE, although sponsors and IRB policies can vary. Finger tendonitis may not constitute a disability for most people, but it would be for a professional violinist. It is thus important to consult with the sponsor and IRB when SAE classification is not obvious.<sup>15</sup>

When an SAE occurs:

- Address the subject’s medical condition as the highest priority.
- Aggressively collect pertinent documentation, such as medical records and discharge summaries, in order to complete a report for the Sponsor that is accurate and timely.
- Make sure the report is consistent with source documents, CRFs and other study records. Ensure that start/stop dates and especially the event description in the SAE report are consistent with the CRF and other study documents. Concomitant medications described in the report should also be consistent with respect to medication names and their usage (start/stop dates, dose, route, frequency). Document any inconsistencies.
- Do not delay submitting the report, even if it is not complete or certain; amend it when new information arrives.
- Continue collecting and documenting pertinent information until the reporting period concludes, as defined by the study protocol.

Timelines, processes and forms for AE and SAE reporting vary by protocol, as well the follow-up at the end of the study. Requirements should be clearly written and understood at study initiation.

## **Conclusion**

Adverse event reports are the foundation of safety analysis for clinical trials. Investigative sites that take the time to prepare for a study, carefully interview their study subjects during a clinical trial, and document and review these observations will better handle the task of safety reporting, thereby protecting the subjects and generating useful data.

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