

## **Adverse Event Reporting: Site Preparation**

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The reporting of adverse events (AEs) is a standard task for investigative sites involved in pharmacological clinical trials. This article will focus on four steps of initial preparation that a site should take to facilitate the proper identification and handling of AEs during a clinical trial.

### **Step 1. Investigative site personnel should be knowledgeable about applicable laws, regulations, guidances and guidelines:**

Federal regulations:<sup>1</sup>

- 21 CFR 312.32: Investigational New Drug (IND) Safety Reports. This regulation states the definition and pertinent aspects of a Serious Adverse Event (SAE), including the key aspects of causality and unexpectedness. Sponsor responsibilities are also described.<sup>1</sup>
- 21 CFR 312.56 (c), (d): This regulation states the responsibility of the sponsor to review safety information.
- 21 CFR 312.62 (b): This regulation states the responsibility of the investigator to keep accurate records of observations (including AEs).
- 21 CFR 312.64 (b): This regulation states the responsibility of the investigator to report AEs to the sponsor.
- 21 CFR 312.66: This regulation states the responsibility of the investigator to report specific AE information to the presiding Institutional Review Board (IRB).

FDA guidance:<sup>4</sup>

- Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs — Improving Human Subject Protection

Sections of the International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guideline:<sup>2</sup>

- 1.1: Adverse Drug Reaction (ADR) definition.
- 1.2: Adverse Event (AE) definition.
- 1.50: Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) definition.
- 1.60: Unexpected Adverse Drug Reaction definition.
- 3.38 (c): Requirement for the investigator to report specific ADRs to the IRB.
- 4.3.2: Responsibility of the investigator to ensure care for subjects with AEs.
- 4.7: Unblinding procedures involving SAEs.
- 4.11: Investigator responsibility for safety reporting.
- 5.16: Sponsor responsibility for evaluating and reporting safety information.
- 5.17: Sponsor responsibility for reporting adverse drug reactions.
- 8.3.17: Filing of documents about unexpected adverse drug reactions and other safety information.

**Step 2. Investigative site personnel should be knowledgeable about the sections of the study protocol that concern adverse events. The following information should be provided in the protocol; if not, the site should request clarification:**

There should be a clear statement of the timelines for reporting AEs and SAEs. Sometimes a clause in the protocol specifies that any abnormal physical exam or laboratory finding identified during the screening period is to be considered part of the medical history and not an AE. It is not unusual for the AE/SAE reporting timelines to be different, i.e., AE reporting ends at the last study visit and SAE reporting ends thirty days after date of last dose of investigational product (IP). Some protocols specify that any AE/SAE that an investigator deems related to the IP should be reported, regardless of when it occurred.

There should be guidelines on how the site should handle an AE/SAE that is ongoing at the end of the study reporting period. Commonly, sponsors require investigative sites to follow all AE/SAEs that were deemed related to the IP administration until the event is resolved or assessed as chronic and stable. Some sponsors require that all SAEs be followed by the investigative site until resolution, regardless of whether the event was related to IP administration.

Some protocols provide reporting exceptions for SAEs. For example, some sponsors do not require the site to report an SAE if the subject has an elective hospital procedure during the study.

In some clinical trials, disease symptoms and/or other expected clinical outcomes associated with the disease under study, which might technically meet the ICH definition of an AE or SAE, are collected and assessed as efficacy parameters rather than safety parameters. An example might be severity scoring of prospectively defined disease symptoms at each clinic visit during a rheumatoid arthritis study. The hypothesis underlying this approach is that the study treatment will have a positive impact on disease symptoms. If prospectively defined clinical outcomes, such as symptoms of a studied chronic disease or death due to disease progression in an oncology trial, are to be assessed as efficacy endpoints and not as AEs/SAEs, the protocol should clearly describe the methods for recording and analyzing these data.<sup>3</sup>

Some protocols define specific events of interest and require investigators to expeditiously report them to the sponsor for real-time monitoring. Examples include events of scientific or medical concern specific to the development program, and events that might be precursors to more serious medical conditions. The protocol should clearly define events of interest with precise specifications. Although they are to be reported expeditiously to facilitate the sponsor's real-time review, events of special interest are classified as SAEs only if the investigator determined that they meet the regulatory criteria.<sup>3</sup>

**Step 3. Investigative site personnel should be knowledgeable about applicable reporting requirements for the IRB presiding over the study. The site should request a copy of the IRB's reporting requirements and maintain it in an accessible location for all staff, e.g., in the regulatory binder. Common IRB reporting requirements include:**

- Report all adverse events that are deemed both unexpected and related to test article administration.
- Report all serious adverse events. Many IRBs now want reports only on SAEs that are both unexpected and related to IP administration. See below for recommendations from the FDA.
- Submit all IND Safety Reports.
- Report events of interest, as identified by the sponsor.

- Report any other event that requires a change at the site or in the protocol level to assure the protection of the rights and welfare of the research subjects.

FDA guidance states that only the following AEs should be considered as “unanticipated problems” that must be reported to the IRB.<sup>4</sup>

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals a higher rate in the drug treatment arm versus a control).
- An AE that is described or addressed in the investigator’s brochure, protocol or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator’s brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects.
- A serious AE that is described or addressed in the investigator’s brochure, protocol or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator’s brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

**Step 4. Obtain a thorough baseline medical history and conduct a comprehensive physical exam for each study subject. With this information, site personnel can correctly identify and characterize adverse events that occur during the study.**

If possible, obtain a well-written clinical summary from the subject’s primary physician or specialist, along with relevant lab reports and related documents. Request photocopies of supporting medical records if required to clarify the eligibility of the subject. If the subject is the investigator’s patient, the investigator should provide the supporting medical records as discussed below.

In lieu of a clinical summary, try to obtain a copy of the subject’s most recent medical records. The extent of the records should be based on the protocol eligibility requirements. For example, if the protocol states that a subject cannot have a certain condition for the past 90 days, the site should request the last three months of the subject’s medical records. Since there will be inclusion/exclusion criteria specifying various lengths of time, the longest time period should be used when requesting the medical records.

Regardless of whether a clinical summary or medical records are provided, the process should include an interview with the subject. Most preferable is having the aforementioned records available as reference during this interview so you can obtain clarifications as necessary. If the summary or records arrive later, review them at that time and ask the subject for appropriate clarifications.

At minimum, if a clinical summary or recent medical records are not available, interview the subject to complete a medical history questionnaire. The history-taker must be clinically knowledgeable in order to ask the appropriate questions and probe for additional information when needed.<sup>3</sup> Unfortunately, this responsibility is often delegated to a study coordinator without medical training, who does not know what questions to ask. Any deficiencies usually come to light during the study when apparently adverse events are difficult to categorize as continuing, worsening or new. At that point, amendments to the medical history appear to be attempts to avoid documenting AEs or general sloppiness in source documentation.

The medical history should describe, in detail, prior and existing conditions, including severity, pattern of occurrence, and treatments. Serious conditions and conditions in which a health professional was involved in the diagnosis, treatment or both should be listed. The subject may provide additional conditions that are not or were not under the care of the subject's primary care physician or specialist. Exercise good medical judgment in the inclusion of this additional information, particularly if it has no defined pattern and/or bearing on the eligibility requirements or the disease entity being evaluated. For example, if a subject had a history of one urinary tract infection, exclude it from the medical history unless it was clinically significant or affected the eligibility requirements of the study. Other reported conditions, such as occasional headaches, pose a greater challenge as to whether they should be included in the medical history because of poorly defined frequency and treatments. In cases like this, include only those conditions for which there are supporting medical records from a physician, and thus report non-specific conditions, such as "occasional headaches," as adverse events only if they occur during the study.

## **Conclusion**

Investigative sites that take the time to complete these four steps will be prepared to handle safety reporting during a clinical trial, thereby protecting the subjects and generating useful data.

## **References**

1. 21 CFR 312
2. International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidance
3. "Good Clinical Practice: A Question & Answer Reference Guide", Barnett International, 2008
4. Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs — Improving Human Subject Protection, January 2009

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