

Adverse Event Reporting and Treatment after the Study

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The reporting of adverse events (AEs) — including serious adverse events (SAEs) — to study sponsors is a standard task for investigative sites in clinical trials. This article, the third in a three-part series, will focus on the handling and reporting of AEs after subjects complete the study and even after study closeout or termination under an Investigational New Drug Application (IND).^{1,2}

AEs that continue or occur after subjects complete the study are important for two reasons. First, human subjects protection obligations do not end until the effect of the study drug ends, which may continue past the end of the study. Second, it is essential to establish the safety of study drugs in the real world, which is not limited by the ending date of a study.

Federal Regulations

The following sections of the Code of Federal Regulations (CFR) Title 21 relate to the reporting of adverse events by investigative sites:

- **312.53 (c) (vi) (e)**. The investigator, per FDA Form 1572, is responsible for reporting AEs to the sponsor in accordance with 21 CFR 312.64.
- **312.53 (c) (vii) and 312.66**. The investigator is responsible for reporting unanticipated problems to the Institutional Review Board (IRB), including certain AEs.
- **312.60**. The investigator is responsible for conducting the study according to the investigational plan, (i.e., protocol, which specifies AE reporting procedures) and protecting the rights, safety and welfare of subjects under the investigator's care (which implies continued treatment of AEs).
- **312.62 (b)**. This investigator is responsible for keeping accurate records of observations (including AEs).
- **312.64 (b)**. The investigator is responsible for reporting AEs to the sponsor.

Guidance Documents

The following guideline and guidance documents relate to the reporting and handling of adverse events:

- Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (FDA version of ICH E6 guideline):
 - **3.3.8 (c)**. Investigator is responsible for reporting serious and unexpected adverse drug reactions (ADRs) to the IRB/IEC.
 - **4.3.2**. Investigator is responsible for ensuring care for subjects with AEs during and following the study.
 - **4.11**. Investigator is responsible for reporting AE/SAEs to the sponsor and, depending on applicable regulations, to the IRB/IEC.
- International Conference on Harmonisation (ICH) E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting:
 - **III**. Investigator is responsible for expedited reporting of certain serious and/or unexpected ADRs (similar to unanticipated problems).

- **III.E.3.** Investigator is responsible for expedited reporting of “serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) to the sponsor... [based on] a causality assessment and determination of expectedness.”
- FDA Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection discusses the reporting of adverse events as a subset of unanticipated problems.
- FDA Guidance for Industry: Investigator Responsibilities — Protecting the Rights Safety, and Welfare of Study Subjects states that investigators are responsible for ensuring medical care for any adverse event related to study participation, no matter when the AE occurs.
- FDA Guidance for Industry: Premarketing Risk Assessment states: “In some cases, it is recommended that all subjects be followed...even after the formal end of the study...for ascertaining important safety events...for subjects...who drop out of the trial or who finish the study early due to meeting a primary outcome of interest.”

The Study Protocol and Clinical Trial Agreement

The investigator is bound by regulation and contract to conduct the study according to the protocol (21 CFR 312.60).

ICH E6 4.11.2, states, “Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.”

The protocol should specify AE handling and reporting requirements for the periods after a subject completes the study and after the study ends at the research site. If it does not provide clear and complete information, the site should ask the sponsor to provide it in writing.

The clinical trial agreement may also include relevant text in the site duties or subject injury sections.

Reporting AEs to the Sponsor

None of the Federal regulations specifically discuss reporting to sponsors in the post-subject-completion period, but it can be assumed that the investigator should keep the sponsor informed about any open AEs.

ICH E2A III.E.3 states that the investigator is responsible for expedited reporting of “serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) to the sponsor... [based on] a causality assessment and determination of expectedness.” This guideline is limited to SAEs that the investigator concludes are related to the test article and unexpected, according to the protocol and investigator’s brochure.

The sponsor should specify in the protocol what SAEs (and problematic AEs), if any, it would like to receive information about post-subject-completion. An example directive would be:

Serious Adverse Events (SAEs) that are considered at least possibly related to the investigational product (IP) should be reported at any time during or after the study.

If the protocol does not provide this information, the site should ask the sponsor for clarification, in writing. If the protocol is not specific and further clarification has not

been provided by the sponsor, the site should notify the sponsor of any AE/SAEs observed post-study that are deemed related to the IP and let the sponsor decide the extent of the reporting.

Reporting AEs to the IRB

None of the Federal regulations specifically discuss AE reporting in the post-subject-completion period but it can be assumed that the investigator should keep the IRB informed about any open medical conditions. The regulations only require investigators to report adverse events to IRBs in connection with unanticipated problems (21 CFR 312.53 (c) (vii) and 21 CFR 312.66).³

Investigators should carefully review their IRB approval letter and other requirements and ask the IRB for clarification, if needed. The protocol and clinical trial agreement may also include IRB reporting requirements.

Treatment of AEs

FDA Guidance for Industry: Investigator Responsibilities — Protecting the Rights Safety, and Welfare of Study Subjects (B.1.) states that, "Subjects 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 at the investigative site." (Italics added.) In other words, investigators are responsible for providing medical treatment to subjects that experience AEs during or after the study, provided the AE is related to the study intervention, which, based on the stent placement example provided in the guidance, includes controls and procedures.

After the subject's participation in the study concludes, how long does this responsibility extend? According to the FDA, "In general, the section of the guidance concerning the investigator's responsibility to protect the rights, safety and welfare of subjects is motivated by our compliance and enforcement experience with relatively inattentive investigators who didn't take adequate steps to protect subjects. Thus, the goal is not to suggest an onerous imposition of responsibility for all aspects of care for an indefinite period of time, but rather to have investigators be attentive and take reasonable steps to provide care, or see that needed care is provided, to subjects for medical issues related to study participation."⁴ In other words, the duration of the post-study period should be reasonable.

ICH E6 4.3.2 sets forth a similar standard in stating, "*During and following a subject's participation in a trial*, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware." (Italics added.)

The above rules do not state when the investigator's responsibilities for an AE end. Here again, the protocol can provide direction to the investigator. For example, the protocol may state the following requirements:

All AE/SAEs will be followed through to resolution or until the investigator attributes the AE/SAEs to a cause other than the study drug or assesses them as chronic or stable.

If the protocol is more stringent than the guidances, the investigator should follow the protocol. If the protocol is less stringent than the guidances, the investigator should

follow the guidances. However, because guidances do not have the full legal force of regulations, some latitude may be appropriate.

The clinical trial agreement and informed consent form should state how treatment decisions will be made and who will pay for the medical care.

Summary

Investigators are responsible for reporting and treating AEs, even after the subject completes the study and even after the study ends. The regulations are silent on the post-subject-completion period, but the guidances are fairly clear. Study sponsors and IRBs are responsible for telling the investigator various details about AE reporting and treatment. A well-written protocol, investigator's brochure, informed consent form, and clinical trial agreement are thus essential.

References

1. "Adverse Event Reporting: Site Preparation Requirements", Journal of Clinical Research Best Practices, Volume 5, Number 3, March 2009.
2. "Adverse Event Reporting: During the Study," Journal of Clinical Research Best Practices, Vol. 8, No. 3, August 2009.
3. "Reporting Unanticipated Problems to IRBs," Norman M. Goldfarb, Journal of Clinical Research Best Practices, Vol. 6, No. 6, June 2010.
4. FDA Office of Good Clinical Practice, email communication, July 22, 2010

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