

Adverse Events before Drug Administration

By Annette Kinsella

The purpose of reporting adverse events is to protect the safety of the subject experiencing the event, other subjects in the trial, and anyone else potentially exposed to the risk. Clinical investigators are required to report to the sponsor adverse events "that may reasonably be regarded as caused by, or probably caused by, the drug." (21 CFR §312.64(b)) In addition, investigators must "promptly report to the IRB... all unanticipated problems involving risk to human subjects or others." (21 CFR §312.66)

There are significant differences between these two requirements:

- Sponsors receive reports on events caused by the drug, regardless of whether or not they were anticipated or involve risk to human subjects or others.
- IRBs receive reports on events that are unanticipated and involve risk to human subjects, whether or not they are caused by the drug.

The FDA has adopted the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Guideline as its GCP Guidance. This guideline defines an adverse event as:

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

Once a trial is well-underway, it can be difficult to determine causation of an adverse event (AE). For example, a subject may crash into a tree while driving away from the research center, breaking a leg. On the surface, there may appear to be no relationship between the study drug and the broken leg. However, in one out of 10,000 people, the study drug may decrease inhibitions, thereby increasing risk-taking behavior and dangerous driving. If we know this risk exists, reporting traffic injuries is clearly appropriate. Since we cannot know that the risk does not exist, reporting traffic injuries is still appropriate.

The ICH Guideline says "administered a pharmaceutical product," not "to be administered" a pharmaceutical product," so the definition of adverse events clearly excludes the period prior to administration of the study drug.

If the study could not possibly have caused the injury, there is no safety benefit for reporting it as an adverse event, and no regulatory requirement. In fact, reporting such an injury indirectly reduces safety benefits:

True Story

Subject TK has given informed consent. He returns for the screening and randomization visit with a new illness. Rather than capture the illness as baseline medical history (requiring documentation but not follow-up), the sponsor requires that it be documented as an adverse event. Although the subject screen-fails, the sponsor requires follow-up (with no compensation to the site) to ensure that the adverse event is resolved.

- Superfluous adverse event documentation reporting and follow-up wastes research site, study sponsor, institutional review board, and government resources that could be better utilized on activities that do benefit safety. Following up with the subject until the adverse event resolves can be very time-consuming.
- Superfluous adverse event documentation and reporting conceal the real adverse event “needles” in a “haystack” of reports.

Taking the conservative approach may seem safe, but excess conservatism causes trials to bog down and run over budget. In addition to the time wasted documenting and reporting adverse events, time is wasted following-up with the subject until the event resolves.

When should we start documenting and reporting adverse events?

1. At the beginning of the first study-related visit?
2. After the subject signs the informed consent form?
3. Once physical screening begins?
4. After the subject is randomized?
5. After the study drug is administered?

Until the study drug is administered, there is no regulatory requirement or safety benefit to report an AE to the sponsor because the study drug could not have caused it. Also, there is no regulatory requirement or safety or welfare benefit to report it to the IRB unless the AE is unanticipated or involves risks to human subjects or others. There are cases where IRB reporting has value prior to drug administration. For example, unexpected AEs may be caused by procedures that are not standard of care. However, mild adverse events caused by fasting or medication washout can be anticipated and therefore should not require reporting.

Nevertheless, many study sponsors require documentation, reporting and follow-up of all AEs that occur before administration of the study drug. Clinical research is very expensive and time-consuming. If there is no safety benefit, and no regulatory requirement, there is no need to report adverse events prior to administration of the study drug. With some common sense, we can put valuable resources to their best use.

Author

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