Introduction

The term "adverse event" is often used generically to describe a problem that occurs in a clinical trial that poses a potential or actual risk to a subject. However, that usage is confusing because within the regulations that address these incidents, there are inconsistencies and variations.

In fact, the term "adverse event" itself is a specific, regulatory term employed by the FDA, and individuals involved in clinical research should remember that the term has specific meaning in the context of the FDA, in addition to its generic usage.

Familiarizing yourself with the following regulations will help you understand how adverse event reporting is carried out.

The Common Rule

The "Common Rule" for the protection of human subjects involved in research is found in the Code of Federal Regulations (CFR), Subpart A of 45 CFR Part 46. It governs almost all research that is federally funded. The Common Rule does not use the term adverse event. Instead, it uses the phrase "unanticipated problems involving risks to subjects or others."

The Office of Human Research Protections (OHRP) provides the most definitive guidance on adhering to the Common Rule requirements. OHRP addresses adverse event reporting in its guidance on *Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*.

The FDA also addresses adverse event reporting in its guidance *Adverse Event Reporting—Improving Human Subject Protection*.

An unanticipated problem, the Common Rule's terminology, is not the same as an adverse event. But it is important to understand the necessity for reporting unanticipated problems.

In FDA terms, an adverse event is simply something bad that happens. A serious adverse event, however, is something that is life-threatening or requires significant medical intervention, such as hospitalization or surgery, and it's these serious adverse events that require reporting to the agency.

In contrast, an unanticipated problem under the OHRP guidance might be something that is a significant deviation from a protocol, a significant risk that a subject or group of subjects faced. It is reportable and it qualifies as an unanticipated problem even if no actual injury occurred to study subjects.

The Common Rule includes no minimum risk threshold for unanticipated events.

The Common Rule requires an IRB to examine the adverse event reporting and data monitoring. The IRB shall determine, "when appropriate, [that] the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects," according to 45 CFR 46.111(a)(6).

FDA Regulations for Drugs

The FDA drug regulations, which govern trials that are intended to be submitted to the FDA as part of a drug application, address several types of adverse events. Under FDA, any adverse

experience associated with the use of the drug that is both serious and unexpected must be reported to the FDA and all investigators participating in the trial, according to 21 CFR Part 312.32(c)(A).

The key terms from 21 CFR Part 312.32(a) that determine whether an adverse event is reportable are the following:

- Associated. There must be a reasonable possibility that the experience may have been caused by the drug.
- Serious. The injury is fatal or life-threatening, permanently disabling, requires inpatient hospitalization, or is a congenital anomaly; and
- Unexpected. Not identified in the investigator's brochure or plan.

FDA Regulations for Devices

FDA regulations also address adverse events in trials conducted under an Investigational Device Exemption.

The FDA standards for devices align more closely with the Common Rule in requiring that the investigator report "unanticipated problems involving risks to human subjects." They use the same broader standard that OHRP uses in 45 CFR Part 46.

In the device world, there also is also the unique term "unanticipated adverse device effect" that the FDA requires sponsors to evaluate and report (21 CFR Part 812.46(b)).

"Unanticipated adverse device effect" means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects," according 21 CFR Part 812.3(s).

The part of the definition that states, "caused by or associated with a device," has often caused investigators and sponsors to stumble and has led to a good deal of device-related enforcement action by the FDA.

Often, when investigating an unreported adverse effect, the FDA will be told by investigators that they didn't report an adverse effect because they didn't believe that the adverse effect on the patient was caused by or associated with the device. It was caused by something else.

The FDA prefers that investigators report suspected device effects to the sponsor and that someone at the sponsor level be the one to make a decision about whether something is caused by or associated with a device, rather than letting the individual investigators make their own determinations.

The failure to report adverse events in device trials has been a major point of vulnerability for researchers who have been funded for their studies by private device companies, and the terms and their meanings often are at the center of the disputes.

The "unanticipated adverse device effect" is comparable to the "serious adverse drug experience." Serious adverse drug experience is defined in 21 CFR Part 312.32(a) as "an adverse drug experience

occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect." It also must be a side effect that the sponsor did not anticipate when the trial was designed, and not included in the investigational brochure or the informed consent documents.

Regulatory Reporting Obligations

The specific regulatory reporting obligations for adverse events and unanticipated problems in the course of research depend on who is reporting to whom, including the following reporting relationships:

- The investigator to the IRB;
- The investigator to the sponsor;
- The sponsor to the FDA;
- The sponsor to other investigators in a multisite trial (sharing the external adverse events);
- The sponsor to the IRBs; and
- The IRB to OHRP, the FDA and high administrative officials within hospitals, community health centers, medical schools or clinics.

The timelines and requirements also vary slightly, depending upon whether the trial involves a device or a drug.

Devices - Investigator to IRB

Under the Common Rule and the FDA regulations, investigators must promptly report unanticipated problems — bad things that happen even if the bad event or the bad effect does not come to fruition on the individual subject — involving risks to human subjects or others (45 CFR Part 46.103(b)(5) and 21 CFR Part 56.108(b)(1)).

Investigators also must report unanticipated adverse device effects to the IRB. The time period for this is 10 working days after the investigator first learns of the effect, according to 21 CFR Part 812.150(a)(1). This is also a matter of some controversy because some investigators defend their failure to report by saying they delayed while determining if an event was related to the device and then started the 10-day clock. But that is not how the FDA interprets the requirements. The FDA's interpretation is when the investigator first learns about the effect, it is the investigator's responsibility to take those 10 days to investigate, report within the 10 days to the IRB and make the other reports.

The investigator also is required to send a summary of all adverse events and unanticipated problems involving risks to subjects to the IRB at continuing review, which must occur at least annually. Any information about risks associated with the research, such as any results of additional animal studies or other completed trials that involved the same experimental device, also must be reported at continuing review.

Devices - Investigator to Sponsor

The investigator must report to the sponsor the unanticipated adverse device effects as soon as possible, but not later than 10 working days after the investigator first learns of the effect (21 CFR Part 812.150(a)(1)).

Investigators also must maintain records of all adverse device effects (whether anticipated or unanticipated), according to 21 CFR Part 812.140(a)(3)(ii).

It's not a good defense for an investigator to say to the FDA, "I didn't record the anticipated bad events, I just recorded the unanticipated events." Monitors visiting research sites must be aware of all of the adverse effects — whether reported or unreported — and make sure that those are recorded in study forms.

Devices - Sponsor to the FDA

The sponsor monitoring obligations under the IDE regulations state that the sponsor must determine what effects should be reported to the FDA, IRB and other investigators. The sponsor must then make sure they have been reported. Sponsors must immediately evaluate any unanticipated adverse device effect and, if a sponsor determines that the effect presents an unreasonable risk to subjects, terminate all investigations or part of investigations presenting that risk. Terminated studies of significant risk devices may not resume without FDA and IRB approval, according to 21 CFR Part 812.46(c).

After the sponsor receives a report, it has 10 working days to report the results of its evaluation to the FDA. The FDA can ask for additional information about the report (21 CFR Part 812.150(b)(1)). In total, there are at most 20 days from the time that the investigator learns of an event for the sponsor to receive the report, interpret it and pass it to the FDA if necessary.

Devices - Sponsor to IRB and Other Investigators

The obligation for device trial sponsors to report to IRBs and other investigators is an important difference from the drug world, because there is no parallel obligation of a sponsor to report the adverse experiences with drugs to an IRB. But sponsors do have to report to all of the IRBs and all of the investigators in a multisite study about all of the unanticipated adverse device effects that they receive and believe are unanticipated adverse device effects. Results of a sponsor's evaluation of an unanticipated adverse device effect must be reported within 10 working days of the sponsor receiving notice of the effect, according to 21 CFR Part 812.150(b)(1)).

This multitude of confusing sponsor obligations is one reason IRBs and investigators should beware of studies in which the investigator holds an IDE and becomes the sponsor, with all regulatory and reporting obligations of a sponsor and an investigator. It is better for sponsors, with their compliance and reporting infrastructures, to fulfill the role of sponsor and not rely on investigators in that role. If they rely on the investigators to act as sponsors and run an investigator-initiated trial, then sponsors run the risk of having funded a trial that does not meet regulatory standards. In the end, the sponsor probably will not be able to use it to support an FDA application.

Drugs - Investigator to IRB

The requirements for drug trials include rough timelines for sponsors to make reports to IRBs, but in some cases do not give specific deadlines. For example, unanticipated problems and serious and unexpected adverse drug reactions must be reported promptly. In addition, a summary of all adverse events and unanticipated problems in all the sites in a multisite study must be reported to the IRB at least at the annual continuing review, which is conducted by the IRB or research ethics committee.

The reporting requirements include the following:

- Unanticipated problems involving risks to subjects or others, to be reported promptly;
- Summary of adverse events and any unanticipated problems involving risks to subjects or others, to be reported at continuing review;
- Any information about risks associated with the research, to be reported at continuing review; and
- Serious adverse events in human gene transfer protocols that are unexpected and associated with the use of the gene transfer product, to be reported within 15 calendar days after receipt of information or within seven calendar days if the event is fatal or life-threatening. Under National Institutes of Health (NIH) guidelines, the investigator also must report such events to the NIH Office of Biotechnology Activities, the FDA and OHRP, if applicable.

Drugs - Investigator to Sponsor

The level of urgency for the investigator reporting events to the sponsor is reflected in the use of the term "immediately" rather than "promptly" for some events.

"Promptly" could mean, in many cases, about 15 days. "Immediately" is used to indicate something much more pressing. The reporting requirements include the following:

- Adverse events that could be reasonably regarded as caused by or probably caused by the drug, to be reported promptly unless the event is alarming, in which case, to be reported immediately); and
- Serious adverse events, to be reported immediately unless the protocol or other documents indicate otherwise. It is essential to specify clearly in the protocol and the adverse event reporting section of the protocol what is and is not expected as well as what is and is not regarded as serious.

One of the most important distinctions in terms of the reporting obligations is that investigators should report events to sponsors, regardless of whether they are severe or unexpected. The sponsor, however, is required to report only serious, unexpected and related adverse experiences to the FDA. The sponsors are allowed to winnow out the mass of adverse event reports that had no severity or expectation threshold and to report to the FDA only those that they analyze and regard as serious, unexpected and related to the administration of the drug or the protocol.

The sponsor is charged by law with acting as the interpreter of the adverse event reports. It is a duty that the sponsor can't discharge by simply stamping and then passing on all of the adverse event reports to the other sites in a multisite study or the FDA.

Drugs - Sponsor to the FDA

Reporting requirements for the sponsors to the FDA include important deadlines of 15 and seven calendar days. They include the following:

- Adverse experiences that are associated with the use of the drug and that are both serious and unexpected, to be reported within 15 calendar days after receipt of information;
- A finding from tests of the drug in laboratory animals suggesting a significant risk to human subjects, to be reported no later than 15 calendar days after receipt of information;

- Unexpected fatal or life-threatening experience associated with use of the drug, to be reported by telephone or fax no later than seven calendar days after sponsor's receipt of the information;
- Any adverse drug experience after drug approval that is both serious and unexpected, whether domestic or foreign, to be reported within 15 working days of receipt of information; and
- Any adverse experience with a licensed product that is both serious and unexpected, whether domestic or foreign, to be reported by the license holder within 15 calendar days after receipt of information by the licensed manufacturer.

In postmarketing studies, sponsors must not only report under the MedWatch requirements but also be consistent with reporting obligations for IND research that require reporting serious consequences or adverse effects of an already-approved and legally marketed drug. Investigators may report to MedWatch, but are not required to do so. MedWatch, the FDA's safety information and adverse event reporting program, provides information about safety issues and provides an online gateway for reporting adverse events. The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research have developed the Adverse Event Reporting System to allow electronic submission of postmarketing drug and therapeutic biological product safety reports.

Sponsor to Other Investigators

Sponsors are required to report to other investigators in a multisite trial. The requirements are similar to those for sponsors reporting to the FDA. The reporting obligations include the following:

- Adverse events that are serious, unexpected, and associated with the drug, to be reported promptly;
- Tests on animals indicating significant risk to humans; and
- Any new observations discovered by or reported to the sponsor about the drug (other than the other safety information) as the investigation proceeds.

Drugs - Sponsor to IRB

There is no specific FDA obligation for sponsors to report to IRBs for adverse experiences with the use of drugs. It is the investigators' obligation to relay information to their own IRBs or research officials according to the policies of the IRB and their own institutional policies.

In investigator-initiated studies, the investigators have the obligation not only to fulfill the role of investigator in the study but also to complete the sponsor's reporting obligations to other sites in a multisite study with respect to serious unexpected events that are related to the drug and to the FDA.

This role of investigators is one reason why, when sponsors fund investigator-initiated studies, they should be careful to put in the study agreements that they are not acting as the sponsor but are funding investigator-initiated studies. Sponsors must make sure in the way they craft their funding agreements that they are alerting the investigator and the institution that the investigator, in discharging the funding obligation and conducting the activities that are required by the grant, will be required to act not only as an investigator but also as a sponsor. It is a way to protect sponsors in case something goes wrong and the investigator points to the sponsor as the one who should have reported to the FDA.

IRB to OHRP, the FDA and Institutional Officials

Both the Common Rule and FDA regulations require IRB policies that ensure prompt reporting to IRB, institutional officials, OHRP, and the FDA of any unanticipated problems involving risks to subjects or others. The investigator has the responsibility, under FDA regulations, to report unanticipated problems involving risks to the IRB.

Responsible IRB Policies on Adverse Event Reporting

IRBs should have their own guidelines for what they regard as reportable adverse events and reportable unanticipated problems. IRB policies also often include a required time frame for reporting to the IRB and specific forms on which to report. One of the issues that often arises is whether the investigator is respecting the sponsor's protocol, regulatory requirements and his or her own institution's requirements for adverse event reporting. Monitors need to make sure that all reporting requirements are adhered to, including those unique to a specific study.

The IRB terms of approval for protocols might include mandates that are specific to that study and study drug about a higher threshold for reporting adverse events. The IRB's approval terms could be stricter or more specific than the federal regulations, for example, requiring a shorter time frame for reporting.

If the IRB-imposed reporting requirements are stricter, then the investigator and sponsor must follow the stricter requirements. It is essential for the sponsor to propose specific parameters for adverse event reporting in the initial submission to the IRB so that all parties understand the requirements. Adverse and serious adverse events should be clearly defined in the context of each protocol and should include the following considerations:

- What events are considered adverse?
- What events are serious?
- What events are expected to occur? (Anything not included will be unexpected.)
- Have the expected adverse events been included in the proposed informed consent document?

By spelling out these expectations, all parties will have a single source for understanding what needs to be reported.