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Reporting Unanticipated Problems to IRBs

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Identifying and reporting unanticipated problems (UAPs) involving risks to subjects or others is a very high priority in clinical studies because it may prevent future harm. Institutional review boards (IRBs) that require investigators and sponsors to report all adverse events (AEs), serious adverse events (SAEs), and IND safety reports distract investigators and themselves from important events that may have significant impact on human subject protection. Similarly, study sponsors should not require excessive reporting to IRBs. Instead, they should allow IRBs to tell sites what reporting they require.

U.S. federal regulations specify different reporting requirements to sponsors and IRBs because they have different responsibilities. In simple terms, sponsors need complete information to manage their clinical research programs and prepare NDA marketing applications. IRBs need only the information that is pertinent to human subjects protection; anything else is a distraction.

Regulations and Guidances

The federal regulations and guidances that govern the reporting of UAPs are not a seamless web, so a given entity must determine which of the following regulations apply to its operations. Nevertheless, when the rules are looked at together, federal intent seems fairly clear. Regulations establish a minimum standard. The goal of protecting human subjects is not limited by loopholes in the regulations.

The regulations state that, "An investigator shall promptly report 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." (21 CFR 312.64) However, federal regulations do not require investigators or sponsors to report AEs, even SAEs, to IRBs, unless they constitute UAPs involving risks to subjects or others: "The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others…" (21 CFR 312.66)

IRBs and study sponsors may impose their own requirements on the site, but at the risk of diluting focus from the important events. Therefore, U.S. federal regulations require IRBs only to collect information on "unanticipated problems involving risks to subjects or others":

> Each IRB shall… [f]ollow written procedures… for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of… [a]ny unanticipated problems involving risks to human subjects or others… (21 CFR 56.108)

Federal regulations place symmetrical requirements on research sites with a Federalwide Assurance:

> Assurances applicable to federally supported or conducted research shall at a minimum include…[w]ritten procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of… [a]ny unanticipated problems involving risks to subjects or others… (45 CFR 46.103)

Federal regulations require reporting of unanticipated adverse device effects, a form of unanticipated problems:

> "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. (21 CFR 812.4(s)
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> …An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.145(a)(1))

Two guidance documents provide extensive Office of Human Research Protection (OHRP) and Food & Drug Administration (FDA) guidance on which AEs constitute unanticipated problems involving risks to subjects or others.

OHRP's "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" clarifies which AEs (including SAEs) should be reported:

> [T]his guidance clarifies that only a small subset of adverse events occurring in human subjects participating in research are unanticipated problems that must be reported under 45 CFR part 46… OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:
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> > (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
> >
> > (2) related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
> >
> > (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
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> …OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.
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> …To determine whether an adverse event is an unanticipated problem, the following questions should be asked:
>
> - Is the adverse event unexpected?
> - Is the adverse event related or possibly related to participation in the research?
> - Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?
>
> If the answer to all three questions is yes, then the adverse event is a UAP and must be reported.

FDA's "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection" adds two additional criteria: A reportable UAP must also (a) be serious and (b) have implications for the conduct of the study:

> In general, an AE [or SAE] observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol, such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

Both OHRP and FDA guidances indicate that the risk must be related to the study. OHRP's guidance clarifies that "possibly related" means "there is a reasonable possibility." FDA's guidance does not include a similar clarification, but one might assume that FDA's thinking is similar to ORHP's. An IRB could clarify the rule for its site(s) by setting a threshold probability of perhaps one-third.

The regulations and guidances do not define the term "unanticipated," but a problem can be considered unanticipated if its existence, severity, frequency or circumstances are not described in the protocol, informed consent form, investigator's brochure, label or package insert. Even if a risk is not described in one of these documents, it may not be unanticipated. For example, universal precautions should not need to be spelled out in these documents.

Reportable Problems

A broad range of possible UAPs might be reportable. The risk posed by the problem may be new, increased or different in some way. It may be physical, psychological, economic or social. It may be past, present or future. (Fixing the problem does not eliminate the reporting requirement because it is triggered at the time of the event.) Further, reportable UAPs might consist of a single event or a pattern of events, for example, one or more of the following might constitute a reportable UAP:

- An AE, SAE, adverse device effect, or precursor event
- An IND safety report
- A laboratory finding
- A protocol violation or deviation not pre-approved by the IRB
- A change in the protocol taken without prior IRB approval to eliminate an apparent immediate hazard to a subject
- A defect in the test article
- A deficiency in equipment used to collect data relevant to safety monitoring
- A complaint from a subject, study personnel, or other person
- A change to the test article's safety profile in the investigator's brochure, label or package insert
- An event that requires reporting to the sponsor
- An action or finding by the sponsor
- An action or finding by a governmental authority
- A breach of subject privacy
- Negligence or misconduct by study personnel
- Incarceration of a subject (in a study not approved to enroll prisoners)

- An injury or potential injury to study personnel, caregiver or other person
- New information from the study that indicates an increase in risk or decrease in benefit to the subjects, such as a data and safety board interim analysis
- New information from an external source, such as a scientific publication, newspaper article, animal study, or other clinical study
- Any other problem related to, or possibly related to, the study that indicates an increase in risk for the subjects

This long list of possible problems does not mean reportable UAPs should be common. On the contrary, most potential problems should be expected, unrelated or not harmful. When using the acronym "UAP," or the shorthand term "unanticipated problem," it is important to remember the entire term: "unanticipated problems involving risks to subjects or others." A major purpose of the OHRP and FDA guidances is to allow IRBs to focus on the important problems; replacing the current flood of AE reports with another flood of non-AE reports is not helpful. Adapt the FDA's three questions to determine which problems are reportable:

- Is the problem unexpected?
- Is the problem caused by or related to the study with a reasonable possibility? (Its existence, severity, frequency or circumstances are not described in the protocol, informed consent form, investigator's brochure, label or package insert.)
- Does the problem suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

Use common sense when determining what constitutes a reportable problem. A pattern of lab values is more likely to qualify than a single lab value. Many complaints from subjects, e.g., about compensation, are better handled by suggesting that the subject contact the IRB directly, as provided for in the informed consent form. Ask the IRB how stringently it wants sites to screen problems before reporting. Different IRBs can fall in different places on the spectrum of "don't waste my time" to "better safe than sorry."

A Form for Reporting Unanticipated Problems

The form should collect relatively complete information. It should help the investigator and IRB identify and understand the problem and determine a timely course of action to address it. The IRB may therefore require the site to attach a corrective action plan to the form, when appropriate.

Problems that are important enough to report should occur infrequently, so completing the form should not be a great burden on the site. Nevertheless, the form should be as short, simple, unambiguous and easy to use as possible. It should not, without good reason, ask for information the IRB already possesses. It should not be combined with the form for reporting any particular type of event that may or may not constitute a reportable UAP. Instead, any such reports should be attached as supporting documentation.

The author found great diversity among 18 forms used by independent IRBs for UAP reporting. It would be helpful for independent IRBs to use a standardized form so research sites do not need to deal with a different form for each IRB.

MAGI's standard form for reporting UAPs is available at http://www.magiworld.org/standards.

Conclusion

Identifying and reporting unanticipated problems involving risks to subjects or others is critical in protecting human subjects in clinical studies. Burying IRBs in paperwork that is

not pertinent to human subjects protection is not productive. Appropriate IRB reporting requirements with a well-designed, standardized form will facilitate the process.

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