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Institutional Review Board Safety Reporting Policies: Are Changes for the Better?

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Many U.S. institutional review boards (IRBs) have examined and revised their safety reporting requirements in the past five years. Several well-publicized incidents during clinical trials, such as Jesse Gelsinger's death in September 1999 at the University of Pennsylvania and Ellen Roche's death at Johns Hopkins in June 2001, brought IRBs under increased media scrutiny with respect to their review and oversight of clinical trials.[1,2,3] During the same time period, the Office of Human Research Protections (formerly Office for Protection of Research Risks) temporarily shut down several overburdened IRBs for compliance violations, including the IRBs of high-profile institutions such as Rush Presbyterian and Duke University.[4,5] Also, some reviewing divisions within the U.S. Food and Drug Administration (FDA) have occasionally encouraged sponsors to "report everything" related to safety when the sponsor is investigating a novel therapy or treatment of an indication that is not well understood. These factors prompted many IRBs to modify their safety reporting policies to improve efficiency and the quality of risk information submitted for review. Through these efforts, IRBs may have lessened their review burden, but the policies may have reduced the effectiveness of safety oversight.

Vague US regulatory requirements for investigators and IRBs have resulted in considerable variability in safety reporting practices across IRBs. However, one trend is apparent - many IRBs have adopted reporting criteria that are similar to sponsor obligations for expedited safety reporting to the FDA.

This article reviews the policies of 10 medium to large academic medical center IRBs, and five central IRBs operating in the U.S. The sample includes several high-profile academic institutions and major central IRBs. The procedures of the IRBs are compared and examined for consistency with current U.S. regulatory requirements. This article also assesses IRB practices in terms of the ability of an IRB to evaluate the overall risk/benefit profile of a trial.

Regulatory Requirements

The U.S. Code of Federal Regulations (CFR) 21 CFR Part 56 – Institutional Review Boards and 21 CFR Part 312 – Investigational New Drug Applications define the responsibilities of IRBs and clinical investigators for safety reporting in clinical trials of investigational drugs regulated by the FDA. The standards are meant to promote the rights and welfare of human subjects participating in clinical investigations.

Per 21 CFR §56.108, an IRB is required to have written procedures for ensuring "prompt reporting to the IRB….[of] any unanticipated problems involving risks to human subjects or others." Similarly, per 21 CFR §312.66, investigators must "promptly report to the IRB…. all unanticipated problems involving risk to human subjects or others." The regulation in 21 CFR §312.64(b) (below) defines investigator obligations for reporting of adverse events to sponsors. However, none of these regulations stipulate timeframes for investigator reporting of adverse events to the IRB, nor for investigator reporting to the sponsor. The timeline for an investigator's report to the IRB is IRB-mandated, and reporting to the sponsor is protocol-specific.

The regulations are inconsistent in the language regarding safety reporting. The requirements for IRB reporting do not use the term "adverse event" nor include any reference to expectedness or relationship of the investigational drug to the event, although the language as noted above requires the investigator to report "any unanticipated problem involving risk" (thus, encompassing non-drug related events). On the other hand, 21 CFR §312.64(b) requires the investigator to report to the sponsor only those adverse events "that may reasonably be regarded as caused by, or probably caused by, the drug." Study sponsors are obligated per 21 CFR 312.32(c) to notify "all participating investigators in a written Investigational New Drug (IND) safety report of any adverse experience associated with use of the drug that is both serious and unexpected." Although timeframes are specified for the sponsor's submission of IND safety reports to the FDA, there is no explicit requirement for investigators to notify their IRBs of such reports, nor a time period for such reporting.

Although sponsor requirements for investigator reporting of serious adverse events (SAEs) are typically consistent, the absence of clear requirements and consistent language within U.S. federal regulations has led to considerable variation of IRB policies for submission and review of safety information.

IRB Policies

A review of 15 IRB policies illustrates the differences in the timeframes for adverse event and safety reporting and the types of reports required. However, some similarities exist – all of the IRBs sampled mandate that investigators report "unanticipated problems involving risks to participants or others," and all but two of the IRBs specify specific time periods for reporting. Reporting time requirements range from 24 hours to 10 working days for locally occurring serious adverse events that are unanticipated and at least possibly related to the investigational drug or study procedures. Some IRBs expressed timelines in terms of business days, others in terms of calendar days. In a number of cases, no report is required at all. For these reasons, no meaningful average timeline can be computed. Some IRBs specify more prompt reporting for deaths or life-threatening events, while others make no such distinctions. Some of the IRBs have separate criteria for reporting nonserious events, typically requiring a report if the event affects the risk/benefit profile of the study.

There is substantial variation in IRB requirements for reporting adverse events. Seven of the 15 IRBs require expedited reporting of serious, unexpected events not related to the study or investigational drug. Two IRBs have provisions for including events that are nonserious, related and unexpected, or serious and expected in continuing review reports. Thus, approximately half of the IRBs do not require expedited reporting of events that are expected and related, or not related to study intervention or study drug. Table 1 summarizes the differences in reporting requirements:

Table 1. IRB Reporting Requirements

IRB	Timeline for report of an event that is:					
	Nonserious	An IND safety report	Serious, expected and related	Serious, unexpected or expected and not related	Serious, unexpected and related	Fatal/life-threatening, related and unexpected
1	With continuing review	If fatal/life threatening 48 hrs, otherwise within 10 days	With continuing review	With continuing review	10 days	48 hrs local or nonlocal
2	No report	In periodic summary	No report	10 days	10 days	10 days
3	No report	No report	No report	No report	"prompt report"	"prompt report"
4	No report	5 week days	5 week days	No report	5 week days	5 week days, excluding events related to disease
5	Not specified	Not specified	72 hours	Not specified	72 hours	Not specified
6	Promptly if ≥ moderate severity, related or if significantly changes risk/benefit ratio	Promptly	Not specified	Not specified	Not specified	Not specified
7	Not specified	Not specified	Not specified	Not specified	2 business days	5 business days
8	No report	5 days	5 days	5 days	5 days	5 days
9	If unanticipated, 10 working days	Not specified	5 working days	Not specified	If local, within 24 hours	If local, within 24 hours
10	If moderate in severity, not necessarily serious and unexpected, but in the investigator's opinion, should be considered by the IRB due to a possible relationship	10 days	Not specified	10 days	10 days	10 days

IRB	Timeline for report of an event that is:					
	Nonserious	An IND safety report	Serious, expected and related	Serious, unexpected or expected and not related	Serious, unexpected and related	Fatal/life-threatening, related and unexpected
11	If related, reported on log during periodic report	10 days	If related, reported on log during periodic report	No report	10 days	10 days
12	Not specified	Monthly basis	24 hours	24 hours	24 hours	24 hours
13	Not specified	10 working days	10 working days	10 working days	10 working days	10 working days
14	10 calendar days if harmful to subject participation, increases the risks of harm or has an unfavorable impact on the risk/benefit ratio	30 calendar days	No report	10 calendar days	10 calendar days	10 calendar days
15	No report	10 business days if unexpected and related	No report	No report	10 business days	10 business days

Note: IRBs 1–10 are academic medical center IRBs; 11–15 are central IRBs.

Six of the 15 IRBs do not require reporting of expected events or events not directly related to the investigational drug. This policy raises concerns about the IRB's ability to assess the safety of the trial in the local population. Just because a serious event falls into these categories does not make it inconsequential. The study experience in the local population may be different than for the study as a whole. For example:

- A washout of concomitant standard-of-care therapy that is common locally may pose increased risk.
- The local population may have more severe cases of the disease under study, or possess other unique characteristics that result in a higher rate of expected events.
- A standard-of-care study procedure may be performed differently than elsewhere in the country.
- Site personnel may misunderstand the protocol, or not monitor subjects as closely as at other sites, giving rise to more SAEs.

If an IRB does not collect or ignores reports of events unrelated to the study drug or expected serious events, such issues will be overlooked and unevaluated.

IRBs should take an active interest in SAEs occurring at other sites, and thus review all expedited safety reports. These reports provide substantial additional information to

supplement locally generated reports. If they are not received and reviewed in a timely manner, it severely compromises the IRB's ability to make timely decisions about suspending or terminating approval of a trial at a given site per its authority under 21 CFR §56.113.

Handling of IND safety reports varies considerably among the IRBs. Some IRBs have taken the position that they should receive complete, unambiguous reports and not be put in the position of interpreting drug relationship. If the FDA consistently enforced expedited reporting requirements according to the regulatory definitions, all IND safety reports that IRBs receive would be related to the drug. Although IRBs should have members with adequate medical expertise to assess safety, their role is not to determine causality. Rather, they should base their decisions on the investigator's or sponsor's assessment of relationship. Their function is to ensure that trial benefits continue to outweigh the risks, and this judgment should include, but not be based solely on, the actual causality of adverse events. During blinded, placebo-controlled trials in the U.S., IND safety reports are often evaluated in blinded manner (although the trend is towards unblinding). IRBs are also typically blinded to treatment assignment in such studies. Therefore, the actual drug relationship cannot be the IRB's primary criterion for risk evaluation, nor the criterion for acceptance of an investigator's submission of an adverse event or IND safety report. The IRB might also not be privy to the reasoning that led the sponsor to submit an IND safety report to the FDA. Ultimately, the IRB should weigh the report in terms of overall risk, and not reevaluate it.

To address the issue of IND safety reports that are not consistent with expedited reporting regulatory definitions, some IRBs require the local investigator to evaluate drug causality, and to submit to the IRB only if the investigator assesses the event to be related to the investigational drug. By definition, IND safety reports are SAEs that the originating investigator deemed related (however, on occasion, a sponsor may report based on its own determination). Having a second, local investigator second-guess causality has questionable value because the second investigator cannot clinically evaluate the subject first-hand and may not have access to all relevant study and medical records.

Three of the IRBs sampled do not require investigators to submit IND safety reports in an expedited manner; they either have a longer timeline (up to 30 days) or specify that they be provided with the continuing review report. This practice is inconsistent with the FDA's handling of such reports. IND safety reports are those that the FDA wishes to receive in an expedited manner; thus, it seems logical that the IRB should treat them with the same degree of urgency.

IRBs are responsible for ongoing monitoring of the risk/benefit ratio of a trial, and in addition to the FDA (and a data safety monitoring board, if one exists), have the authority to stop a trial based on safety. Such a decision is difficult and complex. The quality of the information on which it is based is obviously important. Investigators and IRBs have voiced the difficulties of interpreting individual adverse event reports,[5] and there are efforts to provide "digested" safety information for IRB review. But the gathering and analysis of such information takes considerable time, and moreover, even in aggregate, such information in the research setting may still not be in sufficient quantity to reveal safety trends, particularly for events of low incidence. This issue applies to an even greater degree early in a trial or development program. Therefore, it is prudent to evaluate safety using more immediately available information. Digested reports are very useful, but cannot replace prompt individual reports.

Recommendations

Despite IRB efforts to streamline their polices and obtain more meaningful safety information for evaluation, current regulations require refinement to promote consistency. The FDA should consider implementing the following:

- The standard industry policy of requiring investigators to report all SAEs regardless of relationship to the sponsor should be incorporated into the regulations. (§312.64 (b) requires the investigator to report only events that "may reasonably be regarded as caused by, or probably caused by, the drug."
- 21 CFR Part 56 should more clearly address the reporting of "unanticipated problems involving risks to subjects or others," and divide the definition into risks associated with the investigational drug, and those that are not, and define submission requirements for each.
- Explicitly state within 21 CFR Part 312 the investigator's obligations for reporting SAEs to the sponsor and to the IRB, including coherent timelines.
- Clarify the requirements for reporting events requiring hospitalization, and not require expedited reporting of elective or anticipated hospitalizations.
- The FDA should revise FDA Form 3500A to support reporting of events not meeting expedited reporting criteria, but that are of interest for a given indication or therapy.
- The FDA should develop a standard form similar to Form 3500A for investigators to report adverse events to IRBs. If an IRB wants additional information, it can provide a supplemental form.
- FDA and NIH rules should use consistent terminology for adverse event classification across all rules.

Institutional review boards should continue to refine their policies for more efficient and accurate reporting and review of SAEs, in a manner that includes evaluation of all risk information. Some institutions manage reporting of IND safety reports on an IND basis, i.e., they only require submission of events once, even if more than one study under that IND is being conducted at the institution. This policy perhaps will limit some duplication of reports, but not many and only at large institutions conducting several trials under an IND concurrently. For central IRBs, the sponsor should always be required to submit IND safety reports to IRBs on the investigator's behalf to eliminate duplication of effort by the investigators. An FDA guidance could define procedures for such reporting. It also would be prudent to assign a qualified subgroup of the IRB to review adverse event reports, and provide interpretation for the rest of the board. And, although the author disagrees with having the investigator reevaluate causality of IND safety reports, the investigator should participate in identifying trends. At least one IRB in the sample placed the burden of safety information interpretation on the sponsor, and required an analysis of similar events with any safety report. This also is a prudent policy.

In summary, in spite of the inconsistencies, all of the IRBs sampled have procedures in place for the review of unanticipated problems involving risks to human subjects or others, and therefore meet the regulatory requirement. None of the policies appear to jeopardize subject safety to a significant degree, although it does appear that evaluation of overall safety could be improved if reporting criteria encompassed all types of serious, fatal or life-threatening events, regardless of causality. The lack of specificity in U.S. regulations remains, and there definitely is a need for clarification and consistency of language. Such revisions would provide a better framework for IRBs and investigators to develop sound safety reporting practices.

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