

**Reporting of Adverse Events to Institutional Review Boards: Public Hearing
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- 1. The role of IRBs in the review of adverse event information from ongoing clinical trials.** *Given the number of parties with responsibilities related to adverse events that occur during the course of a clinical trial, what role should IRBs play in the review of adverse event information from an ongoing clinical trial? How does that role differ from the current role of IRBs? Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?*

IRBs have a primary responsibility to the subjects of research enrolled at a given site, or under the auspices of the local principal investigator (PI). In regard to reporting adverse events, the role of the IRB goes beyond the review of individual adverse event reports. The role of the IRB is to ensure there is an adequate plan in the individual study protocol for

- capturing adverse event data,
- submitting such data to the sponsor or Data Monitoring Committee (DMC) for compilation,
- periodic assessment of such data, as in an interim analysis,
- defining ‘triggers’ or ‘stopping rules’ that will dictate when some action is required, and
- promptly reporting any unanticipated problems to the IRB.

The detail and sophistication of such a plan will depend on the individual protocol features. What is the level of risk posed by the protocol? What is the phase of the study? Is this a single-site or multicentered protocol? Does an independent DMC exist? Is there blinding of intervention arms being utilized?

IRBs need to be attuned to unanticipated problems which may alter the risk:benefit ratio of an approved protocol, or may result in the need for change in the procedures or consent form. Thus, unanticipated problems that occur with an investigational agent are of interest regardless of site. In addition, IRBs must ensure that local investigators in multicenter trials are being adequately informed of new information that may affect the trial. The local PI, being the on-site ‘expert’ in the trial intervention, should receive new information and assess it. Part of this assessment should involve decisions about whether the new information prompts a change, in either study design, protocol procedures, or informed consent. If the PI believes a change is warranted, the information and amended protocol or consent form should be submitted promptly to the IRB for review and approval.

The IRB should serve as an advisor to the local PI in assessment of important new information as the PI receives it.

2. The types of adverse events about which IRBs should receive information. *Based on your view of the role of IRBs in the review of adverse event information from ongoing clinical trials, what types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs? For example, should IRBs generally receive information only about adverse events that are both serious and unexpected? Are there circumstances under which IRBs should receive information about adverse events that are not both serious and unexpected (e.g., if the information would provide a basis for changing the protocol, informed consent, or investigator's brochure)? In a multicenter study, should the criteria for reporting adverse events to an IRB differ, depending on whether the adverse events occur at the IRB's site or at another site?*

IRBs should be immediately informed if a serious, unanticipated event thought to be related to the study protocol has taken place. This is especially crucial if the event happened at the local site, under the purview of the local PI. In such a case, the IRB has direct access to the investigative team and may work with the team to determine what, if any, additional information is required to do an adequate assessment. IRBs should work together with the PI to decide if changes are warranted by such an event. The IRB retains the authority to require changes if necessary.

While the IRB retains primary responsibility for on-site subjects of human research, important information can certainly come from other sites. Thus, serious unanticipated events that happened at another site, or using the investigational agent under a different protocol, may have relevance. These reports should be sent by the sponsor to the local PI, who should assess them, and forward them to the local IRB if they are considered serious, unanticipated, and related to the study agent in some way.

Anticipated events should not be reported to the IRB unless their frequency or magnitude exceed expectations. This requirement underscores the fact that all events need to be captured, collected, and compiled, and then periodically assessed to ascertain whether something unexpected is occurring. The responsibility for this activity rests with the sponsor and Data Monitoring Committee, if one exists.

There may be circumstances when a thoughtful local PI is prompted to make a change to the protocol or consent form based upon something other than a serious unexpected report. In such a case, the event triggering the request for change (amendment) should also be submitted to the IRB in support of the requested change.

3. **Approaches to providing adverse events information to IRBs.** *There seems to be a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not informative to permit IRBs to assess the implications of reported events for study subjects. What can be done to provide IRBs adverse event information that will enable them to better assess the implications of reported events for study subjects? For example, if prior to submission to an IRB, adverse event reports were consolidated or aggregated and the information analyzed and/or summarized, would that improve an IRB's ability to make useful determinations based on adverse event information it receives? If so, what kinds of information should be included in consolidated reports? And when should consolidated reports be provided to IRBs (e.g., at specified intervals, only when there is a change to the protocol, informed consent or investigator's brochure due to adverse event experience)? Who should provide such reports? Should the approach to providing IRB's adverse event reports be the same for drugs and devices?*

Data should not be confused with information. Information is data bestowed with meaning and utility. It is important to note that immediate changes to protocols or consent forms should NOT be prompted by isolated adverse event reports. This is especially the case when studies involve blinding of the interventions.

Adverse events occur locally (that is, under the direct purview of a local P.I.), or they may have happened at a different center participating in a multi-centered trial. Indeed, it is common that adverse events are reported from multiple countries, as multinational trials are now very routine. It is important to note, however, that these 'off-site' reports are often made without breaking the blind, so it is impossible to know which arm the subject was assigned to, and there is no ability for the local person forwarding the report to get any additional information to allow an assessment. These reports are seldom provided within any context; that is, there is seldom an analysis by the sponsor of the occurrence of similar events, nor an analysis of total numbers of subjects exposed to a given product. Further, these external reports often involve uses in other disease states, different doses, and with or without concomitant medications. All of these factors serve to confound the analysis of a given adverse event report, and render the report rather meaningless. It is generally agreed that a single report would not prompt action, as it is being reported in a large void.

In contrast to this situation, the advent of protocol-specific monitoring committees, such as Data and Safety Monitoring Boards or Data Monitoring Committees (DMCs), promises to offer an improved methodology for safety monitoring. The sponsor or steering committee of a study charges the DMC to protect subject safety by examining the accruing data for indications that clear benefit or harm may be occurring. The DMC then makes a judgment as to whether the trial should continue. The DMC usually looks at global data, as investigators forward all adverse event reports to a data coordinating center, which then compiles the data for the DMC to review at predefined intervals. Data

presented to the DMC is either completely unblinded, or categorized by treatment arm. As such, the DMC is able to determine whether a clear effect is being seen in one arm versus the other(s). The DMC will then issue recommendations regarding the further conduct of the study based on this review. Thus, when a DMC exists, the recommendations from any meeting of the DMC must be submitted promptly to the IRB. Recommendations to continue the study as planned assure the IRB that this level of review is taking place. Likewise, recommendations for change from the DMC will necessitate prompt action on the part of the local PI and IRB.

DMC oversight may not be an option in a number of studies, however. In the absence of a DMC, a sponsor's analysis of a given serious, unanticipated event is mandatory. The analysis must provide a context for assessment, including both number of similar events as well as extent of exposure to the investigational agent (that is, numerator and denominator data). The sponsor should make an assessment about the need for changes, and this then should be provided to the local PI. The local PI should review the report and likewise make an assessment. The report with analysis and assessments should then be submitted to the IRB.

Adverse events that occur with investigational devices should follow the above recommendations. Again, it is necessary for the IRB to get input from the local PI in assessing any adverse device events. Sponsor notification of the IRB directly circumvents this step, and is undesirable.