

**Re: DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
[Docket No. 2005N-0038]
Reporting of Adverse Events to Institutional Review Boards**

We respectfully submit the following comments:

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 events 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?

The parts of IRB responsibilities that are most relevant with respect to adverse events are the requirement to ensure that risks to subjects are minimized, that risks to subjects are reasonable in relation to anticipated benefits, and that informed consent is sought. Therefore IRBs should review adverse events in the context of whether the event represents a change in the risk of participation.

The IRB should be responsible for reviewing all adverse events from single center trials for which they are the IRB of record. These studies are often investigator-initiated and are probably less likely than multicenter trials to have a DSMB or other outside monitoring body; thus the IRB has considerable responsibility to determine whether an adverse event represents a change in risk. In a single center trial the IRB will receive all the adverse event information for the study and will be able to place it in the context of overall subject accrual. In addition, the principal investigator in a single center trial should be in a position to provide the IRB with an requested additional information that will help to determine the overall importance of the event with respect to subject safety.

In contrast, in a multicenter trial, both the local PI and the IRB are frequently deluged with reports of adverse events without interpretation of relationship to study agent or the importance of the event. There is virtually no way for either the local PI or the IRB to place these reports in context or to make a reasonable determination about whether they contain new or important information about the safety of the agent. Thus the reports are essentially useless in terms of permitting the IRB to fulfill its duty to perform meaningful continuing review. Furthermore, it seems unlikely that a local IRB, even if provided with all the necessary information, would arrive at a more accurate understanding of the importance of an adverse event than will a DSMB or other safety monitoring body reviewing all the events centrally.

IRBs should not be responsible for reviewing individual adverse events from subjects accrued at other sites. Instead, a DSMB or other safety monitoring body should provide aggregate reports at reasonable intervals and with interpretation of the relationships of the

events to the study agent, the importance of the events in terms of subject safety, and whether the subjects should be provided with new information based on the events. At any time when any event raises an immediate concern for patient safety, this information should of course be distributed to all sites along with an action plan, and the report and plan should be reviewed by all the IRBs.

An additional problem is the issue of multiple adverse event reports or IND safety reports from studies of the same agent in completely different protocols and/or patient populations. These reports also generally lack sufficient interpretation from the sponsor to allow the IRB to make reasonable determinations about whether they contain new or important information about the safety of the agent. This problem can occur in both multicenter and single center clinical trials. IRBs should not be responsible for reviewing these reports except in aggregate and with interpretation as discussed above.

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 receive information about all the adverse events on a clinical trial, but most of these could be presented to the IRB already summarized and interpreted at the time of continuing review. Serious and unexpected events that occur at the IRB's site should be reviewed individually and promptly by the IRB because of its responsibility for understanding the local research context (although the IRB may not be able to do more than acknowledge that the event occurred until the sponsor or DSMB puts it into perspective) . Serious and unexpected events that occur at other sites can be reviewed already summarized and interpreted at the time of continuing review. Any adverse event at any site that requires changes in the protocol or consent should be reviewed along with the action plan or protocol amendment that documents the changes, at the time that the amendment or plan is submitted. Any adverse event that requires immediate action for subject safety should be submitted to all IRBs promptly.

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 (see, e.g., the SACHRP letter, NIH Regulatory Burden v. Human Subjects Protection—Workgroups Report, available at <http://grants2.nih.gov/grants/policy/regulatoryburden/humansubjectsprotection.htm>, which states that data that are neither aggregated nor interpreted do “not provide useful information to allow the IRB to make an informed judgment on the appropriate action to be taken, if any.”). 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 the 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 events experience)? Who should provide such reports? Should the approach to providing IRB’s adverse event reports be the same for drugs and devices?

The IRB needs to receive information about adverse events that affect the risk-benefit ratio of the protocol, could potentially affect the willingness of subjects to continue participation, or otherwise adds relevant new information. As discussed above, the IRB needs to receive this information in a format that permits it to reach conclusions about these matters. Sponsors should be actively discouraged from deluging the IRB with uninterpreted information. Sponsors should not consider that the mere distribution of an AE report shifts the burden of interpreting the event to the IRB or provides legal or ethical “cover” to the sponsor.

For single center trials, receiving at least SAE information on a “real time” basis does not appear to be a major problem. However, for multicenter trials this is a major issue. Consolidated and interpreted information would be far more valuable than individual reports arriving sporadically. The sponsor of the research should provide the reports. The information should include the types and number of events, the denominator, a reasonable attempt at attribution at least for serious adverse events, and a summary of protocol changes made due to the events. The IND annual report format provides this information, and using it would prevent unnecessary duplication of sponsor effort for studies involving an IND agent. In addition, the findings of the DSMB or other safety monitoring body with respect to safety of continuing the research should be included.

For multicenter studies, adverse events that require changes to the protocol or consent or immediate action for subject safety should be reviewed by all IRBs. The former category can be reviewed at the time of the protocol amendment and do not need to be sent separately. The latter should be reviewed when the information is provided to the local PI.

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On behalf of Baylor College of Medicine IRBs