

STANFORD UNIVERSITY
Office of the Dean of Research
Stanford University
Stanford, CA 94305-5401

Research Compliance Office
(650) 723-4697
(650) 736-2783 FAX

1215 Welch Road
Modular A
MC 5401

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Nancy L. Stanisic
Center for Drug Evaluation and Research
Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, R. 1061
Rockville, MD 20852

Docket No. 2005N-0038

Subject: Reporting of Adverse Events to Institutional Review Boards

Dear Ms. Stanisic:

Stanford University's IRBs appreciate the fact that the FDA has initiated a review of the reporting of adverse events. We are confident that more meaningful and appropriately analyzed adverse event reports can be accomplished and will help strengthen the protection of human research subjects.

Background

The problems of the present system are well-articulated and summarized in the February 8, 2005 issue of the Federal Register (70 FR 6693):

- IRBs receive large volumes of adverse event reports of varying clinical significance and relevance.
- Many of these reports "are often not sufficiently informative to permit IRBs to assess the implications of reported events."
- "It may be difficult for IRBs to review and interpret the significance of large volumes of individual adverse event reports received in isolation (unsegregated and unanalyzed) at sporadic intervals over the course of the study."

We believe that ALL SERIOUS ADVERSE EVENTS, expected or unexpected, "related" or "not related," should be reported to IRBs.

Not ALL SAEs, however, need to be reported emergently.

Improving Reporting of Adverse Events to IRBs

The primary rationale for emergently reporting SAEs to an IRB is to determine if it is appropriate for that study to continue unaltered. This requires the prompt reporting of all serious, unexpected adverse events that are reasonably related to a specific study intervention.

- Reporting of every AE or SAE, specifically those AEs not related to a specific study intervention, diverts the resources of IRBs without improving subject safety.
- Individual IRBs must have written procedures to ensure that they receive prompt reports of all serious, unexpected adverse events which occur at their institution. They must further ensure that such reports are promptly forwarded to the sponsor, the FDA and appropriate institutional officials.
- In multicenter studies, IRBs must also ensure that they receive prompt reports of all serious, unexpected adverse events REGARDLESS OF WHERE THE EVENT OCCURRED. This process could be facilitated by an IRB Data Safety Plan whereby these events are first reviewed by a formal DSMB.

To be meaningful, reports must include not only the facts of the event, but also an analysis by the investigator, the sponsor, a Data Safety Monitoring Board, the FDA, or other qualified individuals or groups as to the significance of the event. Only then can the IRB make an informed decision as to whether or not the study should be halted or revised, the IRB's primary charge.

Serious adverse events that are not unexpected should continue to be reported to IRBs, but not on an emergent basis. This is true whether or not the SAEs are reasonably related to the study. Over time patterns may emerge which suggest that events previously thought unrelated may in fact be linked to a device, drug or study intervention. Such reports should also be aggregated and analyzed and should be submitted to the IRB at the time of protocol renewal, no less than annually.

IRB's Role in Adverse Event Reporting

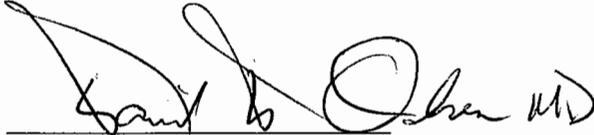
In summary, the role of IRBs should be threefold:

1. To insure the prompt receipt and reporting of serious, unexpected adverse events regardless of where they occurred.
2. To determine whether the specific study or any related clinical study should be halted or altered, that decision being informed by outside analysis of the SAE by the investigator, the sponsor, the FDA, the DSMB, or other individuals or agencies with appropriate expertise to judge the relevance and significance of the event.
3. To analyze, at the time of the protocol renewal, all adverse events, whether serious or non-serious, expected or unexpected, "related" or "not related,"

looking for patterns which might suggest that the study should be halted or modified.

Thank you for the opportunity of discussing how to optimize the process of adverse event reporting and review. We believe that the responsible and effective reporting of adverse events will strengthen and further ensure the protection of human research subjects.

Sincerely yours,



David D. Oakes, M.D.
Chair, IRB 01



Donald R. Stanski, M.D.
Chair, IRB 03



Ronald L. Ariagno, M.D.
Chair, IRB 04



Darrell M. Wilson, M.D.
Chair, IRB 05

cc: Ann M. Arvin, M.D.