



MHIRB Administration
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March 8, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5260 Fishers Lane RM 1061
Rockville, MD 20852

RE: Docket No. 2005N-0038 comments

To Whom It May Concern:

Please accept the attached comments for **Docket No. 2005N-0038, "Reporting of Adverse Events to Institutional Review Boards."**

Thank you for your time in reviewing them.

Sincerely,

A handwritten signature in black ink, appearing to read "Rexann G. Pickering".

Rexann G. Pickering, Ph.D., R.N.
Administrator, Human Protection
Administrative Director
Methodist Healthcare IRB

2005N-0038

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Docket No. 2005N-0038

Comments from Dr. Rexann G. Pickering, Methodist Healthcare IRB Administration
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Submitted: 3/8/2005

Question #1: The IRB must be the protector of human subjects enrolled in research studies, and therefore it is imperative that adverse events (AE) be reported to and reviewed by the IRB, particularly the local IRB. The IRB is the only entity within the local organization/hospital that has access to all aspects of a study, and therefore must compile and review AE data in a timely manner and then act upon that data. Our IRB (a local IRB within a hospital system) requires that investigators review all safety and local AEs prior to IRB submission and has on occasion required the investigator to attend an IRB meeting to discuss AEs and their planned action to obviate their occurrence. The IRB has also suspended and terminated studies based on AE review and the subsequent risk to subjects.

If the study is a single site at one institution the IRB should require that a data safety monitoring board (DSMB) be established (according to standard guidelines) and functioning during the entire course of the study. There should be required reporting to the IRB from that DSMB and that reporting time frame should be established at the time of initial approval of the study. Our IRB has denied approval of a single-site study when the investigator refused to establish a DSMB. The same careful review should be conducted by the IRB for multi-site studies since IRBs do not get reports from other IRBs.

Question #2: IRBs should receive AE reports regarding serious and nonserious, expected and unexpected events. The rationale for this is that often we have seen AE report that when evaluated as a single event it was indeed nonserious, but when evaluated in the context of the enrolled subjects' comorbid conditions, the AE was a precursor to a serious problem. We have also seen lists of adverse events in protocols that the company/sponsor had obviously edited to reflect only what they believed would be "serious or expected." However, preclinical results or early trial results, when carefully reviewed indicated that there were more risks that should be disclosed to the subjects. We have required that AEs in the informed consent form indicate the likelihood of occurrence of an AE in a bulleted and percentage format. This suggestion came from several of our community IRB members.
Suggestion: Alter MedWatch form to indicate whether the reported has reported the event to the IRB of jurisdiction.

Question #3: Currently we do not receive enough information to determine the prevalence or incidence rates of AEs. We have on numerous occasions had to request more information from sponsors/investigators regarding occurrence rates. The most troublesome of all studies are the device studies. The IRB receives a paucity of AE reports from all device studies. Because of this our IRB places the studies on a short review cycle and will very often require the investigator to report each use of the device and the outcomes. This is very burdensome to both the IRB and the investigator, but with the lack of AE and safety information coming from the sponsor, the IRB, in the best interest of the subject, must require this type of reporting. Public awareness of drug studies and the recent deaths associated with drug trials have helped the AE reporting, but there has been no such awareness regarding device trials. Often AEs are deemed to be only those physical problems that are encountered. However, AEs can be physical, mental, social or psychological and these events also need to be captured. Since our risk determination score is based on all of these effects, the AE reporting should also include all of these.

Suggestions:

- 1) require a denominator when reporting an AE to provide a basis for determining incidence and prevalence of the event**
- 2) standardize AE reporting forms (currently sponsors - such as AstraZeneca create their own formats and do not include all the information in the 3500A form; CIOMS report is different and information provided is not consistent with 3500A form)**
- 3) provide aggregate information regarding AEs and number of sites from which aggregate information derived, when the study is submitted for initial IRB approval**
- 4) require DSMB reports (aggregate and individual listing of AEs) to be sent at regular intervals to the IRB of jurisdiction; analysis of data should be included; reports should be required of phase 1, 2, 3 & 4 studies**
- 5) clarify "voluntary" vs "mandatory" reporting of AEs**
- 6) include on MedWatch form the date the report was submitted to the IRB of jurisdiction along with date submitted to the sponsor**
- 7) all deaths should be reported regardless of reporter's belief as to the relationship to the test article**
- 8) need information as to whether event was expected or unexpected**
- 9) need to include a list of similar events previously reported to the FDA (this allows the IRB to compare their files with the report and also to determine quickly if there is immediate action needed)**
- 10) need information as to how long the subject has been on the study/test article; The 3500A form asks for "length of time on therapy" but it is not possible to determine if that refers to the test article or to therapy for the underlying condition.**
- 11) age of the subject should be included AND age at the time of treatment with the test article**

- 12) must have lab/diagnostic data for medical event**
- 13) need to have space for checking if the event was physical, mental, social or economic in nature**
- 14) dictate time frame in which external AEs must be reported to both FDA, sponsor and IRB of jurisdiction**