



CIRCARE

Citizens for Responsible Care and Research

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RE: FDA Docket 2005N-0038 Reporting of Adverse Events to Institutional Review Boards; Public Hearing

The issue of adverse event reporting in clinical trials is not trivial: thousands of human subjects are impacted and significant investment by industry and researchers is required. Due to the lack of clear, and uniform standards and mandatory reporting requirements, the true extent of adverse events in clinical trials is unknown. A recent survey of FDA warning letters issued to clinical investigators between February 2002 and February 2004 found that in the thirty-six letters issued, nearly half of them described failure to report or late reporting of adverse events.¹

A similar survey of FDA warning letters issued to IRBs between January 1997 and July 2004 found that of the fifty-two letters issued, forty-seven letters described failure to prepare and maintain adequate documentation of IRB activities, and thirty-six described failure to provide adequate continuing review of approved studies.² Such deficiencies surely impact adverse event reporting and analysis, and ultimately effect IRBs' abilities to protect human subjects.

Earlier published analysis suggested that the adverse events were significantly under-reported in studies funded by the National Institutes of Health.³

CIRCARE acknowledges the difficulties faced by IRBs in coping with large numbers of adverse event reports and is mindful of the fact that high volume may impact the IRB's ability to protect research subjects. We are, however, concerned that the reform of reporting requirements occur at all levels.

Ideally, reform should not be done in isolation. The following overarching principles should be seriously considered, which will have a major impact as to the usefulness of reporting adverse events and protecting human subjects.⁴

1. Enactment of a National Human Research Protections Act (NHRPA) (Jesse Gelsinger's Law). All research with human subjects should be under the same regulations, as with animals in the 1966 Animal Welfare Acts. The Act should have teeth for enforcement.
2. A national federal registry of a comprehensive and mandatory adverse events reporting.
3. Managing and reducing conflict of interest.

4. The inclusion of the public and persons without vested interests in the decision-making process at various levels of review including the Institutional Review Boards.

In terms of reporting adverse events to Institutional Review Boards, we offer the following in response to the FDA's three questions:

I. What is the role of the IRB in the review of adverse event information from ongoing clinical trials?

The primary purpose of IRB oversight of research is the protection of research subjects.⁵ The IRB should serve as an independent resource for human subject safety in any particular study, and so should not include persons with a personal stake in the approval or outcome of a particular study. Measures should be taken to insure the IRB's independent status. Importantly, more than half of the panel should include persons who are not connected to the research and seek to represent and advocate for the safety and well-being of human research subjects.

Whatever procedures are put in place for reviewing adverse event information will be of limited effectiveness if IRB members are not substantially independent of the sponsor or parent institution, do not possess a primary concern for research subject safety, or lack training to interpret the adverse events reported.

When a central IRB is used for a multi-site study, the central IRB should be the IRB of record to receive all reports, collate and analyze them. The local IRB should still have responsibility for analyzing and judging adverse events within its particular jurisdiction, while the central IRB should serve as a second check, and in particular collate and analyze data, and look for patterns across several studies that may not be detectable on the local scale.

II. What are the types of adverse events about which IRBs should receive information?

Careful thought should be given to the types of adverse events reported. Generally all serious and somewhat less than serious events should be reported, but not relatively minor events or those not reasonably related to research participation.

Not only serious and unexpected events should be reported, but serious (alone) and unexpected (alone) adverse events. A reportable adverse event could be defined as meeting one or more of the following criteria.

1. Death
2. Hospitalization or prolongation of hospitalization
3. Missed work due to adverse event
4. Doctor visit due to adverse event

5. Persistent symptoms
6. Others to be determined by a panel of experts and lay people.

Required human subject protection training should include adverse event reporting requirements. Research institutions should provide training in adverse event reporting techniques to their investigators in an effort to increase the quality of information received by the IRB.

The FDA should give consideration to adopting the ICH standard definitions for AE reporting as swiftly as possible.

III. What are the approaches to providing adverse event information to IRBs?

Clear, concise, uniform reporting standards should be the foundation of adverse event reporting in clinical research. AE reporting should be standardized such that all researchers should make use of a single basic form (which might have added questions based on particular types of research). This information then could be easily computerized and become web-based and accessible for concerned parties.⁶

Importantly, the reporting form should include critical demographics such that adverse event profiles can be determined for various categories of persons including gender of the person, their age group, vulnerability of group (i.e. use of children or handicapped), their geographic region, their occupation, and previous medical history.

Other critical parameters regarding the study itself include: date, number of human subjects, study duration, type of drug, specific disorder, institutional events, adverse events, investigations, problems with informed consent, non-compliance, action letters, suspensions/terminations, requiring re-review, repeated reporting.

Ideally such a system should be web-based so that forms and information can be immediately collated and tabulated to determine general patterns.

This information would be useful to both FDA for “look backs” on marketed drugs, as well as to designers of future research studies and possibly even to the public in evaluation of marketed products and their safety.

A number of FDA warning letters issued to clinical investigators object to the delegation of tasks to unqualified or unlicensed persons. IRBs should make certain the sponsor has selected well qualified investigators and trial sites with appropriately trained personnel. State law complicates this issue. In several states it’s legal for individuals without any formal training in health care to act as medical assistants with a relatively wide range of patient care responsibilities. This has uneven results in both medical practice and clinical research. It’s a safe assumption that untrained and unlicensed persons are less likely to report adverse events if only because they are relatively less likely to detect them or appreciate their significance. On this basis, FDA may wish to consider clarifying the responsibility of the sponsor in this matter.

CIRCARE urges that steps be taken toward improving the quality and totality of adverse event reporting. Only when a person knows both the benefits and the risk of a particular treatment can he or she make a truly informed choice in the matter.

Sincerely,

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¹ Bramstedt, Katrina A. (2004) A study of warning letters issued to clinical investigators by the United States Food and Drug Administration. *Clin Invest Med* : 27(3):129-34

² Bramstedt, Katrina A. and Katy Kassimatis. (2004). A study of warning letters issued to institutional review boards by the United States Food and Drug Administration. *Clin Invest Med*; 27(6):316-23

³ Shamoo, A. Adverse Events Reporting – The tip of an Iceberg. *Accountability in Research* 2001; 8(3) 197-218

⁴ In general, see the web site at <http://www.circare.org/>

⁵ Salter, E. (2002). IRB Reform. *The New England Journal of Medicine*, 346:1402-1404.

⁶ Shamoo, A. (2005). The need for better reporting of adverse events for human subjects in research. In press *DIA Forum*