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April 21, 2005

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

Docket No. 2005N-0038
Subject: Reporting of Adverse Events to Institutional Review Boards

Dear Ms. Stanisic:

The Council on Governmental Relations (COGR) is an association of 160 research intensive universities, affiliated hospitals and research institutes in the United States. COGR works with federal agencies to develop a common understanding of the impact that federal policies, regulations and practices may have on the research conducted by the membership.

The Food and Drug Administration's (FDA) interest in the reporting and review of adverse events in human subject research reflects the interest and rising concern of COGR's members. During the public hearing on March 21, 2005, the FDA heard some of those concerns. The number of adverse event reports generated on any given study has reached such a significant level that the volume, itself, may come to limit the careful consideration of unanticipated and potentially serious risks to subjects.

The dramatic increase in the number of reports relates directly to the increase in the number of clinical trials conducted in the US and the growth in the use of multiple clinical research sites in the trials. We do not advocate a reduction in clinical trials. However, in the interest of medical research that holds enormous benefits for the public, it is essential to devise a better reporting process. Hearing participants proposed strategies for streamlining the processes for adverse event reporting and review. The Association of American Medical Colleges proposed a process to promote for responsible and effective adverse event reporting. We echo this call for streamlining to ensure the safety and welfare of human participants.

Streamlining Reporting and Review

The streamlining of adverse event reporting and evaluation can be accomplished with minor but important modifications of the current regulations. FDA investigational device regulations direct the investigator to report to the sponsor and to the reviewing IRB any unanticipated adverse device effects. The sponsor is required to evaluate the effects and to report the outcome of its evaluation of unanticipated adverse effects to the FDA, participating Institutional Review Boards (IRBs) and investigators [21 CFR 812.150]. This approach should serve as the basis of a streamlined process for effect and event reporting for all FDA regulated clinical trials, whether device, drug or biologic.

The process should be modified to direct the investigators to provide reports of unanticipated adverse effects or events to the sponsor and to their local IRB rather than to all participating investigators and their IRBs. This revised approach should be incorporated into the regulations covering drugs and biologics and reflected in the regulations governing IRB functions and operations as well [21 CFR 56.108].

IRB Roles

The recommended streamlined approach responds to the concerns about an ever-increasing burden of review for IRBs and investigators and permits IRBs to focus their attention on their critical continuing review role. IRBs need clear and concise information about unanticipated events that pose a risk or unanticipated adverse events that threaten the well-being of subjects by putting them at greater risk.

Most research institutions currently interpret FDA regulations to require each IRB to review all reports of all adverse events occurring on a study from any and all clinical study sites – local and external. We believe the refinement in the process for meeting the IRB review responsibilities that includes streamlining the report and review mechanisms will enhance the protection of study subjects. As a part of the refinement of the process, a distinction should be made in the reporting mechanisms for single site versus multicenter clinical trials.

IRB and Multicenter Clinical Trials

In the case of multicenter clinical trials, we believe that regular and timely summary reports of serious, unexpected events related to the study will enhance IRB review and, most importantly, the protection of subjects. These reports should include relevant, aggregated information and an evaluation or analysis of the information including a determination of risk and a recommendation, as appropriate, for changes to the study. Armed with useful information, the local IRBs, as well as investigators, can assess and act on the recommendations.

As the FDA medical device regulations already acknowledge, the sponsor is the most obvious party to assume this responsibility through the use of an independent data safety monitoring board or other designated group. The sponsor receives study-wide data, and could be

required to establish an independent data safety monitoring board or similar safety review panel of individuals with relevant scientific and technical expertise to review the investigator reports and make a reasonable determination of risk.

Investigator Reporting in Multi and Single Site Clinical Trials

We propose a minor modification in the area of investigator reports. All investigator reports of unanticipated and/or adverse events should be submitted to their local IRB as well as the sponsor whether conducted as a single site or as a part of a multicenter trial. Obviously, these local event reports are a critical component in the evaluation of a specific study and, for a single site trial, the local IRB has the sole responsibility to determine what action must be taken to protect the subjects including whether to halt the trial, change the protocol, or change the consent process.

Local reports also assist the IRB and the institution in a more general, on-going assessment of the performance of the institution's clinical research staff. The event may not pose a risk to the subjects or the continuation of a particular study but may provide information to the institution on staff performance or communication issues.

In conclusion, we believe minor modifications of the current investigational medical device regulations and the incorporation of the entire process of investigator and sponsor reporting into the regulations for drugs, biologics, and IRB functions will achieve a streamlining and efficiency in the process of adverse effect and event reporting. We urge the FDA to take leadership to harmonize its regulations and guidance within the Department of Health and Human Services. Such harmonizing should include the Public Health Services (PHS) regulations for protecting human subjects at 45 CFR 46 and the policies of the National Institutes of Health concerning data safety monitoring boards.

We are grateful the FDA has opened this discussion and believe that a more effective, streamlined approach will help enhance the protection of human research subjects from risks. Thank you for the opportunity to provide comment.

Sincerely,

Katharina Phillips
President