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To: DHHS -- FDA
United States of America

Re: Reporting of Adverse Events to Institutional Review Boards
Docket No. 2005N-0038, Request for comment.

Thank you for the opportunity to comment on questions raised in the Federal Register 2005; 70 (25) pp. 6693-6696.

Question 1. What role should IRBs play in the review of adverse events information from an ongoing clinical trial?

As per Federal regulation 21 CFR 56.111(a)(6), the initial role of the IRB should be to act to assure that "where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of research subjects." The role that IRBs should play in reviewing adverse events information, and the way in which the research plan makes safety provisions relating to new data that emerges during a clinical trial, should depend primarily on whether the trial is a "small or single-center trial" or a "large multicenter" trial: Therefore, it is essential to first arrive at a definition of precisely what constitutes a "large multicenter clinical trial", which should be regulated very differently than a "small or single-center trial": The two main parameters to consider are 1) The number of planned subjects, and 2) The number of study sites involved. For example, a large multicenter clinical trial could be defined as involving more than 50 subjects at more than 3 different sites.

For small or single center clinical trials, current regulations governing the reporting of adverse events are generally adequate, and do not require major modifications in this context. These regulations were originally designed for clinical trials of this type. Any serious or unexpected adverse event, or any obvious trend of adverse events will come to the immediate attention of the local IRB in this context, and can be dealt with using full knowledge of the enrollment and duration of the small or single-center trial.

The same is not true for large multicenter trials. It is well-known that in clinical trials involving thousands of subjects at over 100 different sites large numbers of individual Serious Adverse Event (SAE) reports are generated, where each report usually does not provide full information on the enrollment or the duration of the trial (nor are these reports required to contain this information under current regulations), and frequently does not even provide the required information on the number of "similar adverse events" in the trial related to the report.

Importantly, it must be recognized that local IRBs are not in a position to "police" SAE reports from large Multi-Center Clinical Trials (MCTs) to assure that they contain the required information, nor are local IRBs empowered to require sponsors of MCTs to provide full or adequate information on the enrollment or the duration of the MCTs, unless it is clearly stipulated by each local IRB during the initial review of the study. Furthermore, even if local IRBs had access to complete adverse event information in MCTs, there may not be adequate statistical expertise on each local IRB to correctly process and interpret this information.

Clearly, there is a pressing need for: 1) A mechanism to independently ratify the completeness of adverse event reports that sponsors of MCTs create, before the reports are sent to IRBs, and 2) A mechanism for unbiased processing and

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interpretation SAE reports, in order to produce aggregate safety data that emerges from MCTs, before the SAE reports are sent to IRBs. In MCTs designed to satisfy scientific requirements for FDA approval of a drug or device, this independent, unbiased role in "policing" adverse event reports and processing aggregate safety data should belong to FDA, and not to the "un-empowered" and "under-qualified" local IRBs which currently have this role in many MCTs, which is an outrageously unfeasible, untenable, and unconscionable situation.

For MCTs in which an independent Data and Safety Monitoring Committee (DSMC, or its equivalent) is involved, FDA should nevertheless have a role to ratify the completeness and adequacy of SAE reports that arise from the study, whether or not these reports pass through the DSMC first, before these reports should be sent to local IRBs at participating sites in the MCT.

In conclusion, local IRBs should not be given unprocessed SAE reports arising from MCTs because local IRBs should never be primarily responsible for stopping a study, changing a procedure or protocol, or deciding what additional information should be given to current, past, and prospective study subjects based on new data that emerges during the conduct of MCTs.

Question 2. The Types of Adverse Events about which IRBs should receive Information.

Once again, the answer should depend primarily on whether the adverse events occurred in a small or single-center study, or in a large MCT. Local IRBs should receive reports of all adverse events that occur in small or single-center studies, as is now being done according to current Federal regulations.

However, in large MCTs, local IRBs should only receive reports of adverse events (whether or not the events are serious in nature) that have been fully processed, analyzed, and ratified (as outlined above) in the context of the severity, number of subjects exposed to the drug or device, and the duration of the study, and *only if* the results of the analysis of these events dictates changes in the consent form, the conduct of the study, or otherwise gives rise to new information that must be provided to all research participants. Then, it would be the local IRBs' role to implement the recommended changes at their own research sites.

There should not ever be the perception that local IRBs have a crucial role in the interpretation of the significance of any adverse event that occurs in a large MCT, particularly any serious adverse events, because common sense dictates that a large clinical trial involving thousands of human research subjects and funded by a large pharmaceutical company should not be monitored for safety by small, overworked local IRBs composed mostly of unpaid volunteer Board members. Therefore, no "raw" SAE reports, nor any unprocessed adverse event reports arising from MCTs should be sent to local IRBs under any circumstances.

Question 3. Approaches to Providing Adverse Events Information to IRBs.

As implied above, adverse events information arising from large MCTs should arrive at local IRBs in the form of recommendations of how the informed consent, protocol, or information given to research subjects should be changed, along with an evidence-based explanation of the reasons for the recommended changes. This information could come from the MCT sponsor, DSMC, or FDA. The explanation should include a description of the adverse events that led to the communication with the local IRB, along with an adequate summary of the scientific analysis that led to the conclusion that changes in the research were necessary.

Due to the predominance of large multicenter clinical trials in today's medical research, it stands to reason that new regulations are necessary to assure the safe conduct of these large-scale experiments on human beings. I am confident that FDA will see to the successful implementation of new policies designed to govern the conduct of these much-needed vast clinical trials which are the "superhighway" leading to a better understanding of how to fight human diseases.

Sincerely,
Robert L. Bjork, Jr., MD

