Scripps Cancer Center Institutional Review Board

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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 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.