Children's Hospital Boston

A teaching affiliate of Harvard Medical School

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To Our Biomedical Research Community:

RE: Revised Policy on Adverse Events That Require Prompt Reporting to the IRB (Committee on Clinical Investigation)

Federal regulations (45 CFR 46, and 21 CFR 56) require that institutions establish written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others. The FDA has separate regulations that require the prompt reporting of adverse events (or effects) from the investigators to the sponsor and from the sponsor to the FDA as well as to other clinical investigators using the same test article. In device studies, the FDA requires Sponsors to directly report adverse device effects to the IRBs overseeing the research. Recent guidance from both FDA and OHRP has clarified that while some adverse events (or effects) are also unanticipated problems involving risks to subjects or others, **most adverse events are *anticipated* risks of participation in a study and do not require prompt reporting to the IRB.** *Anticipated* events are those reasonably foreseeable risks that have already been included in the IRB-approved consent document.

Effective immediately, Children's Hospital has adapted its IRB policy to be consistent with the OHRP's "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. These changes are consistent with the FDA draft guidance document entitled "Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting Improving Human Subject Protection," which has been circulated by the FDA for public comment. Children's Hospital investigators are no longer required to report any adverse events or effects, including serious adverse events unless the events are also determined (by the Children's PI or by the Sponsor) to represent *unanticipated problems involving risks to subjects or others* meeting the criteria listed below.

The Children's Hospital IRB policy requires the prompt reporting to the IRB of any unanticipated problems thought to be related to research. Children's considers *unanticipated problems that require reporting*, to include any incident, experience, or outcome that meets all of the following criteria:

(1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
(2) Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

Any event meeting this criteria must be reported to the IRB who will then determine whether the research places subjects or others at a different or greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. If this determination is made appropriate reporting will follow.

Based on our interpretation of the regulations and our experience in reviewing adverse events reports, only a small subset of *adverse events* occurring in human subjects research will meet these criteria and constitute an unanticipated problem. Therefore, Children's investigators and research staff will need to make a determination as to whether or not adverse events and safety reports include unanticipated problems necessitating prompt reporting to the IRB.

In order to reduce unnecessary burden on our investigator community, and to have the IRB focus on reports that are of significance to their role in overseeing the safeguarding of the rights and welfare of subjects enrolled in research, effective June 1, 2008 The IRB at Children's Hospital will no longer accept internal or external adverse events reports, or safety reports unless they have been determined by the Principal Investigator to contain a report of unanticipated problems that is thought to be related or possibility related to the research. All deaths of research subjects enrolled at Children's need to be reported to the IRB if they are thought to be related or possibly related to the research. Please do not hesitate to contact me directly if you require any additional clarification of our policy.

Sincerely yours,

Susan Kornetsky, MPH,
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