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DATE: June 3, 2009
TO: University Researchers and Sponsors
FROM: Daniel K. Nelson, Director
RE: Revised Policy on Reporting Unanticipated Problems and Adverse Events to the IRB

Federal regulations for protection of human subjects (45 CFR 46 and 21 CFR 56) require that institutions establish written procedures for ensuring prompt reporting to the Institutional Review Board (IRB) of any *unanticipated problems involving risks to subjects or others*. The FDA has separate regulations that require the reporting of adverse events/effects from investigators to the sponsor, and from sponsors to the FDA.

For many years, sponsors, researchers, and Institutional Review Boards (IRBs) have over-interpreted these regulations, and this has resulted in over-reporting of adverse events. Much of this reporting has been of questionable value to our shared goal of protecting subjects. This is particularly true in multi-site clinical trials, where local IRBs are seldom in position to evaluate external "IND safety reports" in a meaningful context. Recent guidance from both FDA and OHRP (referenced below) has clarified that much of this reporting is not required and is, in fact, counterproductive. While some adverse events/effects are also *unanticipated problems involving risks to subjects or others*, many are not and therefore do not require prompt reporting to the IRB.

Accordingly, UNC-Chapel Hill has adapted its IRB policy to be consistent with federal regulations and guidance. UNC-Chapel Hill investigators are not required to report adverse events/effects to the IRB, unless they have been determined to represent unanticipated problems that meet the criteria listed below.

For the purposes of reporting to the UNC-Chapel Hill IRB, *unanticipated problems involving risks to subjects or others* are defined as any incident, experience, or outcome that meets both 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 (i.e., 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 these criteria must be reported to the IRB, which will then determine whether the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously recognized. Additional details are available at: http://ohre.unc.edu/ohre_up_submission.php

It is likely that only a small subset of adverse events occurring in human subjects research will meet these criteria and constitute an unanticipated problem. Therefore, we anticipate that fewer reports will be made to the IRB. This is particularly true for external safety reports in multi-site clinical trials, unless an aggregate analysis has been made (e.g., by sponsor, DSMB or lead investigator) to evaluate their relevance and significance to the study-as-a-whole. If an event has been determined to constitute an *unanticipated problem involving risks to subjects or others*, it follows that the report should be accompanied by a corrective action plan to address the problem; individual reports submitted without this evaluation and corrective action plan will not be accepted as reportable problems.

Relevant Federal Guidance

"Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events," Office for Human Research Protections (OHRP), 2007

"Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting-Improving Human Subject Protection," Food and Drug Administration (FDA), 2009