October 1, 2010

To: University Researchers and Sponsors:

RE: MUSC Policy on Reporting Unanticipated Problems and Adverse Events to the IRB

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 (UIRPSOs). 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. These separate regulations have been misunderstood at MUSC as well as other institutions to imply that all adverse events must be promptly reported to the IRB. While some adverse events 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, investigator’s brochure, and product labeling.

Effective immediately, MUSC 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,” which is available online at: http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm. These changes are consistent with the FDA draft guidance document entitled “Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting Improving Human Subject Protection,” which has been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. MUSC investigators should not report any internal or external adverse events or effects, including serious adverse events unless the events are also determined (by the MUSC PI or by the Sponsor) to represent unanticipated problems involving risks to subjects or others meeting the criteria listed below.

The Medical University of South Carolina IRB policy requires the prompt reporting of any unanticipated problems involving risks to subjects or others. MUSC considers unanticipated problems, in general, 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); and

(3) Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

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 three criteria and constitute an unanticipated problem. Therefore, MUSC investigators and research staff will need to make a determination as to whether or not adverse events and safety reports include unanticipated problems involving risks to subjects or others (UPIRSOs), necessitating prompt reporting to the IRB. When there are unanticipated problems involving risks to subjects or others on a study under the MUSC IRB, it must be promptly reported. UPIRSOs should be reported to the IRB within 10 working days (unanticipated deaths of subjects enrolled at MUSC need to be reported within 24 hours).

Further, please note that it is expected that an incident, experience, or outcome that meets the three criteria for a UPIRSO will generally warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. MUSC IRB anticipates that UPIRSOs reported will frequently be accompanied by a revision to the study.

In order to reduce unnecessary burden on our investigator community, and to have our 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, MUSC IRB will no longer accept internal adverse events reports unless they have been determined by the Principal Investigator to contain a report of unanticipated problems involving risks to subjects or others.

MUSC IRB will no longer accept **external** adverse events reports or safety reports unless they have been determined by a Data Safety Monitoring Board (DSMB) or a Central Monitoring Entity (CME) to be:

a. Unanticipated;
b. Related or possibly related to participation in research;
c. Serious or more prevalent than expected; **AND**

d. The DSMB/CME recommends a specific change to the protocol/informed consent based on the event, for example, modification of inclusion/exclusion criteria, and revision of the informed consent to encompass newly identified risks.

**Deaths on Study**
All deaths of subjects who are enrolled at MUSC need to be reported to the MUSC IRB. Unanticipated deaths need to be reported within 24 hours. Anticipated deaths (i.e., due to disease progression) will be reported at the time of continuing review.

Please do not hesitate to contact me directly if you require any additional clarification of our policy.

Sincerely,

Kathryn Magruder, Ph.D.
Director, Office of Research Integrity