Modifications: What Constitutes a Substantive Change?

HHS regulations at 45 CFR 46.110(b)(2) and FDA regulations at 21 CFR 56.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research during the period for which approval is authorized.

Points to consider:

1. All modifications to an approved application and/or consent form must be received and approved by the IRB before they are initiated except where necessary to eliminate apparent immediate hazard to the study participants, as provided in Subpart C, 56.108(a)(4) of the federal regulations. In cases where a protocol has been modified to eliminate apparent immediate hazard, the implemented changes must be reported promptly to the IRB. A review of the changes will be conducted.

2. Modifications may be submitted at any time. A modification is given approval only to the expiration date that was received at the most recent initial or renewal review.

3. Substantive modifications/amendments are reviewed through the full committee review process (unless the protocol was approved via expedited review). Minor modification requests are reviewed through the expedited process. Examples of modifications considered to be major in nature include, but are not limited to, escalation in the drug(s) dosage(s), the introduction of an additional drug(s); the addition of a new invasive procedure. Substantive modifications may impact on the risk/benefit ratio in the study.

4. The initial determination as to whether a modification is major or minor is the responsibility of the principal investigator, who assesses the degree of change in procedures and risks. However, the acceptance of the determination rests with the IRB. The modification is reviewed by the IRB professional staff and a recommendation of whether full IRB review is necessary is made.

5. Minor changes in previously approved research during the period for which approval has been authorized (of 1 year or less) will be done under an expedited review process. The review will be carried out by the IRB Chair, or his/her designee(s) from members of the IRB. If the Chair or designee believes that the "minor" modification is too substantive to receive this type of review, the application will be referred for full IRB review.

6. The regulations do not define “minor changes.”

7. Guidance that identifies changes that are considered to be minor must be provided by the institution.

The following items are examples of modifications that may be considered minor changes: *

a. spelling or grammatical errors;
b. specific additions or subtractions to consent forms, Human Subjects Review Form, or additional materials that lower the risks for subjects or clarify procedures;
c. change of technical terms to lay language in consent forms;
d. letters of cooperation from institutions;
e. deletion of questions from an instrument;
f. change of location for collecting data;
g. changes in contact names, addresses, telephone numbers, advisers, end date, and researchers;
h. changes in the title of the proposal;
i. changes in compensation to the subjects;
j. addition of subjects from the same population as indicated in the original proposal;
k. additional advertisements or changes to approved advertisements;

*Examples only; modifications not on this list may be determined to be non-substantive by the IRB Chair or assigned primary reviewer and therefore be eligible for expedited review.