Attachment B: approved by SACHRP July 20, 2011

SACHRP Recommendation regarding definition of a minor change in research under 45 CFR 46 and 21 CFR 56

The Health and Human Services (HHS) and Food and Drug Administration (FDA) regulations both have sections addressing expedited review (45 CFR 46.110; 21 CFR 56.110.) IRBs may use expedited review to approve certain kinds of research involving no more than minimal risk, and minor changes in approved research. Expedited review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. Expedited review greatly reduces the administrative burden on IRB members and staff, and allows for more efficient review of research.

Although the regulatory language regarding expedited review of a minor change in research is identical in the HHS and FDA regulations, OHRP and FDA have provided differing guidance regarding the definition of a minor change. The guidance documents from each agency are included below in Appendix I. FDA in the preamble comment to the regulations and in the FDA Information Sheets has taken the approach that changes that result in increased risk to human subjects are not minor. OHRP, on the other hand, has taken the approach that changes in research that would materially affect the assessment of risks and benefits are not minor. In its September 29, 2008 letter to CTEP, OHRP re-emphasized that approach as it relates to new or modified risk information, and also added the concept that a minor change in research is one that does not affect any of the determinations for IRB criteria at 45 CFR 46.111. OHRP stated that IRBs can consider "whether the new or modified risk information adversely impacts the overall risk-benefit relationship for the subjects of the research and therefore may significantly alter the prior determinations of the IRBs required for approval of research under HHS regulations at 45 CFR 46.111 (in particular, the determinations under 45 CFR 46.111(a)(1) and (2))."

SACHRP makes the following recommendations regarding the definition of a minor change in research under the HHS and FDA regulations:

OHRP and FDA should issue a single joint guidance on this issue so that IRBs have a single source of information regarding the agencies' viewpoint on this issue. This will reduce administrative burden on IRBs and ease compliance requirements. Currently, it appears that in some cases a change in research may not be a minor change in research under the FDA interpretation but still be considered a minor change in research under the OHRP interpretation.

The joint guidance, regardless of where it is located, should include a formal statement that it is FDA guidance as well as OHRP guidance. This will ensure that institutions, IRBs, and FDA employees are aware that it represents formal FDA guidance.

SACHRP recommends the following definition of a minor change in approved research that can be reviewed through the expedited review process:

> Minor changes in approved research that can be approved through expedited review procedures are ~~minor~~ changes that neither materially increase risk, nor materially decrease benefit, **nor materially decrease scientific merit.**

Commentary: This approach is similar to existing FDA and OHRP guidance. This approach has several advantages. It is familiar to IRBs. Also, if issued in a joint guidance document then IRBs would have the benefit of knowing the expectations of both agencies.

SACHRP recommends that the joint guidance provide examples of the kinds of changes that qualify as minor changes in approved research. It is very helpful when guidance provides examples as well as a definition. The types of examples that would be helpful to IRBs include the following, all of which should be assessed by an experienced reviewer, who would, of course, have the option of referring the change to full board review:

1. Adding a new procedure to a research study, when that procedure is on the expedited list and involves no more than minor risk.

2. Adding a new minimal risk procedure to a research study, when that procedure is <u>not</u> on the expedited list. Two examples are low dose radiation procedures and drawing 3-5 blood draws of less than 550 ml from an in-dwelling catheter. It is SACHRP's understanding that this represents OHRP's current position.

3. A minor change to research that is not on the expedited list, but does not involve the addition of a procedure. Examples include many types of changes to research, such as:
   - Change in the equally qualified individuals who will do statistical analysis.
   - Change in consent form wording that does not increase risk or decrease benefit. For example, changing "nausea" to "nausea and stomach upset," or fixing a run-on sentence or a comma.
   - Replacing old case report forms with essentially equivalent new case report forms, and the change is noted in a revised protocol.
   - Changing the order of questions in a psychology study questionnaire.
   - Adding the word "approximately" to the table of the lab test schedule.

4. The guidance should also address the point from section E of the current OHRP "Guidance on IRB Approval of Research with Conditions," which states that "Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research." These administrative changes to the protocol need to be clearly distinguished from administrative changes to the consent form, which always need at least expedited review.

5. A new media advertisement that is submitted after the research is approved, such as a new newspaper or radio advertisement.

6. A statistically small change to the number of subjects an investigator will enroll. For instance, in a single site study, a change from 100 to 105 subjects, or in multi-center study, and change from 20 subjects to 30 subjects at one site in a study involving 1,000 subjects. Minor decreases in the number of subjects would also qualify for expedited review.

7. A change in equally qualified study personnel (study coordinator, nurse, technician, transcriptionist for anthropology study), e.g., a person leaves the institution and is replaced.

8. A change in equally qualified principal investigators. For example, when a principal investigator leaves the institution and a new principal investigator takes over.

9. Adding a new equally qualified investigator at a new site for a multi-site study, overseen by a central IRB. The IRB should have established criteria for this in its SOPs, such as familiarity with the investigator and the sponsor.

10. In a coronary stent study, an amendment to extend the observational follow-up from 12 to 60 months.

11. Deletion from the protocol of a research biopsy that, without impairing scientific merit, materially decreases risk for study subjects.

Finally, the guidance should note that changes to research that were initially approved through expedited review will qualify for expedited review unless the change increases the overall risk level of the research to more than minimal risk.

In summary, joint OHRP and FDA guidance addressing these issues will greatly aid the regulated community, and particularly IRBs, in reducing burden and ensuring compliance.