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Topic: Minor versus Substantive Amendments

Overview of the Topic

Most researchers are always trying to improve their research projects. They add new questions to surveys, add new data collection points, revise documents, add personnel, etc. This is a good thing because it usually improves the research and hopefully makes it more valid and meaningful. Whether the changes impact the protection of the participants is an issue that the IRB must review and approve. Thus, amendments to approved protocols are very common in the IRB world, either during the approval period or at the time of continuing review. The regulations require prompt reporting to the IRB of proposed changes in previously approved research, and that changes may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject (45CFR46.103(b)(4)(iii)).

The regulations allow for expedited review of **minor** changes in previously approved research during the period (of one year or less) for which approval is authorized (45CFR46.110). The expedited review of amendments may be carried out on projects which were greater than minimal risk and approved by the convened IRB, as long as the amendments meet the definition of minor. An amendment to research originally reviewed by the expedited procedure usually can be reviewed by the expedited procedure, unless the amendment would cause the research to become greater than minimal risk, in which case the study must be elevated to full board and reviewed by the convened IRB. For the most part we will be talking about amendments to protocols approved by the convened IRB.

So, a key determination is whether an amendment is **minor**, and thus can be reviewed via the expedited mechanism, or **substantive**, in which case the convened IRB must review and approve it. Unfortunately, the regulations do not provide a definition of minor or substantive and your IRB must develop these definitions and apply them to this initial decision about classifying an amendment.

Definitions of **minor** may include the following concepts:

- The revision includes procedures or changes that are no more than minimal risk.
- Risks to subjects are not increased.
- The revision is not a significant alteration of the study design.
- The changes do not impact the criteria for approval to a point that needs discussion and approval by the convened IRB.

Example of **minor** revisions may include:

- Change in telephone numbers or other contact information
- Addition of research staff on the project
- Reduction in number of research subjects
- Deletions of questions in a survey
- Minor changes in the consent form

Definitions of **substantive** often include the converse of minor concepts:

- The revision includes procedures or changes that are more than minimal risk.
- Risks to subjects are increased.
- The revision is a significant alteration of the study design.
- The changes have a clear impact on one or more of the criteria for approval that needs discussion and approval by the convened IRB.

Example of **substantive** revisions may include:

- Revising edibility criteria
- Adding a research site
- Changing the principal investigator
- Adding a new risk to the consent form
- Adding children as research subjects to a project originally approved only for adults

Note that while the examples listed generally would fit in the assigned category, individual submitted changes may or may not fit into the category. For example, adding research staff that must meet some requirements, such as experience with terminal patients, may quality as substantive, or adding a research site for a particular study might be considered minor, for example adding an additional mailing list for a low-risk survey.

Since minor amendments are reviewed by the expedited review procedure, the review must be carried out by the IRB Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the IRB. An IRB Staff member can review minor amendments only if they are a rostered primary or alternate member of the IRB. When reviewing minor amendments to research, the reviewers may approve the amendment under the authority of the IRB but the reviewers may not disapprove the amendment. In this case the amendment must be reviewed by the convened IRB (45 CFR 46.108(b). For all amendments reviewed by the expedited procedure all members of the IRB must be notified of the revisions by some mechanism, using the agenda or otherwise.

Amendments classified as substantive must be reviewed and approved by the convened IRB. The amendment should appear as a formal item for discussion on the agenda. When reviewing amendments, the IRB must satisfy the relevant criteria for approval, just as they would at initial or continuing review. Sometimes more than one amendment for a single research project is submitted to the IRB. In this situation the IRB Staff can separate the minor and substantive revisions and deal with them separately, or send them to the IRB to be reviewed as a package. It is not uncommon for amendments to be submitted at the time of continuing review. When this occurs, minor amendments can be reviewed separately by the expedited procedure and reported to the IRB during the continuing review discussion, or again, all amendments can be sent to the convened IRB together. Continuing review may be approved by the IRB, while separately approving or disapproving a substantive amendment to the same project.

Sometimes the sponsor of research, such as a clinical trial, will submit amendments and classify them as minor or substantive. If the IRB Chair does not agree with the sponsor's classification they have the authority to change the assignment for review by their IRB.

When the IRB reviews an amendment the discussion, decision and controverted issues must be documented just like any other review by the IRB. Likewise pertinent information and decisions for an expedited review of amendments must be documented in the IRB records. Proper classification and approval of amendments is as important as the initial and continuing review of research and should be handled appropriately by IRB.

Questions for the IRB to Consider

Questions your IRB Chair, Members or Staff may ask about amendments to previously approved research:

1. Does the proposed change meet the definition of minor and thus can undergo expedited review?
2. Is the proposed change substantive and must be reviewed by the convened IRB?
3. **IRB Decision**: Can the amendment be approved?
4. Has the discussion and determination been documented in the IRB records or IRB minutes?

Case Studies

Case Studies: Would you classify the following as minor or substantive amendments:

- Spanish translation of an approved consent
- Addition of a third arm to a clinical trial
- Addition to a survey, originally reviewed as expedited, of questions regarding alcohol and drug use.
- Addition of pregnant women as research subjects to an expedited survey of infant car seat use
- Addition of children to a study comparing two pain relievers for migraine headaches, initially approved for adults
- Addition of another school to a study of a new math curriculum
- Change in payment of subjects from $25 to $100 because of low participation rates
- Addition of new risk information to the consent form
- Addition of the Beck Depression Index to the study
- Addition of a second database to an existing data analysis study (no contact with subjects)

Prospective Thinking: Provide the IRB with your complete SOPs on reviewing amendments. Review in detail the definitions of minor and substantive and discuss whether the definitions are complete and are resulting in consistent categorization of proposed amendments. Discuss whether changes are needed or add examples which may help.