7.8 Modification of an Approved Protocol

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes, no matter how minor, in approved research** - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazards to the subject (in which case the IRB must then be notified at once). Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant are reviewed by the IRB to determine whether each change was consistent with ensuring the participants' continued welfare.

Modifications may be permanent (Protocol Modification) which make changes to the protocol for all remaining subjects or temporary (Protocol Exceptions) circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient(s)/subject(s) (examples: patient/subject is allergic to one of the medications provided as supportive care; patient/subject is not eligible in a direct benefit study). Usually an Exception is a change that is planned and has prior agreement from the sponsor. See Section 7.8.5 for details on Protocol Exceptions.

(Note: Protocol Deviations [see Section 14.1] are unplanned and are reported to the IRB after the fact.)

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

7.8.1 Procedures

Investigators must submit documentation to inform the IRB about the proposed changes to the study, including, but necessarily limited to:

- Completed modification request form";
- For protocol modifications, a revised protocol, application, and/or study materials (in tracked changes or with a detailed summary of changes and the locations of those changes);
- Revised consent/consent addendum, parental or guardian permission/assent documents (if applicable);When the proposed change(s) to the research might relate to current subjects' willingness to continue to participate in the study and they won't be asked to re-consent using the revised consent form, an information sheet, letter, script, or other mechanism of providing information; and
- Any other relevant documentation provided by the sponsor or coordinating center.

IRB staff will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants convened board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.

7.8.2 Convened Board Review of Modifications

When a proposed change in a research study is not minor, then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members are provided and review all documents provided by the investigator.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB will also determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to future/current/past participants.

7.8.3 Expedited review of Modifications

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members.

The reviewer(s) complete the appropriate IRB reviewer or certification checklist to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

The reviewer will also consider whether information about those modifications might relate to future/current/past participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

7.8.4 Possible IRB Actions after Modification Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 7.6 for a detailed description of these actions):

1. Approved
2. Approvable with Conditions
3. Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

7.8.5 Protocol/Research Plan Exceptions

Protocol/Research Plan exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

Exceptions are planned, and the investigator gets approval from the sponsor and the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required. Depending on the nature of the exception, an expedited review is possible. In order to be approved under expedited review exceptions must not increase risk or decrease benefit, change the risk/benefit analysis, negatively affect the participant's rights, safety, welfare, or negatively affect the integrity of the resultant data. Review of exceptions that represent more than minor changes or risks levels greater than minimal must be done at a convened meeting of the IRB.

Procedures for exceptions are the same as for a Protocol Modification. The investigator must submit a modification request along with any revised documentation to be presented to the subject(s) and documentation of sponsor approval, if applicable.

The only time a protocol/Research Plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an immediate hazard to the participant. In such cased, the exception must be submitted to the IRB as soon as possible.