7.0 DEVIATION and EXCEPTION of a PREVIOUSLY APPROVED PROTOCOL

7.1 OBJECTIVE

To describe the policies and procedures for reviewing a modification or a deviation/exception to a previously approved protocol.

7.2 GENERAL DESCRIPTION

Investigators may not initiate any changes in research procedures or consent/assent form(s) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subject. Examples of modifications that require IRB review include, but are not limited to, changes in:

- Study personnel;
- Advertising materials (flyers, radio spots, etc.);
- Research procedures;
- Subject populations (e.g., age range);
- Location where research will be conducted;
- Consent/assent forms;
- Recruitment procedures; or
- Date for completion of study.

If the investigator makes protocol changes (i.e., modifications, exceptions or deviations) to eliminate apparent hazards to the subject(s) without prior IRB approval, the investigator must immediately report the changes to the IRB for review and a determination as to whether the changes are consistent with the subject's continued welfare (See Protocol Violations SOPP).

Investigators must promptly notify the IRB in writing of any change in a protocol's status, such as discontinuation or completion of a study. See the Continuation Review (CR) SOPP and the Study Closure SOPP for procedures on reporting an activity status change to the IRB.

7.3 DEFINITIONS

Modifications are defined as changes that impact the overall protocol.

Exceptions or *deviations* are changes that impact individual subjects and do not change the overall protocol. Investigators may not initiate these changes without prior IRB review and approval, except where necessary to eliminate apparent hazards to the subject.

The IRB considers enrollment of a research subject in a protocol that fails to meet current IRB approved protocol inclusion criteria or falls under protocol exclusion criteria to be a protocol *exception*.

The IRB considers a departure from the current IRB approved procedures that impact an individual subject to be a protocol *deviation*.

7.4 RESPONSIBILITY

Execution of SOPP: Principal Investigators (PI)/Study Personnel (SP), IRB Chair, IRB, Office of Regulatory Research Compliance (ORRC) Staff, Research Compliance Officer (RCO).

7.5 PROCEDURES

7.5.1 Submission of Modifications, Deviations, and Exceptions

- The PI is responsible for submitting a modification request (MR) or deviation/exception request using the Modification Request Form or the equivalent paperwork prior to the implementation of any change.

- To submit the request, the PI completes the Modification Request Form according to the instructions on the form and submits the form to the ORRC.

7.5.2 Screening of Submissions

- The ORRC staff member receiving an MR forwards the request to the RCO. The RCO then screens the MR form.

- If the request is incomplete, the RCO either returns the MR to the PI or requests additional information from the PI. The RCO forwards the MR to the IRB reviewer once the MR is complete. ORRC staff document who served as primary reviewer.

- If the RCO is unclear about what the MR entails, he/she discusses it with the primary reviewer or obtains clarification from the PI.

- If the modification references an instrument, apparatus, reagent, machine, implement or device, the RCO discusses the modification with the reviewer to determine if the modification involves use of a medical device under FDA jurisdiction (collecting safety or efficacy data). If so, the PI includes FDA language in the informed consent and HIPAA documents and submits the device form and/or applicable information for the IRBs review and regulatory determinations.

- If the modification references a drug, biologic, therapeutic dietary supplement, substance affecting structure or function of the body, or product intended to diagnose, cure, mitigate, treat, or prevent disease, the RCO

discusses the modification with the reviewer to determine if the modification is under FDA jurisdiction (use beyond the course of medical practice). If so, the PI includes FDA language in the informed consent and HIPAA documents and submits the drug form and/or applicable information for the IRBs review and regulatory determinations.

- If the modification adds vulnerable populations or requires documentation of specific regulatory findings, the RCO sends the appropriate IRB forms to the reviewer with the MR. For example, if the PI adds children as subjects, the RCO includes children as subjects review checklist with the MR and sends the HU IRB Policy on Children in Research document to the IRB reviewer.

- Depending on the requested change, the RCO may also secure additional review (i.e., prisoner representative). The IRB is responsible for applying the applicable regulatory requirements.

- If the MR requires consent/assent form changes, the RCO screens to ensure ORRC's telephone number appears on the form(s). The reviewer may direct the RCO to screen the consent/assent form(s) to reflect any recent changes in the IRB template. The RCO alerts the IRB reviewer if the consent/assent form(s) are inconsistent with the template. The IRB has final authority for requiring consent/assent changes.

- If the MR includes additions to study personnel, the RCO screens to ensure that all new SP have completed required human subject protections training. If not, the RCO informs the PI that he/she may not add the untrained SP until they have completed required training. The RCO asks the PI whether he/she wishes to remove the SP in question and continue with the MR. Alternately, the PI may choose to wait until the SP in question completes the training. In that case, the RCO forwards the MR to the IRB after SP training is complete.

- The RCO screens for HIPAA concerns.

- If the protocol is currently undergoing CR, and if appropriate, the RCO incorporates the MR into the CR. If it is not appropriate, the RCO processes the MR independent of the CR.

- If the PI submits the modification with a CR application, the RCO processes the modification as part of the CR (i.e., amendments) as outlined in the Continuation Review SOPP.

7.5.3 Determining Mechanism of Review (i.e., Expedited vs. Full Review)

- If the sponsor or the PI specifically requests full review procedures, the RCO places the MR on an agenda for full review following procedures outlined in the Initial Full Review SOPP.

- If PI/sponsor does not request a full review, the RCO sends the Modification Request Form with attachments and the Modification Reviewer checklist to the IRB Chair or, if he/she is not available, to a voting member of the IRB.

- If the modification involves changes in consent/assent forms, the RCO forwards the highlighted version of the forms to the IRB Chair or IRB member. The clean, unmarked copies of the consent/assent forms remain in the ORRC.

- The IRB Chair or IRB member documents his/her determination regarding whether the IRB can review the request using expedited or full review procedures on the Modification Reviewer checklist. If the change is minor, the IRB Chair or IRB member conducts the review using expedited procedures. A minor change is one which makes no substantial alteration in:
  - The level of risk to subjects;
  - The research design or methodology;
  - The subject population;
  - Qualifications of the research team;
  - The facilities available to support the safe conduct of the research; or
  - Any other factor that would warrant review of the proposed changes by the convened IRB.

7.5.4 Expedited/Full Review Procedures

- The IRB Chair or an experienced IRB member designated by the IRB Chair conducts the MR undergoing expedited review, using standard expedited review procedures. The expedited reviewer exercises all the authority of the IRB except the reviewer cannot disapprove the research. The listing of the item on an agenda for the convened IRB serves to advise the IRB of the expedited review.

- The IRB Chair or designated IRB member documents on the Modification Reviewer checklist his/her determinations regarding:
  - Eligibility for expedited review;
  - Whether the research meets the criteria for IRB approval (criteria for approval checklist is part of the Signature Page);
  - Whether proposed changes to the informed consent/assent process continue to meet requirements as set forth in 45 CFR 46.116 and 117, and 21 CFR 50.25; and
  - Whether the proposed modification affects any research categories of the currently approved protocol.

- The IRB Chair or designated IRB member returns the Modification Request Form and Modification Reviewer checklist to the ORRC.

- If the IRB Chair or designated IRB member recommends full review, the RCO places the MR on an agenda following procedures outlined in the Initial Full Review SOPP.

- For an MR undergoing full review, the RCO invites (e.g., phone call or e-mail) the PI to attend if the IRB requires that he/she attend the meeting. The full IRB reviews the MR following procedures outlined in the Initial Full Review SOPP and applying the federal criteria for approval as applicable to the request.

- For an MR undergoing full review, the IRB Chair or designated IRB member serves as the primary reviewer.
    - Approximately 5-10 days prior to the convened meeting, the RCO sends the IRB Chair or designated IRB member the Modification Request Form, a Modification Reviewer checklist, and the protocol materials affected by the proposed modification (e.g., revised consent/assent or revised investigator brochure). The RCO makes the complete IRB protocol file available to the reviewer and the committee for reference during the convened meeting.
    - The IRB Chair or designated IRB member is responsible for reviewing the proposed modification, determining whether the modified research continues to fulfill the criteria for IRB approval, and documenting his/her determinations on the Modification Reviewer checklist.
    - The IRB Chair or designated IRB member reports recommendations to the IRB at a convened meeting. The IRB Chair or designated IRB member makes recommendations on issues he/she determines do not meet the federal criteria for approval, involve controverted issues, or need additional information. If the IRB Chair or designated IRB member is unable to attend the meeting, the reviewer provides his/her written comments or recommendations to the IRB at the convened meeting.
    - Approximately 5-10 days prior to the meeting, the RCO sends the IRB members scheduled to attend the meeting the Modification Request Form and the protocol materials affected by the proposed modification in sufficient detail to enable a determination as to whether the modified research continues to fulfill the criteria for approval.

7.5.5 Review Outcome(s)

- For expedited review, the outcomes of review are the same as the options outlined in the Initial Expedited Review SOPP. The ORRC staff notifies the PI in writing of the IRB's decision following procedures outlined in the Initial Expedited Review SOPP.

- For full review, the outcomes of review are the same as the options outlined in the Initial Full Review SOPP. The ORRC staff notifies the PI in writing of the IRB's decision following procedures outlined in the Initial Full Review SOPP.

- If the IRB Chair or designated IRB member approves an MR via email without having received an MR form, the RCO notifies the PI following the Initial Review SOPP. In addition, the RCO sends the Modification Reviewer checklist along with a printout of the approval message to the IRB Chair or designated IRB member who then completes and signs the checklist and returns it to the ORRC. The ORRC staff member who receives the returned materials routes them to the appropriate RCO. The RCO adds the email and completed/signed Modification Reviewer checklist to the protocol file.

- If the IRB approves the modification, the end date of the approval period remains the same as that assigned at the initial or CR.

- If an MR is part of a CR, ORRC staff who prepares the correspondence incorporates written notification of IRB approval or disapproval of the MR into the IRB CR approval/disapproval letter.

- If the PI has concerns regarding the IRB's decision, the PI may submit his/her concerns to the IRB in a written document that includes a justification for changing the IRB's decision.

- For inclusion in the IRB files, the RCO staples and files as one action the Modification Request Form, Modification Reviewer checklist and supporting documents, including, as appropriate, a clean copy of the stamped consent/assent forms.

7.6 REFERENCES

21 CFR 56.110(b)(2)
38 CFR 16.110(b)(2)
45 CFR 46.110(b)(2)
38 CFR 16.111
45 CFR 46.111
21 CFR 56.111
21 CFR 312
21 CFR 812