1 PURPOSE

This procedure describes the process for developing, reviewing, and approving protocol amendments that will be used for conducting a clinical study.

2 GENERAL INSTRUCTIONS AND RESPONSIBILITIES

a) The Investigator or qualified designee is responsible for preparing the initial draft of the protocol amendment and forwarding the draft to all designated individuals for review and approval (Reference SOP 102, Document Development and Change Control, for modifying protocol case report forms (CRFs) (Reference SOP 701, Case Report Forms) and informed consent forms (ICFs) (Reference SOP 601, Informed Consent) as necessary, and distributing final IRB-approved amended protocols, revised CRFs, and ICFs to all necessary personnel.

b) The Investigator is responsible for forwarding the final, departmentally approved protocol amendment to the FDA (alone or as part of another document) and other regulatory authorities (for example IRB and/or OHRP), for their review and approval as appropriate and necessary.

c) All participating Investigators are responsible for obtaining local Institutional Review Board (IRB) approval and other internal and external regulatory approvals before implementing the protocol amendment.

d) If the Investigator is the sponsor, a protocol change to eliminate an immediate hazard to subjects may be implemented immediately provided that the FDA and the IRB are notified as soon as possible afterwards, but no more than five (5) days after the change is implemented for IDE studies. For non-IDE studies, only the IRB will need to be notified.

e) In many cases, changes to a protocol will result in necessary changes to the informed consent form. The Author will follow the procedures in SOP 601, Informed Consent, and in SOP 102 to make associated changes to the informed consent form.
3 SPECIFIC PROCEDURES

3.1 Writing Protocol Amendments

a) Minor changes (as defined below by the FDA) can be made to the protocol and related documents provided that they do not affect the study design. Such changes include editorial changes, correcting typographical errors, and appropriate scientific or technical clarifications.

b) These minor changes must be documented on the protocol’s Table of Modifications and approved by the Investigator, and incorporated into the protocol at the time of the next protocol amendment submission.

c) The FDA also permits modifications to the experimental design of Phase 1 protocols that do not affect critical safety assessments to be reported to the FDA only in annual reports.

d) Amendments to a protocol will be numbered sequentially and consistently throughout the study conduct period.

e) The designated Author of the protocol amendment, or his/her designee, will prepare the first amendment draft.

f) The Author will prepare the amendment using a strikeout and highlight-editing program such that all deleted text is marked as strikeout and all new text is highlighted (i.e. track-changes).

g) All changes should be captured using the tracked changes function on the protocol.

3.2 Amendment Review and Approval

a) The suggested amendment to the protocol will be reviewed and approved by all individuals designated by the Investigator and the Author (Reference SOP 102, Document Development and Change Control) for a controlled document.

b) The Author will circulate the appropriately identified protocol amendment draft to all designated individuals and other experts to ensure it is scientifically and ethically sound, and meets all applicable regulations and guidelines.

c) The Author will repeat the review process until all comments are addressed as necessary.

d) The final draft protocol amendment must be reviewed and approved by signature and date of all designated individuals.

e) Once reviewed and approved, the Author will add the proper amendment number and effective date (corresponding to the date of the final approval signature) (See SOP 102 Attachment A).

f) A clean copy of the final amendment should be obtained by the sponsor for approval and signature, if applicable.

g) The protocol amendment submission should be prepared as follows:

- Cover letter or summary page describing the changes made to the previous version of the protocol and referencing the original submission
Investigator Standard Operating Procedures

- A copy of the amended protocol in which the deleted text is marked as strikeout and all new text is highlighted
- A clean copy of the new clinical protocol amendment
- A copy of the IRB approval letter or certifications of IRB action (if applicable)
- If comments are desired from the FDA on the protocol amendment, a request for this is included in the submission
- The protocol amendment may not be implemented until final IRB approval is obtained, and the amendment has been submitted to the FDA.

h) Protocol amendments must be submitted to the FDA and IRB when any revisions are made to the original protocol or subsequent version of the protocol that significantly affects the safety of subjects and/or any change is made that significantly affects the scope of investigation or scientific quality of the study.

i) A protocol amendment cannot be implemented until the protocol has been submitted to FDA for review and it has been approved by the IRB (and other regulatory authorities where applicable, i.e. Independent Ethics Committee).

j) Once final local IRB approval is obtained, the Investigator should obtain a copy of the IRB approval letter.

k) The Investigator will forward a copy of the final IRB-approved and the FDA submitted protocol to the Office of Human Research and all appropriate clinical staff as necessary.

l) The Investigator must sign the signature page of the protocol, indicating that they understand and agree to the changes.

m) The Investigator is responsible for training his/her staff of the changes in the protocol for studies conducted at Memorial Healthcare System, and should ensure that the relevant study personnel are trained on the changes to the protocol. All study related training should be clearly documented including the name of the trainer, names and signatures of persons present, the date of the training and what was covered. Documentation should be kept in the Regulatory Master File.

4 REFERENCES TO OTHER APPLICABLE SOPS
- 102 Document Development and Change Control
- 301 Clinical Protocol Development, Implementation and Compliance
- 601 Informed Consent
- 701 Case Report Forms

5 ATTACHMENTS
- None

6 APPLICABLE REGULATIONS AND GUIDELINES
- Protocol Amendments (21 CFR 312.30)
Investigator Standard Operating Procedures

- Supplemental Applications (21 CFR 812.35)
- The Principles of ICH GCP (ICH E6, Section 2.5 and 2.6)
- Trial Design (ICH E6, Section 5.4)
- Clinical Trial Protocol and Protocol Amendment(s) (ICH E6, Section 6.0)