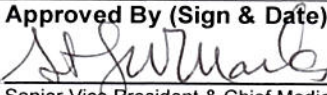
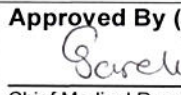


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<b>SOP No.: 301      Clinical Protocol Development, Implementation and Compliance</b>	
<b>Author:</b> Office of Human Research	
<b>Effective Date:</b> Nov 18, 2016	<b>Supersedes document dated:</b> March 3, 2014
<b>Last Reviewed on:</b> Nov 2, 2016	<b>Results of Review:</b> Changes made and tracked
<b>This SOP pertains to:</b> All personnel involved in preparing clinical research protocols for human subject research within the Memorial Healthcare System	
<b>Responsibility for executing this SOP:</b> Investigator and Designated Research Personnel	
<b>Approved By (Sign &amp; Date):</b>  11/17/16 Senior Vice-President & Chief Medical Officer, MHS	<b>Approved By (Sign &amp; Date):</b>  11/16/16 Chief Medical Research Officer, OHR

### 1 PURPOSE

This procedure describes the process for developing, reviewing, approving and implementing clinical protocols and includes all human subject research within the Memorial Healthcare System.

### 2 GENERAL INSTRUCTIONS AND RESPONSIBILITIES

The Principal Investigator is responsible for:

- Supervising the implementation of this procedure. The Investigator may delegate the responsibility for writing the clinical protocol and its associated documents to a designated qualified individual.
- Preparing the initial draft of the protocol, in conjunction with participating Investigator(s), biostatisticians, information technology/database experts and others as appropriate.
- Consulting with the Office of Human Research (OHR) in ascertaining which internal and external regulatory authorities must be included in the overall protocol approval process.
- Forwarding final, internally approved protocols to the FDA (alone or as part of another document) and other applicable external regulatory authorities for their review and approval as required.
- Obtaining all internal and external regulatory authority approvals before enrolling the first subject.
- Ensuring that all participating Investigators comply with the approved clinical protocol and that no deviations from the procedures listed occur.

### 3 SPECIFIC PROCEDURES

#### 3.1 Writing the Clinical Protocol

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a) General Instructions:

- In general, the FDA permits protocols for Phase 1 studies to be less detailed and more flexible than protocols for phase 2 and 3 studies.
  - Phase 1 protocols should provide an outline of the investigation and the FDA suggests those protocols specify in detail only those elements that are critical to safety (Reference 21 CFR 312.23 (a)(6)(i)).
  - For Phase 2 and 3 protocols, the FDA requires detailed protocols.
- b) The Investigator will determine who will write the clinical protocol, and who is required to review and approve the clinical protocol.
- c) Because the protocol is a controlled document, the Investigator will follow the general procedure in SOP 102, Document Development and Change Control to draft the protocol.
- d) The Investigator will develop a protocol that materially conforms to the protocol template (Attachment A).
- e) For investigational medical device protocols, the same format as above should be followed to the extent possible, except that some sections may not be applicable. For example, it may not be possible to perform blinding or randomization procedures for an investigational device study.

### 3.2 Review and Approval of the Clinical Protocol

- a) The Investigator should complete a Document Control Form (See SOP 102 Attachment A) identifying the draft with the protocol number and a draft version number and date.
- b) The Investigator will circulate the draft protocol to designated individuals and other experts (e.g. statistician, database developer) to ensure that the proposed clinical protocol is scientifically and ethically sound, and meets all applicable regulations and guidelines.
- c) The Investigator will repeat the review process until all comments are addressed.
- d) The final draft protocol will be reviewed and approved by all previously designated individuals by the Investigator and in accordance with departments and Memorial Healthcare System policies (Reference SOP 102).
- e) Once reviewed and approved internally, the Investigator will give the protocol a version number and approval date, and sign the final approved protocol signature page (Reference SOP 102).
- f) Further changes made to the protocol after approval of the original version (i.e. an Amendment or Addendum) requires sequential numbering from the original (Reference SOP 302, Clinical Protocol Amendments).
- g) The investigator will include the protocol version number and the effective date in the footer of the protocol.
- h) Certain protocols must be submitted to other external and/or internal regulatory authorities (e.g. the Institutional Biosafety Committee, Radiation Safety Committee, and Independent Feasibility Committee) for review before or concurrently with IRB/FDA submission.



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- i) Protocols for Investigational New Drug (IND) and Investigational Device Exemption (IDE) clinical studies may be submitted to FDA for formal review as part of those IND or IDE submissions, or the protocol may be sent informally for preliminary review (pre-IND or pre-IDE) prior to an IND or IDE submission (Reference SOP 201, Contacts and Submissions for FDA for specific procedures).
- j) When appropriate, the Investigator will distribute the final approved protocol to all prospective participating Investigators.
- k) The Investigator should contact the IRB for instructions on IRB submission preparation.
- l) The Investigator will submit the final protocol, informed consent form and any other required documents to the IRB of record and other applicable regulatory authorities.
- m) The Investigator must obtain a copy of the IRB approval letter and place it in the appropriate section of the Regulatory Master File (Reference SOP 503, Documentation and Records Retention).
- n) The Investigator will not implement the protocol until final IRB approval is obtained, the protocol has been submitted to the FDA and the Investigator has received the FDA's determination either assigning an IND or IDE, or granting an exemption from filing an IND (Reference SOP 201).
- o) If the FDA, the Office of Human Research Protection (OHRP), MHS OHR, the IRB, administration at MHS or any regulatory authority issues a clinical hold, the Investigator will not implement the protocol until all issues have been resolved and the clinical hold has been removed.
- p) Once an IND is in effect, additional new protocols added to the IND may proceed once the IRB approval has been obtained on the new protocol and the OHR has been notified.
- q) A new IRB-approved significant risk (SR) IDE must be submitted to the FDA. The Investigator must receive the FDA's IDE determination either assigning an IDE or granting an exemption from filing an IDE before proceeding.
- r) Subject enrollment may begin after all regulatory authorizations have been obtained and the OHR has been notified.
- s) The Investigator may make editorial or typographical changes to the protocol, as described in the section Minor Protocol Changes (Reference SOP 302), at the time of the next protocol amendment submission (usually Continuing Review, or earlier when deemed necessary).
- t) Changes such as expanding the age of eligibility to participate or capturing new data not previously specified in the protocol of changing other inclusion/exclusion criteria do not qualify as minor protocol changes, and are significant changes to the protocol that must be resubmitted to all appropriate internal and external regulatory authorities for approval (Reference SOP 302, Clinical Protocol Amendments).
- u) The Investigator will retain approved clinical protocols and their attachments, as well as subsequent revisions and any associated correspondence with regulatory authorities and other documents as described in SOP 503 – Documentation and Records Retention.
- v) The Investigator (or designee) will distribute the most recently approved protocol and related documents to all participating sites for submission to the local IRB for approval

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prior to use. If the study is occurring at multiple centers, a central IRB may be used to in an effort to reduce burden, shorten delays due to multiple reviews and maintain consistency across sites regarding changes to the protocol.

### 3.3 Protocol Violations and Waivers

- a) Any deviation from the protocol requires an IRB approved protocol waiver prior to implementation. The waiver will describe the nature of the deviation and a rationale for its implementation.
- b) A deviation to eliminate a hazard or otherwise protect the life or well-being of a subject may be implemented immediately, with IRB, and Sponsor (if applicable) notification of the deviation occurring within five (5) days after the event. For protocols under an IND/IDE, such deviations must be reported to the FDA in a protocol amendment submission within five (5) days of the event.
- c) A protocol for a phase 2 or 3 study (or pivotal device study) should be designed such that, if the Investigator anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives and contingencies to provide for such deviations are built into the original protocol at the outset.
- d) If changes to the protocol are determined to be necessary, then the changes should be managed in the form of a protocol amendment (Reference SOP 201 and SOP 302).
- e) The Investigator must notify the IRB in a timely manner if a protocol violation occurs and the justification for the violation.
- f) If the protocol waiver is approved by the IRB and the sponsor, the deviation from the approved protocol may be implemented on a one-time basis only, and it should be reported to the IRB as soon as possible.
- g) If the deviation is considered a necessary change to the protocol and/or likely to reoccur, the Investigator should immediately initiate an amendment to the protocol and an amendment (or supplement if for a medical device) to the IND/IDE (Reference SOP 302 and SOP 201).

## 4 REFERENCES TO OTHER APPLICABLE SOPS

- 102 Document Development and Change Control
- 201 Contacts and Submissions for FDA
- 202 Reporting Requirements for FDA
- 302 Clinical Protocol Amendments
- 303 Investigators Brochure
- 503 Documentation and Records Retention

## 5 ATTACHMENTS

- A. Protocol Template

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### **6 APPLICABLE REGULATIONS AND GUIDELINES**

- Requirements for an IND (21 CFR 312.20)
- Phases of an Investigation (21 CFR 312.21)
- IND Content and Format (21 CFR 312.23)
- Adequate and Well Controlled Studies (21 CFR 314.126)
- Investigational Plan (21 CFR 312.25)
- Determination of Safety and Effectiveness (21 CFR 314.60.7)
- The Principles of ICH GCP (ICH E6, Section 2.2, 2.4, 2.5, 2.6, and 2.11)
- Compliance with Protocol (ICH E6, section 4.5)
- Trial Design (ICH E6, Section 5.4)
- Clinical Trial Protocol and Protocol Amendment(s) (ICH E6, Section 6.0)
- General Considerations for Clinical Trials (ICH E8, December 1997)
- Statistical Principles for Clinical Trials (ICH E9, September 1998)
- Choice of Control Group and Related Issues in Clinical Trials (ICH E10, May 2001)