Investigator Manual

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Scope

Throughout this document "institution" refers to Tampa General Hospital (TGH). This Handbook includes institution-specific information for research conducted at TGH or Tampa General Medical Group (TGMG).

What is the purpose of this manual?

This document "INVESTIGATOR MANUAL (OCR 103)" is designed to guide you through policies and procedures related to the conduct of Human Research that are specific to this institution.

General information regarding human research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see below: "What training does my staff and I need in order to conduct Human Research?"

What is Human Research?

The "HUMAN RESEARCH PROTECTION PROGRAM PLAN (OCR 101)" defines the activities that this institution considers to be "Human Research." An algorithm for determining whether an activity is Human Research can be found in the "WORKSHEET: Human Research (OCR-710)," located on the Office of Clinical Research Web site. Use this document for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the reviewing IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

You are responsible not to conduct Human Research without prior IRB review and approval and a feasibility review by the TGH Office of Clinical Research (OCR). If you have questions about whether an activity is Human Research, provide a written request to an institutionally designated IRB who will provide you with a determination.

The following activities are not considered research:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, which focus directly on the specific individuals about whom the information is collected.
- Public health surveillance activities conducted by a public health authority, limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance.
    - Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
    - Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.

  - Including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by the relevant federal agency) in support of intelligence, homeland security, defense, or other national security missions.

What is the Human Research Protection Program?

The document "HUMAN RESEARCH PROTECTION PROGRAM PLAN (OCR 101)" describes this institution's overall plan to protect subjects in Human Research.

- The mission of the Human Research Protection Program.
- The ethical principles that the institution follows governing the conduct of Human Research.
- The applicable laws that govern Human Research.
- When the institution becomes "engaged in Human Research" and when someone is acting as an agent of the institution conducting Human Research.
- The types of Human Research that may not be conducted.
- The roles and responsibilities of individuals within the institution.

What training does my staff and I need to conduct Human Research?

This section describes the training requirements imposed by the Institution. You may have additional training imposed by other federal, state, or institutional policies.

Investigators and staff conducting research involving human subjects must complete the Collaborative Institutional Training Initiative (CITI) human subjects online training program.

The CITI site can be accessed at http://www.citiprogram.org/.

Training is valid for a three-year period, after which time the training must be repeated.

All members of the research team involved in the design, conduct, or reporting of the research must complete training. Members of the research team who have not completed human research protections training may not take part in aspects of the research that involve human subjects.

What financial interests do my staff and I need to disclose to conduct Human Research?

Individuals involved in the design, conduct, or reporting of research, research consultation, teaching, professional practice, institutional committee memberships, and service on panels such as Institutional Review Boards or Data and Safety Monitoring Boards are considered to have an institution responsibility.

All individuals involved in the design, conduct, or reporting of research are required to disclose the financial interests:

- On submission of an initial review.
- At least annually as part of continuing review.
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

Individuals with reimbursed or sponsored travel by an entity other than a federal, state, or local government agency, higher education institution or affiliated research institute, academic teaching hospital, or medical center are required to disclose the purpose of the trip, the identity of the sponsor or organizer, the destination, and the duration of the travel.

Individuals subject to this policy are required to complete financial conflicts of interest training initially, at least every three years, and immediately when:

- Joining the institution
- Financial conflicts of interest policies are revised in a manner that changes investigator requirements
- Non-compliant with financial conflicts of interest policies and procedures

Additional details can be found in "SOP: Investigator Financial Conflicts of Interests (OCR-055)."

How do I submit new Human Research to the OCR and the USF IRB?

All studies that will be conducted at TGH or TGMG must be reviewed by the TGH OCR. Investigators and study staff are expected to complete the TGH OCR Research Study Proposal Form and provide any other applicable documents to the TGH OCR either before or in conjunction with IRB submission for a feasibility review. Before submitting the research to an IRB for initial review, you must:

- Obtain the financial interest status ("yes" or "no") of each research staff.
- Obtain the agreement of research staff to his/her role in the research.

For protocols that will be submitted to the USF IRB, complete the New Study SmartForm in the electronic IRB system and attach all requested supplements, have the SmartForm submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

How do I request to rely on an external IRB (other than USF IRB)?

For protocols to be submitted to other external IRBs, indicate this on the OCR Research Study Proposal Form, and follow the instructions provided by the institutionally designated IRB for the submission of new protocols. TGH recommends the use of external commercial IRBs for industry-sponsored research. Maintain electronic copies of all information submitted to the OCR and to the reviewing IRB in case revisions are required.

How do I write an Investigator Protocol?

Use the "TEMPLATE PROTOCOL (OCR-503)" as a starting point for drafting a new Investigator Protocol, and reference the instructions in italic text for the information the reviewing IRB looks for when reviewing research. Here are some key points to remember when developing an Investigator Protocol:

- The italicized bullet points in the "TEMPLATE PROTOCOL (OCR-503)" serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB. All italicized comments are meant to be deleted prior to submission.
- For any items described in the sponsor's protocol or other documents submitted with the application, investigators may simply reference the page numbers of these documents within the Investigator Protocol rather than repeat information.
- When writing an Investigator Protocol, always keep an electronic copy. You will need to modify this copy when making changes to the Investigator Protocol.
- If you believe your activity may not be Human Research, contact an institutionally designated IRB prior to developing your Investigator Protocol.
- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your Investigator Protocol. Indicate this as appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria as the inclusion of subjects in these populations has regulatory implications.
    - Adults unable to provide legally effective consent
    - Individuals who are not yet adults (infants, children, teenagers)
    - Pregnant women
    - Prisoners
- If you are conducting community-based participatory research, you may contact an institutionally designated IRB for information about:
    - Research studies using a community-based participatory research design
    - Use of community advisory boards
    - Use of participant advocates
    - Partnerships with community-based institutions or organizations

How do I create a consent document?

Use the "TEMPLATE CONSENT DOCUMENT (OCR-502)" to create a consent document.

Note that all long form consent documents and all summaries for short form consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. Review the "Long Form of Consent Documentation" section in the "WORKSHEET:

Criteria for Approval (OCR-314)," to ensure that these elements are addressed. When using the short form of consent documentation the appropriate signature block from "TEMPLATE CONSENT DOCUMENT (OCR-502)" should be used on the short form.

We recommend that you date the revisions of your consent documents to ensure that you use the most recent version approved by the IRB.

What are the different regulatory classifications that research activities may fall under?

Submitted activities may fall under one of the following four regulatory classifications:

- Not "Human Research": Activities must meet the institutional definition of "Human Research" to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight or review. Review the "WORKSHEET: Human Research (OCR-310)" for reference. Contact an institutionally designated IRB Office in cases where it is unclear whether an activity is Human Research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of an institutionally designated IRB, not the investigator, to determine whether Human Research is exempt from IRB review. Review the "WORKSHEET: Exemption (OCR-312)" for reference on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the "WORKSHEET: Eligibility for Review Using the Expedited Procedure (OCR-313)" for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

What are the decisions an institutionally designated IRB can make when reviewing proposed research?

The IRB may approve research, require modifications to the research to secure approval, table research, or disapprove research:

- Approval: Made when all criteria for approval are met. See "How does the IRB decide whether to approve Human Research?" below.
- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized.
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.

- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications the might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

How does the IRB decide whether to approve Human Research?

The criteria for IRB approval can be found in the "WORKSHEET: Exemption (OCR-312)" for exempt Human Research and the "WORKSHEET: Criteria for Approval (OCR-314)" for non-exempt Human Research

You are encouraged to use these resources to write your Investigator Protocol in a way that addresses the criteria for approval.

What will happen after IRB review?

The reviewing IRB will provide you with a written decision indicating that the IRB has approved the Human Research, requires modifications to secure approval, or has disapproved the Human Research.

- If the IRB has approved the Human Research: The Human Research may commence once all other institutional approvals have been met, including the feasibility review by the OCR. IRB approval is usually good for a limited period of time which is noted in the approval letter.
- If the IRB requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response and submit it to the IRB.
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable, and give you an opportunity to respond in writing. In most cases if the IRB's reasons for the deferral are addressed in a modification, the Human Research can be approved
- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting.

What are my obligations after IRB approval?

1) Do not start Human Research activities until you have the final IRB approval letter.

2) Do not start Human Research activities until you have obtained all other required institutional approvals, including feasibility review by the OCR, approvals of departments or divisions that require approval prior to commencing research that involves their resources.
3) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
4) Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
5) Update the reviewing IRB with any changes to the list of study personnel.
6) Personally conduct or supervise the Human Research. Recognize that the investigator is accountable for the failures of any study team member.
    a) Conduct the Human Research in accordance with the relevant current protocol as approved by the reviewing IRB, and in accordance with applicable federal regulations and local laws.
    b) When required by the reviewing IRB ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB.
    c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
    d) Protect the rights, safety, and welfare of subjects involved in the research.
7) Submit to the reviewing IRB:
    a) Proposed modifications as described in this manual. (See “How do I submit a modification?”)
    b) A continuing review application as requested in the approval letter. (See “How do I submit continuing review?”
    c) A continuing review application when the Human Research is closed. (See “How Do I Close Out a Study?”)
8) For protocols overseen by the USF IRB, complete the Report New Information SmartForm within five business days for any of the following information items:
    a) Information that indicates a new or increased risk, or a new safety issue. For example:
        i) New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
        ii) An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
        iii) Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
        iv) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
        v) Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
        vi) Any changes significantly affecting the conduct of the research
    b) Harm experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.

i) A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
ii) A harm is "probably related" to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.

c) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
d) Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g. FDA Form 483.)
e) Written reports of study monitors that includes a finding of another issue on this list.
f) Failure to follow the protocol due to the action or inaction of the investigator or research staff.
g) Breach of confidentiality.
h) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
i) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
j) Complaint of a subject that cannot be resolved by the research team.
k) Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
l) Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

9) For other external IRBs, report the information described above according to the reviewing IRBs instructions.
10) Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
11) Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
12) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
13) See additional requirements of various federal agencies in Appendix A. These represent additional requirements and do not override the baseline requirements of this section.
14) If the study is a clinical trial and supported by a Common Rule agency, one IRB-approved version of a consent form that has been used to enroll participants must be posted on a public federal website designated for posting such consent forms. The form must be posted after recruitment closes, and no later than 60 days after the last study visit. Please contact the study sponsor with any questions.

What are my obligations as the overall study PI for an sIRB study?

1) Coordinating with HRPP personnel to determine which institutionally designated external IRB will assume oversight.

2) Identifying all sites that will be engaged in the human research and requiring oversight by the IRB.
3) Ensure that all sites receive a request to rely on the reviewing IRB and that all institutional requirements are satisfied before a study is activated at a relying site.
4) Collaborate with the reviewing IRB to document roles and responsibilities for communicating and coordinating key information from study teams and the IRB or HRPP at relying sites.
5) Respond to questions or information requests from study teams or the IRB or HRPP staff at relying sites.
6) Provide relying site investigators with the policies of the reviewing IRB.
7) Provide relying site investigators with the IRB-approved versions of all study documents.
8) Preparation and submission of IRB applications on behalf of all sites. This includes initial review, modifications, personnel updates, reportable new information and continuing review information for all sites.
9) Establishing a process for obtaining and collating information from all sites and submitting this information to the reviewing IRB. This includes site-specific variations in study conduct, such as the local consent process and language, subject identification and recruitment processes and local variations in study conduct.
10) Ensuing that consent forms used by relying sites follow the consent template approved by the reviewing IRB and include required language as specified by the relying sites.
11) Providing site investigators with all determinations and communications from the reviewing IRB.
12) Submitting reportable new information from relying sites to the reviewing IRB in accordance with the terms outlined in the authorization agreement or communication plan.
13) Reporting the absence of continuing review information from relying sites if they do not provide the required information prior to submission of the continuing review materials to the reviewing IRB. Notifying the relying site of their lapse in approval and applicable corrective actions.
14) Providing study records to the relying institution, reviewing IRB or regulatory agencies upon request.

What are my obligations as investigator when relying on an external IRB?

1) Obtain appropriate approvals from this institution's OCR prior to seeking review by an external IRB.
2) Comply with determinations and requirements of the reviewing IRB.
3) Provide the reviewing IRB with requested information about local requirements or local research context issues relevant to the IRB's determination prior to IRB review.
4) Notifying the reviewing IRB when local policies that impact IRB review are updated.
5) Cooperating in the reviewing IRB's responsibility for initial and continuing review, record keeping and reporting and providing all information requested by the reviewing IRB in a timely manner.
6) Disclosing conflicts of interest as required by the reviewing IRB and complying with management plans that may result.

7) Promptly reporting to the reviewing IRB any proposed changes to the research and not implementing those changes to the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants.
8) When enrolling participants, obtain, document and maintain records of consent for each participant or each participant's legally authorized representative.
9) Promptly reporting to the reviewing IRB any unanticipated problems involving risks to participants or others according to the requirements specified in the reliance agreement.
10) Providing the reviewing IRB with data safety monitoring reports in accordance with the reviewing IRB's reporting policy.
11) Reporting non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the reliance agreement.
12) Specifying the contact person and providing contact information for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the use of the reviewing IRB.

How do I document consent?

Use the signature block approved by the reviewing IRB. Complete all items in the signature block, including dates and applicable checklists.

The following are the requirements for long form consent documents:

- The subject or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the consent document.
- Whenever the reviewing IRB or the sponsor require a witness to the oral presentation, the witness signs and dates the consent document.
- For subjects who cannot read and whenever required by the IRB or the sponsor, a witness to the oral presentation signs and dates the consent document.
- A copy of the signed and dated consent document is to be provided to the subject.

The following are the requirements for short form consent documents:

- The subject or representative signs and dates the short form consent document.
- The individual obtaining consent signs and dates the summary.
- The witness to the oral presentation signs and dates the short form consent document and the summary.
- Copies of the signed and dated consent document and summary are provided to the person(s) signing those documents.

How do I submit a modification?

For protocols overseen by the USF IRB, complete the Modification SmartForm in the electronic IRB system and attach all requested supplements, have the SmartForm submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received. Updates to the list of study personnel will be acknowledged unless the update represents a modification to the research.

For other external IRBs, submit the information relevant to the modification according to the instructions of the reviewing IRB.

How do I submit continuing review?

For protocols overseen by the USF IRB, complete the Continuing Review SmartForm in the electronic IRB system and attach all requested supplements, and have the SmartForm submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Before submitting the research for initial review, you must:

- Determine whether any member of the research staff has a financial interest related to the research. A "yes" or "no" answer is sufficient. There is no need to obtain additional details.

- Obtain the verbal or written agreement of each member of the research staff to his/her role in the research.

If the continuing review involves modifications to previously approved research, submit those modifications either as a combined Modification and Continuing Review or as a separate request for modification using the Modification SmartForm the electronic system.

For other external IRBs, submit the information relevant to the continuing review according to the instructions of the reviewing IRB.

If the continuing review application is not received by the date requested in the approval letter, you will be restricted from submitting new Human Research until the completed application has been received.

If the approval of Human Research expires all Human Research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing Human Research procedures is a violation of institutional policy. If current subjects will be harmed by stopping Human Research procedures that are available outside the Human Research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the reviewing IRB chair and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

How do I close out a study?

For protocols overseen by the USF IRB, complete the Continuing Review SmartForm in the electronic IRB system and attach all requested supplements, and have the SmartForm submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

For other external IRBs, submit the information relevant to the study closure according to the instructions of the reviewing IRB.

If you fail to submit a continuing review form to close out Human Research, you will be restricted from submitting new Human Research until the completed application has been received.

If the continuing review application for closing out a Human Research study is not received by the date requested in the approval letter, you will be restricted from submitting new Human Research until the completed application is received.

How long do I keep records?

Maintain your Human Research records, including signed and dated consent documents for at least three years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least six years after completion of the research.

If your Human Research is sponsored contact the sponsor before disposing of Human Research records.

What if I need to use an unapproved drug, biologic, or device and there is no time for IRB review?

Contact an institutionally designated IRB or IRB chair immediately to discuss the situation. If there is no time to make this contact, see the "WORKSHEET: Emergency Use (OCR-322)" for the regulatory criteria allowing such a use and make sure these are followed. Use the "TEMPLATE EMERGENCY USE CONSENT DOCUMENT (OCR-506)" to prepare your consent document. You will need to submit a report of the use to an institutionally designated IRB within five days of the use.

If you fail to submit the report within five days, you will be restricted from submitting new Human Research until the report and IRB application for initial review have been received.

Emergency use of an unapproved drug or biologic in a life-threatening situation without prior IRB review is "research" as defined by FDA, the individual getting the test article is a "subject" as defined by FDA, and therefore is governed by FDA regulations for IRB review and informed consent. Emergency use of an unapproved device without prior IRB review is not "research" as defined by FDA and the individual getting the test article is not a "subject" as defined by FDA. However, FDA guidance recommends following similar rules as for emergency use of an unapproved drug or biologic.

Individuals getting an unapproved drug, biologic, or device without prior IRB review cannot be considered a "subject" as defined by DHHS and their results cannot be included in prospective "research" as that term is defined by DHHS.

How do I get additional information and answers to questions?

This document and the policies and procedures for the Human Research Protection Program are available on the Office of Clinical Research Web site.

If you have any questions or concerns, about the Human Research Protection Program, contact the OCR at:

TGH Office of Clinical Research
409 Bayshore Blvd., 5th Floor
Tampa, FL 33606 (Get Directions)
Tel: (813) 844-CORE (2673)
research@tgh.org.

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program that cannot be addressed by contacting the OCR Office, follow the directions in the "HUMAN RESEARCH PROTECTION PROGRAM PLAN (OCR-101)" under "Reporting and Management of Concerns."

Appendix A-1 Additional Requirements for DHHS-Regulated Research

1. TGH applies the same policies and procedures regardless of whether research is covered by DHHS regulations or the Common Rule, except, for reporting of unanticipated problems, serious or continuing noncompliance, suspensions or terminations when such reporting is not required in regulation.
2. When a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent may continue. The investigator should explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.
3. Investigators are allowed to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject.
4. For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.
5. When seeking the informed consent of subjects, investigators should explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.

Appendix A-2 Additional Requirements for FDA-Regulated Research

1. When a subject withdraws from a study:[1]
    a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
    b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
    c. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
    d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
    e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.
2. For FDA-regulated research involving investigational drugs:
    a. Investigators may not begin the research until a valid IND is in effect. This includes recruiting, obtaining consent, and screening subjects for a specific study that is subject to the IND. The IND must be validated according to the Worksheet on Drugs and Biologics and approved by the IRB of record.
    b. Investigators must abide by FDA restrictions on promotion of investigational drugs:[2]
        i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
        ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for

[1] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf
[2] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7

which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

iii. An investigator must not commercially distribute or test market an investigational new drug.

c. Follow FDA requirements for general responsibilities of investigators[3]
   i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.
   ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
   iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.
d. Follow FDA requirements for control of the investigational drug[4]
   i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
   ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
e. Follow FDA requirements for investigator recordkeeping and record retention[5]
   i. Disposition of drug:
      1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
      2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
   ii. Case histories.
      1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
      2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes.

[3] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60
[4] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61
[5] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62

The case history for each individual must document that informed consent was obtained prior to participation in the study.

iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

f. Follow FDA requirements for investigator reports[6]
   i. Progress reports: The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
   ii. Safety reports: An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
   iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
   iv. Financial disclosure reports:
      1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
      2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

g. Follow FDA requirements for assurance of IRB review[7]
   i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR §56 will be responsible for the initial and continuing review and approval of the proposed clinical study.
   ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

h. Follow FDA requirements for inspection of investigator's records and reports[8]
   i. An investigator must upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62.

[6] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64
[7] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66
[8] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68

ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

i. Follow FDA requirements for handling of controlled substances[9]
   i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

3. For FDA-regulated research involving investigational devices:
   a. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.
   b. General responsibilities of investigators.[10]
      i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.
   c. Specific responsibilities of investigators[11]
      i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
      ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
      iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
      iv. Financial disclosure:
         1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.

[9] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69
[10] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100
[11] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110

2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

d. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:[12]

i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

ii. Records of receipt, use or disposition of a device that relate to:

1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
2. The names of all persons who received, used, or disposed of each device.
3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records must include:

1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
2. Documentation that informed consent was obtained prior to participation in the study.
3. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

[12] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140

v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

e. Inspections[13]
   i. Entry and inspection: A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
   ii. Records inspection: A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.
   iii. Records identifying subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

f. Prepare and submit the following complete, accurate, and timely reports[14]
   i. Unanticipated adverse device effects. An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
   ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
   iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
   iv. Deviations from the investigational plan:
      1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
      2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
      3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the

[13] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145
[14] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150

plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Appendix A-3 Additional Requirements for Clinical Trials (ICH-GCP)

1. Investigator's Qualifications and Agreements
    a. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.
    b. The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.
    c. The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
    d. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
    e. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
    f. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
2. Adequate Resources
    a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
    b. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
    c. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
    d. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
3. Medical Care of Trial Subjects
    a. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
    b. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

c. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
d. Although a subject is not obliged to give his/her reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.

4. Communication with IRB
    a. Before initiating a trial, the investigator/institution should have written and dated approval opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
    b. As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.
    c. During the trial the investigator/institution should provide to the IRB all documents subject to review.
5. Compliance with Protocol
    a. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
    b. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazards to trial subjects, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).
    c. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
    d. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial subjects without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendments should be submitted: a) to the IRB for review and approval opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authorities.
6. Investigational Product
    a. Responsibility for investigational product accountability at the trial site rests with the investigator/institution.
    b. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
e. The investigator should ensure that the investigational product is used only in accordance with the approved protocol.
f. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
g. Randomization Procedures and Unblinding: The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.

7. Informed Consent of Trial Subjects
   a. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to subjects.
   b. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.
   c. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
   d. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to

waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

e. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
f. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
g. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
h. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
i. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
j. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
    i. That the trial involves research.
    ii. The purpose of the trial.
    iii. The trial treatments and the probability for random assignment to each treatment.
    iv. The trial procedures to be followed, including all invasive procedures.
    v. The subject's responsibilities.
    vi. Those aspects of the trial that are experimental.
    vii. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

viii. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
ix. The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.
x. The compensation and/or treatment available to the subject in the event of trial related injury.
xi. The anticipated prorated payment, if any, to the subject for participating in the trial.
xii. The anticipated expenses, if any, to the subject for participating in the trial.
xiii. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
xiv. That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
xv. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
xvi. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
xvii. The persons to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
xix. The expected duration of the subject's participation in the trial.
xx. The approximate number of subjects involved in the trial.

k. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
l. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's

understanding and, if capable, the subject should sign and personally date the written informed consent.

m. Except as described above, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

n. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval opinion of the IRB is expressly sought on the inclusion of such subjects, and the written approval opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

o. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

8. Records and Reports

a. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

b. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

c. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

d. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the

applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

e. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
f. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

9. Progress Reports
    a. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
    b. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
10. Safety Reporting
    a. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.
    b. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
    c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
    d. Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:
        i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where

applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.

ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.

iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

11. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

Appendix A-4 Additional Requirements for Department of Defense (DOD) research

1. TGH does not conduct research involving chemical or biological agents, including research for prophylactic, protective, or other peaceful purposes involving chemical or biological agents.
2. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
3. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
4. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
5. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
6. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
7. There may be specific educational requirements or certification required.
8. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
9. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
    a. Prohibit an individual from receiving pay of compensation for research during duty hours.
    b. An individual may be compensated for research if the participant is involved in the research when not on duty.
    c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
    d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
10. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
11. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (OCR-318)."

Appendix A-5 Single IRB Studies

1. That National Institutes of Health expects that all sites participating in multi-site studies involving non-exempt human subjects research funded by the NIH will use a single Institutional Review Board (sIRB) to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46.
    a. This policy applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program. It does not apply to career development, research training or fellowship awards.
    b. This policy applies to domestic awardees and participating domestic sites. Foreign sites participating in NIH-funded, multi-site studies will not be expected to follow this policy.
    c. Exceptions to the NIH policy will be made where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy. Requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception. The NIH will determine whether to grant an exception following an assessment of the need.
2. [Reserved.]

Appendix A-6 Additional Requirements for Research Subject to EU General Data Protection Regulations (GDPR)

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.
2. For all prospective Human Research subject to EU GDPR, contact institutional legal counsel or your institution's Data Protection Officer to ensure that the following elements of the research are consistent with institutional policies and interpretations of EU GDPR:
    a. Any applicable study design elements related to data security measures.
    b. Any applicable procedures related to the rights to access, rectification, and erasure of data.
    c. Procedures related to broad/unspecified future use consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
3. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research remain consistent with Appendices A-1 and A-2 above.