Submission Guide and Policies

Version 1

Pearl IRB
Investigator Manual

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1.1 Pearl IRB overview

Pearl IRB's goal is to provide you with the most efficient, quality review possible. The IRB is committed to maintaining a current IRB Roster of qualified individuals for a quality review. To ensure that your project is not delayed, we have adjunct members that go through the same rigorous training and meet the qualifications of a Pearl IRB core member. These adjunct members may be called upon to ensure a majority and a quorum for your review. At times, we will need additional expertise to ensure a quality review of your proposed research. Pearl maintains a team of consultants to advise the Board in specific areas of expertise. These advisors will not vote on the protocol, but solely provide consultation to the Board.

Types of Reviews Conducted

Pearl IRB conducts the following types of reviews:

- New submission
  - Full Board Review
  - Expedited Review
  - Informed Consent review
  - Waiver of Consent
  - Exemption determinations
  - General/Generic Recruitment (or Advertising) Material

- Approved Study Reviews (associated with previously approved submissions)
  - Continuing Review
  - Amendments
  - Close-Out

One of the keys to success is clear communication and transparency. If at any time you need additional information or clarification, don't hesitate to contact us directly at 317.899.9341 or info@pearlirb.com. Regular business hours for Pearl IRB are 8:00am – 5:00pm EST Monday through Friday (excluding holidays). However, we know this business may necessitate the exchange of information at any time, day or night. If you require consultation with Pearl IRB during off-hours, call the IRB Coordinator at 317.899.9341.

1.2 What is the purpose of this manual?

Throughout this document "organization" refers to Pearl IRB. This INVESTIGATOR MANUAL is designed to guide you through policies and procedures related to the conduct of Human Research Protection that are specific to this organization.

1.3 What is Human Research?

"Human Research" is defined in the Department of Health and Human Services (DHHS) regulations at 45 CFR §46.102(d) and 45 CFR §46.102(f) for OHRP (Office of Human Research Protection) and in FDA regulations at 21 CFR §56.102(c), 21 CFR §56.102(e), and 21 CFR §812.3(p). An algorithm for determining whether an activity is Human Research can be found on HHS.Gov (http://www.hhs.gov/ohrp/policy/checklists/index.html). The "HUMAN RESEARCH PROTECTION PROGRAM PLAN" (HRPP plan) defines the activities that this organization considers to be "Human Research" as defined by these regulations.

Human Research as defined by DHHS (for OHRP):
A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through Intervention or Interaction with the individual, or (2) information that is both Private Information and Identifiable Information. For the purpose of this definition:

- **Intervention** means physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- **Interaction** means communication or interpersonal contact between investigator and subject.
- **Private Information** means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- **Identifiable Information** means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

Human Research as defined by FDA:

- An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. A human subject includes an individual on whose specimen (identified or unidentified) a medical device is used.

Use this for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

As an investigator you assume responsibility for not conducting human research (or an IRB determination that the Human Research is Exempt) without prior IRB approval. If you have questions about whether an activity is Human Research, contact the IRB Office who will assist you with the determination. If you wish to have a written determination, provide a written request to the IRB Office.

1.4 What is the Human Research Protection Program?

The Human Research Protection Program (HRPP) Plan document describes this organization's overall plan to protect individuals participating in Human Research including;

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

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

Please note that all members of the research team involved in the design, conduct, or reporting of the research are required to complete appropriate training. IRB approval will not be granted for proposed research in which the investigators and their staff are not qualified.

1.6 How do I submit new Human Research to the IRB?

Prior to submitting documents for IRB review, it is important that all the information required for your submission is complete and ready for review. All forms must be answered completely. Should a question not apply to your submission, please use the answer "N/A". Incomplete forms or missing requested documentation (for example CVs) will constitute an incomplete submission and result in a possible delay in review. Our submission specific requirements are as follows:

New Submissions:

1. Sponsor Agreement
2. Sponsor Submission Form
3. Principal Investigator Agreement
4. Investigator/Site Submission Form

Continuing Review:

- Amendments (Minor or Major)
- Unanticipated Problem/Reportable New Information (form)
- Continuing Review Form
  - Most recent signed ICF (with subject information redacted) *if applicable
  - Review of Investigator/Site Form for changes/updates (confirmation of existing data on form or updated form with changes)
    - If any updates (CV, license renewal, FDA inspection, etc.) supply appropriate documentation.
    - Changes in primary researchers may require revision of additional forms.

General/Generic Recruitment (Advertisement) Material:

- Sponsor Agreement
- Sponsor Submission Form
- Principal Investigator Agreement (for this type of submission, the sponsor's Medical Director is frequently considered the P.I.)
- Investigator/Site Submission Form

Close-Out:

- Close-Out Form

To facilitate this process, forms are available on the Pearl IRB website at www.pearlirb.com/resources/forms. Should you have difficulty completing these forms, we will be happy to help. Contact the IRB coordinator at info@pearlirb.com or 317.899.9341. Pearl IRB utilizes a secure server for submission of completed materials. You will find instructions on how to upload your documents onto the EGNYTE portal on the Pearl IRB website at www.pearlirb.com/resources/forms.

Pearl IRB holds full board meetings on a weekly basis. Completed materials must be submitted by end-of-business on the Monday (5pm EST) of each week to be considered for review the Wednesday of the following week at 5pm EST. Incomplete documents will result in a delayed submission and, therefore, a delayed review. If you think your submission may be delayed, contact Pearl IRB (info@pearlirb.com or 317.899.9341) to discuss options that may allow you to still meet your timeline. The Board will review your documents prior to the scheduled weekly meeting. Please be prepared should you or your PI be asked to attend the meeting. Advance notice will be given should your attendance be requested. By the end-of-business day of the day after the full board review (Thursday of each week), information on the determination of the submission will be sent to you via email. A final letter of determination will be sent on Pearl IRB letterhead the following day.

IRB PROCESS OVERVIEW

Day 1 (Monday)	Completed Documents received by Pearl IRB (by 5pm EST)
Day 7 (Tuesday)	Board members complete review
Day 8 (Wednesday)	Full Board Meeting 4 pm EST
Day 9 (Thursday)	Communication of IRB determination sent to you

1.7 How do I write an Investigator Protocol?

Guidance may be found at the International Conference on Harmonisation (ICH) website (http://ichgcp.net/6-clinical-trial-protocol-and-protocol-amendments). Additionally, specific requirements for investigational design are set forth at [21 CFR 312.23] (drugs) and [21 CFR 812.25] (devices).

You may request a Protocol Template from Pearl IRB as a starting point for drafting a new Investigator Protocol. Here are some key points to remember when developing an Investigator Protocol:

- 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 the IRB Office 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 if appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research.
    - Adults unable to consent
    - Neonates
    - Pregnant women
    - Prisoners

1.8 How do I create a consent document?

You may request an Informed Consent Template from Pearl IRB to create a consent document.
Note that all consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. Below is a brief listing of the basic items to be included in the informed consent form (ICF). Also see "How do I document consent?" below.

Table 1: ICF Elements

Element
A statement that the study involves research.
The name(s) of the funding agency(ies).
An explanation of the purposes of the research in language that is understandable to an individual of about 10-12 years of age.
The expected duration of the subject's participation.
A description of the procedures to be followed and what the subjects will be required to do in the study.
Identification of any procedures which are experimental.
A description of any reasonably foreseeable risks or discomforts to the subject. Risks are not limited to physical injury, but also include psychological, social, financial, legal, and others.
A description of any benefits to the subject or to others that may reasonably be expected from the research; there may be none other than a sense of helping the public at large when balanced by the appropriate level of risk.
A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. In most studies the alternative will be to not participate in the study.

Element
A statement describing the extent to which confidentiality of records identifying the subject will be maintained. For most studies the subject should be informed that private, identifiable information will be kept confidential and will only be used for research and statistical purposes. If, due to sample size or some unique feature, the identity of the individual cannot be maintained, the subjects need to be explicitly notified. If the investigator intends to disclose any information, the subject needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The subject must be informed of any potential risks which may result from this disclosure and must explicitly provide prior written consent.
For research involving more than minimal risk*, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
An explanation of whom to contact for answers to questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject. This should include name and telephone number or other appropriate methods.
A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
Informed consents documents and processes must include the following statement which will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: *"A description of this clinical trial will be available onhttp://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."*
* Minimal risk is defined in section 46.102(i) as "... the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

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

1.9 What are the 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 DHHS or FDA definition of "research" involving "human subjects" for the activity to fall under IRB oversight. Activities that meet neither definition of "Research involving "Human Subjects" are not subject to IRB oversight or review. Contact the IRB Office in cases where it is unclear whether an activity meets the regulatory definition of Human Research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require an IRB determination of exemption. It is customary for the IRB, or a third party, not the investigator, to determine whether Human Research is exempt from IRB review. An algorithm for determining whether an activity is exempt can be found on HHS.Gov (http://www.hhs.gov/ohrp/policy/checklists/index.html).
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure. An algorithm for determining whether an activity qualifies for review using the expedited procedure can be found on HHS.Gov (http://www.hhs.gov/ohrp/policy/checklists/index.html). Ultimately Pearl IRB will make the decision as to whether or not the study qualifies for expedited review.
- 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.

1.10 What are the decisions the 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: The IRB approves research when it determines that the regulatory and IRB SOP requirements are met. The IRB is approving the research to begin or continue as written per the current Protocol Version Date. IRB approval is usually good for a limited period of time which is noted in the approval letter.
    - *Further action required: None. Congratulations! Get started.*
- Approve pending modification(s): The IRB approves research with the designation "approved pending modifications" when it determines that the regulatory and IRB SOP requirements for approval are met, but the IRB requires minor, directed modifications. Substantive changes or requirements, requests for more information for IRB consideration, and other issues related to the criteria for approval require review and approval by the convened IRB. Minor or prescriptive changes or requirements may be reviewed for approval by the IRB.
    - *Further action required: Submit modifications for approval (frequently these can be completed by expedited review). Please contact Pearl IRB about the required modifications if you are uncertain about hot to complete.*
- Approve with query(ies): The IRB approves research with a "query" or "queries" when it determines that the regulatory and IRB SOP requirements for approval are met, no modifications are required, and the IRB requests information that does not impact participant safety. The regulatory and IRB criteria for approval are met without the requested information. The IRB is approving the research to begin or continue as written per the current Protocol Version Date.
    - *Further action required: You don't have to reply, but if you choose to, the response will be reviewed by the expedited process.*
- 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 the 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.
    - *Further action required: 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.*
- Disapproval: The IRB disapproves research when it determines that the regulatory and IRB SOP requirements for approval are not met.
    - *Further action required: When the IRB **disapproves** a new study it is rejecting the research as submitted. If you wish to revise the study, it must be resubmitted as a new study. When the IRB votes to disapprove a change in research, the change cannot be implemented but the research may continue as previously approved by the IRB*. **When Pearl IRB disapproves a study or study amendment, you can count on a phone call or email requesting further discussion and explanation!**
- Suspend Accrual: The IRB suspends accrual when it determines that continuing accrual, or enrollment of new subjects, could threaten the safety or well-being of potential study participants.
    - *Further action required: A conference call with the client is required to obtain any additional information prior to the IRB's determination to suspend accrual. If a conference call cannot be scheduled during the IRB meeting, the IRB Co-chair may conference with you prior to the IRB meeting. Remember - The vote to suspend accrual will not be taken*

until you are notified. Accrual remains suspended until the IRB votes to lift suspension of accrual. The IRB informs the local IRBs, if applicable and the client of the suspension of accrual.

- Suspend Study Intervention: The IRB suspends study intervention when it determines that continuing the intervention could threaten the safety or well-being of study participants.
    - *Further action required: A conference call with the client is required to obtain any additional information prior to the IRB's determination to suspend study intervention. If a conference call cannot be scheduled during the IRB meeting, the IRB Co-chair may conference with you prior to the IRB meeting. Remember - The vote to suspend study intervention will not be taken until the conference call has occurred. The study intervention remains suspended until the IRB votes to lift suspension of study intervention. The IRB informs the local IRBs, if applicable, of the suspension of the study intervention.*
- Suspend Approval of Research: The IRB suspends approval of research when it determines that continuing research activities could threaten the safety or well-being of study participants.
    - *Further action required: A conference call with the client, is required to obtain any additional information prior to the IRB's determination to suspend approval of research. If a conference call cannot be scheduled during the IRB meeting, the IRB Co-chair may conference with you prior to the IRB meeting. Remember - The vote to suspend approval of research will not be taken until the conference call has occurred. The study remains suspended until the IRB votes to lift suspension of approval of research. The IRB notifies the Office for Human Research Protections (OHRP) and when applicable, FDA, of the suspension of IRB approval. The IRB informs the local IRBs, if applicable, for which they are the IRB of record of the suspension of the approval of research*
- Terminate Approval of Research: The IRB terminates approval of research when it determines that the research irreparably and adversely affects the safety or well-being of study participants.
    - *Further action required: A conference call with the client is required to obtain any additional information prior to the IRB's determination to terminate approval. If a conference call cannot be scheduled during the IRB meeting, the IRB Co-chair may conference with you prior to the IRB meeting. Remember - Before the IRB terminates approval of research, the IRB considers enrolled participants. Where the termination could harm subjects further, the IRB will consider alternative actions. The vote to terminate will not be taken until the conference call has occurred. The IRB notifies OHRP and when applicable, FDA, of the termination of IRB approval. The IRB informs the local IRBs, if applicable, for which they are the IRB of record of the termination of the approval of research.*
- Lift Suspension: The IRB lifts any type of suspension when it determines that the safety or well-being of study participants is no longer threatened.
    - *Further action to obtain a lift of suspension: You may request a suspension be lifted. The request must include a corrective action plan. The request and corrective action plan are reviewed by the convened IRB. The IRB may request modifications to the submitted corrective action plan if the IRB determines that additional modifications are necessary before the suspension may be lifted. The IRB may choose to require documentation of implementation of the corrective action plan prior to lifting its suspension. The IRB votes whether or not to lift its suspension. Pearl IRB notifies the client, and any local IRB, if applicable when suspension has been lifted. When lifting suspension of approval, the IRB will consider notifying OHRP and FDA.*

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting. Please contact Pearl IRB at info@pearlirb.com or 317-899-9341 to discuss your specific concerns and as necessary have your concern addressed at an IRB meeting.

1.11 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 the stamped approved protocol and ICF.
3) Do not start Human Research activities until you have the approval of departments or divisions that require approval prior to commencing research that involves their resources.
4) 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.
5) Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study.
6) Personally conduct or supervise the Human Research.
   a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB.
   b) When required by the 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 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) Report any of the information items on page one (1) of the "Unanticipated Problem/Reportable New Information" form to the IRB within five business days.
9) Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
10) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
11) See additional requirements of various federal agencies in Appendix A.

1.12 How do I document consent?

Use the ICF approved by the IRB. Also see section 1.9.

The following are additional 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 required by the IRB the subject's or representative's signature is to be witnessed by an individual who 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 additional requirements for short form consent documents:

- The subject or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the summary.
- The witness to the oral presentation signs and dates the consent document and the summary.
- Copies of the signed and dated consent document and summary are provided to the subject or representative.

A researcher must make adequate provisions to solicit assent from minors. DHHS regulations regarding assent may be found in 45 CFR 46.408 and FDA regulations may be found in 21 CFR 50, Subpart D.

1.13 How do I report unanticipated problems?

Unfortunately during the course of research, unanticipated problems arise. When an incident occurs that potentially places subjects or others at greater risk of physical or psychological harm than was previously recognized and warrant consideration of substantive changes in the protocol or informed consent process/document of other action in order to protect the safety, welfare or rights of the subjects, Pearl IRB must be notified within 5 (five) working days. If you are not sure that the problem you have identified meets these criteria, let us know anyway. Pearl IRB will assist you in making the determination. Please understand that serious unexpected adverse events are considered an unanticipated problem. It is imperative that the proper corrective actions take place in order to protect the safety, welfare, or rights of subjects or others connected to the study. To submit an unanticipated problem, complete the "Unanticipated Problem/Reportable New Information" (found at http://www.pearlirb.com/resources/forms).

1.14 How do I submit a modification (i.e., minor or major amendment)?

Modification to an approved study is called an "amendment." Submit the amendment as a "redlined' version of the original Pearl IRB approved document, attach all necessary documents/ forms and if applicable have the documents signed appropriately The IRB will review the submission and determine if it is a MINOR amendment or MAJOR amendment based on requested modifications. Please 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.

1.15 How do I submit continuing review?

The IRB will let you know how often they would like to see an update or continuing review of your study. An update will be required on at least an annual basis Pearl IRB will send you a timeline for the submission of materials back to Pearl IRB for review. It is important that you keep the IRB current on any protocol changes, deviations, or unanticipated problems. Even if you have stopped the research; we need to know.

To submit a continuing review, complete the "Continuing Review Form" (found at http://www.pearlirb.com/resources/forms), attach all requested documents, have the forms signed by the individuals listed in the form, and provide the documents to the IRB Office. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

If the continuing review involves modifications to previously approved research, submit those modifications as a separate amendment request.

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 and analysis of private identifiable information. Continuing Human Research procedures is a violation of federal regulations. 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 IRB chair (at the number listed below) and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

IRB Coordinator
Pearl IRB
29 East McCarty Street, Suite 100
Indianapolis, IN 46225
Email: info@pearlirb.com
317.899.9341

1.16 How do I close out a study?

Congratulations! You've reached a milestone in completing your study. Contact Pearl IRB to ensure the closure of the study is properly documented. It is important that the IRB document your study as completed.

Complete the "Study Close Out Form" (found at http://www.pearlirb.com/resources/forms), attach all requested documents, have the form signed by the individuals listed in the form, and submit to the IRB. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

If the 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.

In the event of premature completion of a study, report this to the IRB.

1.17 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.

1.18 What if I need to use an unapproved drug or device in a life-threatening situation and there is no time for prior IRB review?

Contact the IRB Office or IRB chair immediately to discuss the situation. If there is no time to make this contact, see the HHS website (http://www.hhs.gov/ohrp/policy/hsdc97-01.html) and the FDA website (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm) for the regulatory criteria allowing such a use and make sure these are followed. You will need to submit a report of the use to an IRB within five days of the use and an IRB application for initial review within 30 days.

If you fail to submit the report within five (5) days or the IRB application for initial review within 30 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 in a life-threatening situation 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 or device in a life-threatening situation 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.

1.19 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 IRB Web Site at http://www.pearlirb.com/.

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

IRB Coordinator
Pearl IRB
29 East McCarty Street, Suite 100
Indianapolis, IN 46225
Email: info@pearlirb.com
317.899.9341

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program, contact the IRB Office.

APPENDIX A ***Additional Requirements for DHHS (also called OHRP)-Regulated Research***[1]

1. 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.
2. 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.
3. 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.
4. 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.

[1] http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html

APPENDIX B ***Additional Requirements for FDA-Regulated Research***

1. When a subject withdraws from a study:[2]
    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 must abide by FDA restrictions on promotion of investigational drugs:[3]
        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 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.
    b. Follow FDA requirements for general responsibilities of investigators[4]
        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.

[2] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf
[3] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7
[4] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60

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.

c. Follow FDA requirements for control of the investigational drug[5]
   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.

d. Follow FDA requirements for investigator recordkeeping and record retention[6]
   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. 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.

e. Follow FDA requirements for investigator reports[7]
   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:

[5] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61
[6] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62
[7] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64

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.

f. Follow FDA requirements for assurance of IRB review[8]
   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.

g. Follow FDA requirements for inspection of investigator's records and reports[9]
   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.
   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.

h. Follow FDA requirements for handling of controlled substances[10]
   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. General responsibilities of investigators.[11]
      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.
   b. Specific responsibilities of investigators[12]
      i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the

[8] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66
[9] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68
[10] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69
[11] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100
[12] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110

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.
    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.

c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:[13]

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

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

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.
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.

d. Inspections[14]
   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.

e. Prepare and submit the following complete, accurate, and timely reports[15]
   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 plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

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

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 C ***Additional Requirements for Clinical Trials (Good Clinical Practices, GCP)***

1. Investigator's Qualifications and Agreements
    a. 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.
    b. 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.
    c. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
    d. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
    e. 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 in 4.8.14, 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, enrolment 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.