Human Research Protections Program
Research Investigator Handbook

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Version 2.0

Conducting research with human subjects is a privilege not a right.

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What is the purpose of this manual?

McLaren Health Care Corporation is committed to protecting the rights and welfare of subjects in human research. Whether the research is social, behavioral, or biomedical, human subjects research must be conducted responsibly and it must protect the rights, welfare and safety of human subjects. This Investigator Handbook is designed to guide investigators through policies and procedures related to the conduct of human research that are specific to McLaren Health Care.

General information regarding Human research protections and relevant federal regulations and guidance is incorporated into the required human subject protections training. For more information on training see: *"What training do my staff and I need to conduct Human Research?"*

This handbook is intended to be flexible and readily adaptable to changes in regulatory requirements. It highly recommended that you become familiar with the entire content of this handbook. The table of contents lists critical aspects of research conducted in an "asked question" format. This will allow you to hone in on those areas of specific concern.

McLaren Human Research Protections Program

Human Subjects Protections Program at McLaren Health Care (HRPP) is a centralized system that ensures the safe and ethical conduct of human participant research by all researchers and research teams of McLaren and its subsidiary hospitals. This program includes:

1. Review of proposed research by the McLaren Corporate *Institutional Review Board* (MHC IRB);
2. Continuing oversight for compliance with applicable regulations and policies by the *Office of Research Compliance and Quality Improvement;*
3. Education and training for investigators, staff, and committee members by the *Office of Education, Training and Resources* and
4. *Committee on Conflict of Interest*

The mission of the HRPP is to:

- To safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected
- To provide timely and high quality education, review and monitoring of human research projects; and
- To facilitate excellence in human subjects research.

AAHRPP Accreditation

In 2013 McLaren Health Care achieved full accreditation through the Association for the Accreditation of Human Research Protection. Their vision is to ensure that all human research participants are respected and are protected from unnecessary harm (www.aahrpp.org) through their worldwide network of accredited programs. We are proud to be part of this elite network.

Ethical and Regulatory Framework

Ethics

McLaren and its subsidiaries are committed to conducting research with the highest regard for the welfare of human subjects. It upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

1) **Respect for Persons**, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
2) **Beneficence**, which is guaranteed by ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
3) **Justice**, the equitable selection of subjects.

Regulations

The HRPP is responsible for ensuring compliance with federal regulations, state law, and institutional policies throughout McLaren Health Care and its subsidiaries. All human subjects research at MHC subsidiaries is conducted in accordance with the policies and regulations found in the **Common Rule and 21 CFR 50 and 56**. In addition, MHC and its subsidiaries follow the **International Conference on Harmonization/ Good Clinical Practice** (ICH-GCP) **that** are adopted by FDA.

- **Federal Policy for the Protection of Human Subjects (Common Rule)**
  In 1991, the U.S. Department of Health and Human Services codified into regulation the Policy for the Protection of Human Subjects (Title 45, Part 46). The HHS regulation, 45 CFR part 46, includes four subparts: subpart A, also known as the Federal Policy or the "Common Rule"; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children.

  The Code of Federal Regulations (Title 45 Part 46) can be found at:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

- **FDA Regulations on Protection of Human Subjects (21 CFR 50) and Institutional Review Boards (21 CFR 56)**

  The U.S. Food and Drug Administration (FDA), under the Department of Health and Human Services, regulates clinical research seeking approval for drugs, devices, and biologics. Title 21, Part 50 contains the federal definition of human subjects, federal requirements for informed consent, and the required safeguards for clinical investigations.

  Title 21, Part 56 contains specific regulations regarding the composition, organization, and functions of Institutional Review Boards.

  The FDA standardizes drugs, devices, and biologics through a series of regulations that must also be addressed by researchers and sponsors. They are: Biologics (21 CFR part 600), Investigational New Drugs (21 CFR Part 312), and Investigational Device Exemptions (21 CFR part 812).

  The Code of Federal Regulations Title 21; Part 50 (Protection of Human Subjects) can be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

  The Code of Federal Regulations Title 21; Part 56 (Institutional Review Boards) can be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56

  The U.S. Food and Drug Administration guidance for IRBs and Clinical Investigators can be viewed at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm#

- **Good Clinical Practice Guidelines**

  The International Conference on Harmonization, an organization formed by the US, Canada and Japan to simplify drug approvals between these countries, has written guidelines for drug studies that have been adopted into law in many countries, but are only used as guidance in the U.S.

  Good Clinical Practice (GCP) is the international ethical and scientific standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials. Compliance with GCP provides regulators assurance that data are presented as reported, results are credible and accurate, and the rights, safety, confidentiality, and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

  The Guidance for Good Clinical Practice (GCP) can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

Health Insurance Portability and Accountability Act (HIPAA)/(Privacy Rule)

The Health Insurance Portability and Accountability Act (HIPAA) is a federal privacy law that generally prohibits health care providers (such as physicians or other health care practitioners, hospitals, nursing facilities and clinics) from using or disclosing patients' "protected health information" (PHI) without written authorization.

When an investigator intends to obtain or release PHI* to others (e.g., sponsors, other investigators, collaborators) in connection with their research, he/she must indicate so in the IRB application. Research subjects must sign a *HIPAA authorization form for release of information specific to research*. The authorization form can be a stand-alone document or incorporated into the informed consent form.

Protected Health Information (PHI)* is health information *transmitted or maintained* in any form or medium that includes ALL of the three following conditions:

- identifies, or could be used to identify, an individual; and
- is created or received by a healthcare provider, health plan, or healthcare clearinghouse; and
- relates to the past, present, or future physical or mental health or condition of an individual; the provision of healthcare to an individual; or the past, present, or future payment for the provision of healthcare to an individual.

Classifications of Information

- Anonymous: Information obtained that is not and has never been traceable to the contributing individual.
- Coded: The information does not contain the identity of the contributing individual but has a specific code that links back to the individual's identity. There may be several unique codes between the information and the contributing individual's identity.
- De-identified: Information that at one point was identifiable, either directly or through a code, but has been stripped of all identifiers and codes. The information can no longer be traced back to the contributing individual.
- Identifiable: The information contains the identity of the contributing individual.

Information on the Privacy Rule can be found at:
http://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html
https://privacyruleandresearch.nih.gov/authorization.asp

Institutional Policies

MHC Standard Operating Policies and Procedures (SOPs) for human research protection detail guidelines to ensure that all individuals involved in research, conduct said research in a manner that protects the rights and welfare of research participants in compliance with all applicable federal, state, and local laws and regulations, as well as ethical standards in human research.

The SOPs also identify the requirements for submitting research proposals for review by MHC IRB. These are not a static documents. The policies and procedures are reviewed annually, and revised by the Corporate Director of the HRPP and the Institutional Official (IO), as necessary. HRRP policies can be found on our website: http://www.mclarenhealthplan.org/centralmichigan/Research-Policies1.aspx

Monitoring, Auditing and Quality Improvement

In order to monitor and ensure compliance, QA/QI routine reviews or for-cause audits will be conducted. These may be carried out by the Office of Research Compliance and Quality Improvement, or external auditors who have expertise in federal and state statutes and regulations.

1. **Routine QA/QI Reviews**
   QA/QI routine reviews are part of a McLaren Health Care (MHC) institution-wide research education initiative. They are designed to help investigators identify standards of excellence and potential areas for improvement. These routine reviews also provide a mechanism for the MHC Human Research Protection Program (HRPP) to provide internal oversight of the conduct of human research studies that are reviewed and approved by the MHC Institutional Review Board.

2. **Directed For-Cause Audits**
   Directed For-Cause Audits are initiated due to an identified concern or allegations of non-compliance that affect the rights, safety, or welfare of research subjects, or the integrity of the research data. Specific reasons include serious non-compliance, repeated non-compliance, complaints, etc. Directed audits can be initiated at the request of the IRB, IRB Chair, HRPP Director, or a regulatory agency.

McLaren Health Care investigators may obtain further assistance from the Education and Quality Improvement Program (EQuIP), a program within the Office of Research Compliance and Quality Improvement, which provides ongoing support to investigators and their study staff, including:

3. **Investigator-Requested Study Reviews and Consultation**
   Reviews may also be voluntarily requested by PI/staff (e.g. early-stage QA/QI review to ensure compliance, review of self-assessment review, during staff changes, to prepare for external audit, consultation on developing documents or corrective action plan, evaluate study conduct, organization, record-keeping and documentation). To request services, the principal investigator or designee can call our office or complete the service request form found on the website:
   http://www.mclarenhealthplan.org/centralmichigan/research-service-contact-form.aspx

4. **Education/Additional Training**

    a. **In-Service -** EQuIP staff is available to conduct small group in-service sessions, addressing a variety of topics relating to research compliance, HRPP policy, and good clinical practice.

    b. **New Investigator/Research Coordinator Orientation -** EQuIP is available to meet with new study staff (PIs, Coordinators, etc.) in order to familiarize them with HRPP policies and procedures with a focus on the IRB review and approval process.

    c. Brown Bag Series - Brown bag sessions are offered via live webinar throughout the year. Offerings are open to all personnel in the research community. Sessions are meant to engage in knowledge sharing, keep abreast of current with changes in research, or review of key information.

    For more information on accessing CITI and educational offerings visit on website: http://www.mclarenhealthplan.org/centralmichigan/research-education-training-and-resources.aspx

5. **Study Management Tools**

    EQUIP offers a variety of study management tools to assist research sites in maintaining and organizing essential study documents. These tools are available on the HRPP website: http://www.mclarenhealthplan.org/centralmichigan/research-study-templates-and-tools.aspx

Who can be a Principal Investigator?

Physicians, faculty, residents, and students associated with MHC can be a principal investigator. In general the expectation is:

- The Principal Investigator is qualified by education, training and experience to personally conduct and/or supervise the research described in the protocol.
- The Principal Investigator has completed all applicable institutional credentialing processes
- The Principal Investigator has sufficient resources to carry out this research as proposed.
- The protocol is scientifically valid and employs research procedures which are consistent with sound research design.
- The Principal Investigator will conduct the protocol in accordance with requirements in the INVESTIGATOR HANDBOOK.

Resident and Student Principal Investigators

Residents and students wishing to assume roles as principal investigators must have an academic advisor who fulfills the principal investigator eligibility criteria and will serve as a faculty advisor on the study. Residents and students acting as principal investigators are held to the same ethical and regulatory standards as attending physician investigators. They are expected to follow all MHC HRPP policies and processes regarding human research, including conducting their research in accordance with this Investigator Handbook.

As part of the initial application process, residents and student investigators must complete a "Confirmation of Scholarly Review for Validity" form which must be signed by the Academic Advisor. This form can be found at: http://www.mclaren.org/Main/Research-Guidance1.aspx

Residents and students must also follow any and all departmental requirements for conducting research. It is the responsibility of the resident or student to know and follow such requirements.

Academic Advisors

Academic Advisors play an important role in human subject protections. They are responsible for advising resident/students on research projects, and bear ultimate responsibility for the ethical conduct of the research. The efforts and commitment of the Academic Advisor can significantly affect the success of resident/student projects, the quality of data, and the time elapsed from submission to IRB approval.

During the protocol submission process, all MHC investigators agree to certain assurances in the conduct of research. The MHC IRB expects the Academic Advisor to accept responsibility to monitor and verify that the resident/student is compliant with all aspects of research conduct.

Academic Advisor Requirements

When a resident/student submits a protocol for IRB review, the Academic Advisor should ensure student projects are successful by:

- *Adopting an active role in mentoring (meet with resident/student on a regular basis to monitor study progress, keep current of developments that may impact the research or welfare and safety of subjects or integrity of data)*
- *Accept responsibility for resident/student research (both planning and conduct)*
- *Be aware of the obligations of a research investigator*
- *Ensure all project personnel will conduct research in compliance with applicable HRPP policies, federal, state, and local regulations*
- *Notify IRB immediately of any violations of DHHS regulations (45 CFR 46), FDA*

regulations (21 CFR 50, 56), HIPAA regulations (45 CFR 164.530), state/local laws, or HRPP policies for the protection of human subjects.

- *Per HIPAA Privacy Rule regulation (if applicable to the study), ensure that only the minimum necessary data to achieve the goals of research described in the protocol is accessed*
- *Approve study design and methodology*
- *Ensure the information provided in the protocol application represents an accurate description of the study.*
- *Ensure timely reports of unanticipated problems involving risks to subjects or others according to MHC HRPP policies*
- *Ensure required research records will be maintained and made available in accordance with applicable regulations and HRPP policy*
- *Allocate adequate time for each student*
- *Assure scientific merit in student projects*
- *Know if an informed consent or a waiver is needed*
- *Help students determine the level of risk (minimal risk or greater than minimal risk)*
- *Know the levels of IRB review: Exempt, Expedited, Full Board, or Not Human Subjects Research ("NHSR")*
- *Anticipate time required for students to secure IRB approval and conduct the research*
- *Ensure no changes will be made to the protocol without IRB approval except when necessary to eliminate immediate hazards to the subject, in which case the IRB will be notified as soon as possible*
- *Fulfill the human subjects education requirement by successfully completing the CITI online human subjects education training*
- *If unable to supervise the resident/student research personally , arrange for another faculty member to accept responsibility in their absence*

May researchers, who are not employees or affiliates of McLaren Health Care, conduct human subject research at MHC?

Those who are not employees or affiliates of McLaren Health Care and wishing to conduct human subject research, either at McLaren Health Care or with McLaren Health Care patients or employees, must contact MHC IRB Administration for prior authorization to do so.

What are the obligations of a Principal Investigator?

1. Do not start human research activities until you have the final IRB approval letter.

2. Do not start human research activities without the approval of any all departments or divisions that will be impacted by your project. The IRB requires a *project impact statement, signed by the department / manager, for each department involved, as documentation of departmental approval. This form is to be submitted with your application to the IRB.*

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 and, when relevant, privileges) to perform procedures assigned to them during the study

5. Comply with HRPP Policies – see HRPP website:
   http://www.mclaren.org/Main/Research-Policies1.aspx

6. Comply with the following FDA regulations for **FDA-regulated research involving investigational drugs**: 21 CFR §312.7, 21 CFR §312.57, 21 CFR §312.59, 21 CFR §312.60, 21 CFR §312.61, 21 CFR §312.64, 21 CFR §312.66, 21 CFR §312.68, and 21 CFR §312.69

7. Comply with the following **FDA regulations for FDA-regulated research involving investigational devices**: 21 CFR §812.7, 21 CFR §812.100, 21 CFR §812.110, 21 CFR §812.145, and 21 CFR §812.150

8. Comply with the **International Council on Harmonization – Good Clinical Practice Guidelines** (E6) Section 4 for research involving clinical trials, to the extent that doing so corresponds with FDA regulations

9. 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 applicable, ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB.
   c. Do not modify the 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.

10. Submit to the IRB:
    a. Proposed modifications (key personnel, recruitment, consent, procedures, data collection, and data analysis) 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 final application when the research is closed. (See "How Do I Close Out a Study?")

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.")

    More information can be found in the HRPP policy: MHC_RP0125 –Investigator Responsibilities

Do I have to sign any contracts or agreements to be a research investigator?

Clinical Trial Agreements

A Clinical Trial Agreement (CTA) is a contract between McLaren and the sponsor for research in which a private industry sponsor is providing monetary or material support. A completed CTA is required before any clinical trial supported by a sponsor can begin. A CTA defines the scope of work and formalizes the understandings between the parties and contains legal and financial terms related to the conduct of a clinical trial. The investigator over the trial is required to sign the CTA.

FDA 1572

The Statement of Investigator, Form FDA 1572, is an agreement signed by the Investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of a drug, device or biologic.

For additional information see:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

HRPP Investigator Assurance

All McLaren investigators must sign an investigator assurance statement when submitting a new application.

Investigator Assurance Statement
The Principal Investigator of this study provides the following assurances:

The eProtocol application submitted for this study is complete and accurate.

The PI acknowledges responsibility for the conduct of the project as described in the IRB application.

The PI has evaluated the protocol and determined that s/he has sufficient resources to conduct the study as submitted and necessary to protect subjects who enroll in the study. All co- or sub-investigators, study coordinators, and other research personnel to whom the principal investigator delegates study-related responsibilities, will receive thorough training in human subjects protections, as well as in the specific details of study procedures.

The principal investigator will not begin the study until s/he has received notification of final IRB approval. If contract administration approval is required, s/he will not begin the study until s/he have received notification of final contract administration approval.

The principal investigator acknowledges his/her responsibility for the accuracy of all documents research personnel submit to the IRB on his/her behalf.

The principal investigator will comply with all IRB requests to report on the status of the study.

The principal investigator will seek and obtain prior approval from the IRB for modifications in the study, including changes in procedures, study enrollment goal, consent forms, etc.

The principal investigator will promptly submit any reportable UPIRSO (unanticipated problem involving risk to subjects or others) that may occur in the course of this study.

The principal investigator will promptly inform the IRB of the results of external audits performed by the FDA, sponsors, contract review organizations (CROs), cooperative groups, or other external groups.

The principal investigator will notify the IRB when his/her research has been completed or terminated.

What training do my staff and I need to conduct human research?

Investigators and staff conducting research must complete required human research training via the online **Collaborative Institutional Training Initiative** (CITI) program which provides research ethics education to all members of the research community.

CITI Basic Human Subjects Research Course
This training requirement applies to all individuals involved in the conduct of human subject research, regardless of pay status, appointment type, and length of time at this organization, including, but not limited to:

- Investigators
- Academic Advisors
- Study coordinators
- Research assistants
- Other members of the research team
- All members of the research office whose responsibilities include involvement with human research

This training is valid for a three-year period, after which time a refresher CITI course or additional training must be completed. It is recommended that a copy of the completion report is printed and maintained.

IRB approval will not be granted for proposed research in which the Principal Investigator has not completed human research protections training. Members of the research team who have not completed human research protections training may not take part in aspects of the research until such time that the IRB Office has received proof of satisfactory completion of human research protections training.

> *Note: Training provided by another affiliate will be accepted by HRPP as long as it meets the training requirement for Good Clinical Practices and the ethical principles on which human research should be conducted. HRPP will review other training upon request to determine whether or not it meets the requirements of this manual. If other training is accepted by the HRPP, the individual will be required to complete CITI training at the time of the next renewal.*

CITI Conflict of Interest Course
Conflict of Interest training is required of all research investigators (including sub or co-investigators) and academic advisors **prior to the start of any study activities**. The COI training certificate is good for four years.

For more information on accessing CITI and completing required training visit our website:
http://www.mclaren.org/Main/Research-Training2.aspx

What are possible disciplinary actions if I fail to conduct my study according to HRPP standards?

The IRB and Institutional Official may place limitations or conditions on an investigator's or research staff's privilege to conduct human research whenever, in the opinion of the IRB and Institutional Official, such actions are required. Determinations for actions are based on the following HRPP policies:

- MHC_RP0111 – Study Suspension, Termination and Investigator Hold
- MHC_RP0123 – Complaints and Non-Compliance in Human Subject Research
- MHC_RP0124 – Reporting to Regulatory Agencies and Institutional Officials
- MHC_RP0125 – Investigator Responsibilities

What are my obligations for reporting a conflict of interest or financial interests of myself or research staff?

It is McLaren's policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest in the conduct of research. Managing conflicts of interest is essential to ensuring integrity in our business decisions and maintaining the public's trust in MHC and all those connected with it.

Conflicts of interest in the research setting may create professional bias, potentially impacting the selection of research subjects; the collection, analysis, and interpretation of research data; reporting of adverse events; and publication of research results.

In order to minimize the actual or potential conflicts of interest in human research, the IRB requires all individuals involved in the design, conduct, or reporting of the research to report all conflicts or financial interests related to the research. Of note, all individuals involved in the design, conduct, or reporting of the research is broader than principal investigators and co-investigators, and may include study coordinators, research nurses, data coordinators, and other support staff.

When submitting a new study to the MHC IRB via eProtocol, you will be prompted to answer specific questions regarding financial conflict of interest related to research* for yourself and your immediate family members, as well as for the other investigators and research personnel and their immediate family members. Such questions include:

- Nature of the interest (e.g., salary, ownership, stock or stock options, proprietary [patent, trademark, copyright, or licensing agreement], consulting, speaking fee, travel, etc.);
- Value or amount of the financial interest.
  If necessary, the HRPP Conflict of Interest Committee will review conflict of interest issues, including financial interest disclosures, and make the final determination whether subjects are protected.

***The definitions of important terms are as follows:**

"Conflict of Interest": A conflict of interest (COI) occurs when any financial arrangement, situation, or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings.

"Financial Interest Related to the Research" means any of the following interests in the sponsor, product or service being tested, or competitor of the sponsor held by the individual or the individual's immediate family:

- Ownership interest of any value including, but not limited to stocks and options.
- Compensation of any amount including, but not limited to, honoraria, consultant fees, royalties, or other income.
- Proprietary interest of any value including, but not limited to, patents, trademarks, copyrights, and licensing agreements.

Immediate Family means spouse, domestic partner, and dependent children.

Additional details can be found in the following HRPP policies:
MHC_RP0202 – Research Conflict of Interest Committee';

Financial Interest Disclosure Form can be found at: http://www.mclaren.org/Main/Research-IRB-Forms1.aspx

What is or isn't human subjects research?

The first question a researcher should consider with respect to IRB submission, is whether the project fits the definition of **human subjects research**. In order to do so, the project must meet the federal regulatory definitions of both **research** and **human subjects** in order to require IRB approval and oversight. This determination must be made by the IRB.

The MHC HRPP relies on the definition of "human research" as defined in the Department of Health and Human Services (DHHS) regulations at 45 CFR 46.102(d) and 45 CFR 46.102(f) and as defined in Food and Drug Administration (FDA) regulations at 21 CFR 56.102(c) , 21 CFR 56.102(e), and 21 CFR 812.3(p).

A unique category, **non-human subjects research**, is used when the research does not meet the federal definition of **human subjects** and/or **research** and thus will not require IRB review. Activities that do not meet the definition of human subject research are not subject to IRB oversight or review**.**

Determination of Human Subjects Research
In light of the potential regulatory consequences of not obtaining IRB review and approval, the investigator should must consult the IRB when he/she is uncertain if a project is human subjects research.

If an investigator has a project that includes information and/or specimens derived from a human being and feels that the project is not human research (e.g., some classroom activities, quality improvement activities, program evaluations, case studies, oral histories, and surveillance activities), a "*Determination for Non-Human Research "* form should be submitted to the IRB via email. The form can be found at:
http://www.mclaren.org/Main/Research-Training2.aspx

After the IRB has reviewed the request, the PI will receive an email including the IRB determination letter. This document should be kept on file in the investigator's research record.

The letter will clearly state that the project either:

a) **Does not** qualify as human subject research, and is not subject to oversight by the MHC IRB.
b) **Does** fit the definition of human subjects research. In this case, the letter will direct the PI to submit an eProtocol application.

REMEMBER, only the MHC IRB can make the determination of what is or is not human subjects research. Federal regulations do not allow investigators or academic advisors to make this determination themselves.

For more information see:
1. HRPP Policy: MHC_RP0104 – Determination of Human Subject Research
2. Guidance on What is Required to be Submitted to the IRB at: http://www.mclaren.org/Main/Research-Training2.aspx

A detailed explanation of the definition of human subject research can be found on the HHS website:
http://www.hhs.gov/ohrp/policy/cdebiol.pdf
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.102

How do I know if I am engaged or participating in human subject research?

Beyond determination of human subjects research, one would need to *when* an individual is actually engaged in research activity. McLaren (or its employees or agents) are ***engaged*** in the research – as defined by OHRP rules of Engagement of Institutions in Human Subjects Research.
http://www.hhs.gov/ohrp/policy/engage08.html

In general, an institution or individual is considered *engaged* in a particular non-exempt human subjects research project when its employees or agents, for the purposes of the research project obtain:
1. data about the subjects;
2. conduct research through intervention or interaction with them;
3. identifiable private information about the subjects of the research; or
4. the informed consent of human subjects for the research.

How do I submit new human research project application for review by the IRB?

MHC IRB utilizes a secure electronic web-based database called **eProtocol**, which provides a suite of tools for online submission and research protocol management. All IRB applications must be submitted through eProtocol, as well as continuing reviews, final reports, reportable events, and modifications to approved research.

How do I obtain an eProtocol account?

Anyone on the research team can request eProtocol access by sending an email with the following information to hrpp@mclaren.org:

- Name, credentials
- Email address
- Phone number
- Mailing address (for research-related correspondence)
- Area of research (i.e. Internal Medicine, Oncology, Emergency, etc.)
- McLaren subsidiary to which they are attached

Within one business day, the user will receive an email with their user name and temporary password for the eProtocol system.

Users should contact HRPP, if they forget their password: (248) 484-4950 or HRPP@mclaren.org

eProtocol Training

Understanding that the eProtocol system is new to many, an eProtocol Investigator User Guide is available on our website:
http://www.mclaren.org/uploads/Public/Documents/Corporate/irbinvestigatoruserguide.pdf

The IRB analysts are also happy to provide individualized eProtocol training. Please contact our office to set up an appointment: (248) 484-4950 or hrpp@mclaren.org.

Submitting your application in eProtocol

When you enter eProtocol you will have 4 application options to choose from:

Exempt
Full Board / Expedited
Chart Review
Humanitarian Use Device

It is important that you complete the application thoroughly, ensuring consistency with your responses throughout the application. It is critical that answers to questions in the eProtocol application coincide with the protocol and consent documents. Keep in mind - If it is not in the application or the protocol, then is not approved, and cannot be done until IRB approval is granted.

Submit all necessary documents including consent forms, data collection forms, recruitment material, etc. with the eProtocol application. It should be a habit to insert version dates on all supplemental documents. Remember to stay in compliance, every time there is a change to research staff, forms, consents, protocol, etc., IRB approval must be obtained before the change is implemented. All documents in their final form must be approved the IRB before use.

In the event that you are involved in a sponsored study for which the sponsor **requires** the use of a central IRB, you are required to complete a "Request to Use an External IRB as an IRB of Record". This form can be found at: http://www.mclaren.org/Main/Research-IRB-Forms1.aspx

What is the IRB Review Process?

Federal regulations provide for three types of IRB review: **exempt, expedited, and full-board**. The following chapter provides an explanation of each category of review and examples of studies that fall into those categories. The IRB conducts reviews using the criteria contained in the Federal Policy for the Protection of Human Subjects (CFR 45; Part 46, Section 46.111).

Exempt Review

Exempt projects involve no more than minimal risk. Projects that meet the criteria for exempt review qualify as research with human subjects, but are "exempt" from the provisions of the Code of Federal Regulations (45 CFR 46). Although such studies do not require annual continuing review, changes to such projects must be submitted to the IRB to ensure that they have not been amended in such a way that they no longer meet the criteria under which they were initially determined to be exempt.
The IRB – not the researcher – must determine when a research project falls under one of the six exempt categories listed in the federal regulations (45 CFR 46.101(b)).
For more information on exempt categories, see HRPP policy: MHC_RP0105 – Exempt Review of Human Subject Research

Expedited Review

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. It is important to remember that 'expedited' reviews are just as thorough as full board reviews.

For more information on expedited review categories see HRPP policy: MHC_RP0106 – Expedited Review of Human Subject Research

Full Board (Convened) Review

Non-Exempt human research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB. Studies that involve **more than minimal risk** require full board review at a convened meeting, at which a quorum of IRB members is present. For the research to be approved, it must receive the approval of a majority of those members.

While federal regulations do not specifically list categories that require full board review, studies are normally sent to full board for review when the study design involves greater than minimal risk procedures, for example:

- studies involving clinical procedures with drugs, devices, or biologics, or innovative research into new medical or surgery procedures
- studies that are conducted internationally (particularly countries with little or no provisions for protection of human subjects) where subjects may be at physical, psychological or legal risk
- studies in which disclosed information could require mandatory legal reporting (e.g., child/elder abuse, domestic violence, etc.)
- studies involving deception which raises the risk to subjects or others
- studies in which the IRB staff, chair, member, or designee determines risk to subjects or others to be greater than minimal risk
- studies using "vulnerable" populations and, thus, requiring extra protections

For more information on full board review see HRPP policy: MHC_RP0107 – Full Board Review of Human Subject Research.

How does the IRB decide whether to approve human research project?

Federal regulations (45 CFR 46.111 and 21 CFR 56.111) require the IRB to determine if specific criteria be satisfied in order to approve research. Criteria for IRB approval can be found in the HRPP policies:

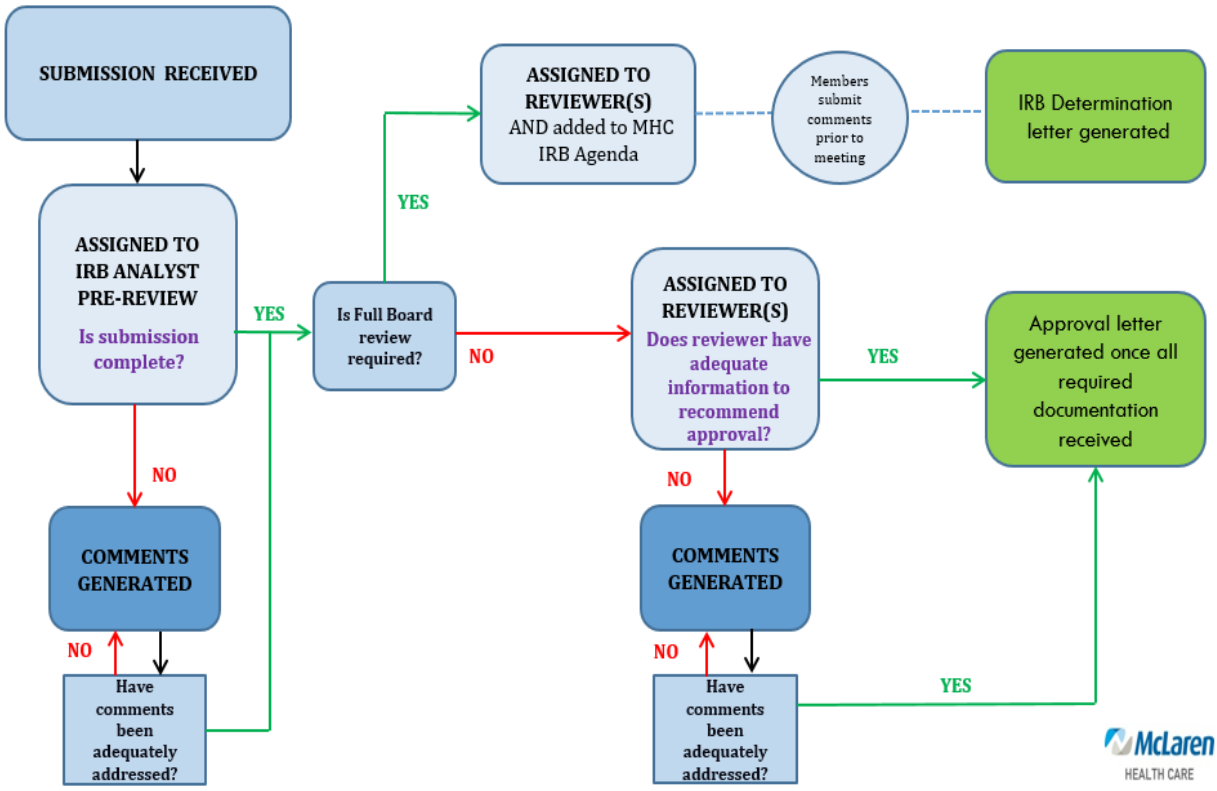
- MHC_RP0109 – Criteria for IRB Approval of Research
- MHC_RP0110 – Additional Consideration during IRB Review and Approval of Research

Are there fees associated with an IRB submission?

McLaren Health Care IRB (MHC IRB) charges for the review of research studies supported by pharmaceutical companies and other for-profit entities. Current IRB fees are listed on our website:
http://www.mclarenhealthplan.org/uploads/Public/Documents/Corporate/irbrates.pdf

What happens after the IRB receives my submission through eProtocol?

Overview of the IRB Process



The Principal Investigator, designated primary contact, and any designated study staff will receive an email indicating when revisions or clarifications are needed. To check on the status of a submission, log in to eProtocol at https://eprotocol-hrpp.mclaren.org/at any time. For questions or concerns, contact your assigned IRB Analyst.

What decisions can the IRB make when reviewing proposed research?

All research proposals that intend to enroll human subjects must meet certain criteria before study-related procedures can be initiated. The criteria are based on the principles of justice, Beneficence, and autonomy as discussed in the Belmont Report and specified below.
IRB reviewers use checklists to make their determination for initial review, continuing review, and review of modifications to previously approved human research.

Except when the expedited review procedure is used, the following **IRB determinations** will be taken by a vote of a majority of the regular and alternate members present at a convened board meeting:

Approved Without Stipulations: the study is approved as submitted. The PI is not required to change any aspect of the protocol or informed consent document. The approval date is the date of the IRB meeting. The approval is valid for one year unless the IRB Committee, IRB Chair or designee designates a shorter period due to the risk in the study.

Approved with Contingencies: Occurs when the stipulations are minor in nature (e.g., require simple concurrence from the PI and do not require substantive judgment by the IRB Committee).

Moved: Occurs when IRB Chair, member or designee has determined that further information regarding the protocol is needed in order for the IRB to make a determination.
Moved studies will be transferred to the next convened IRB meeting.

Not Approved: The IRB has determined that the research cannot be conducted at MHC and its subsidiary hospital or by employees or agents of MHC and its subsidiary hospitals or otherwise under the auspices of MHC. Once a study has been disapproved, it can be submitted as a new application to the IRB for re-consideration. New submissions of previously disapproved protocols must be reviewed by the fully convened IRB. The new application must address all previous concerns outlined by the IRB.

Suspension of IRB Approval: An action of the IRB or Organizational Office
al to temporarily or permanently withdraw IRB approval of some or all research procedures. Suspended studies remain open and are subject to continuing review.

Tabled: the study might be tabled when the quorum was lost during the convened IRB meeting.

Termination: A directive of the convened IRB to permanently cease all activities in a previously IRB-approved research protocol. Terminated protocols are considered closed and no longer require continuing review. Terminations of protocols approved under expedited review must be made by the convened IRB.

Withdrawn: Occurs when the IRB Analyst removes a study from further IRB review and it is placed in the eProtocol Non-Active Protocols list. Withdrawn studies will be removed from further IRB review at the request of the PI, IRB Analyst and/or by the IRB Chair or designee. No further action will be taken unless the PI resubmits the protocol.

For more information see HRPP policy: MHC_RP0109 – Criteria for IRB Approval

What do I have to do after IRB approval?

Once the application is approved, the researcher may begin recruiting subjects and conducting the study, provided all other organizational approvals have been met. IRB approval is valid for up to 364 days. The specific approval period is noted in the approval letter. However, there times when you must communicate with the IRB:

<u>Prompt Reporting to the IRB</u> - The researcher must let the IRB know if any of the following subsequently occur:

1. ***Modifications: Proposing Changes to Previously Approved Research Projects***
   A modification is a change to an IRB approved research project, including exempt projects. Any proposed change to a previously approved study must be submitted to the IRB as an amendment to that project. The IRB must review and approval any proposed changes before investigators can implement them. The only exception to this rule is when modification is necessary to eliminate apparent immediate hazards to the subjects.

   Depending on the risk associated with the change, the modification may be reviewed by the expedited review procedure (i.e. by one reviewer) or by the convened IRB (i.e. reviewed by a committee). Minor changes that do not significantly alter the project's risk/benefit ratio may qualify for expedited review. All modifications to previously approved research must be submitted through the eProtocol system.

2. **Adverse Events and UPIRSO - Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others.**

   MHC IRB complies with DHHS and FDA regarding unanticipated problems involving risks to subjects or others. The SOP: MHC_RP0121 – Reporting Adverse Events and Unanticipated Problem Involving Risks to Subjects or Other (UPIRSO) outlines what has to be reported promptly to the MHC IRB. For example, situations that require prompt reporting include, *but are not limited to*:

   a. Breach of Confidentiality
   b. Local Death
   c. Subject Complaint when the complaint indicates unexpected risks or cannot be resolved by the research team.

   Not all adverse events require reporting to the MHC IRB. Unless stated otherwise in the SOP, the MHC IRB requires adverse events that meet the UPIRSO definition reportable. Per policy the definition of an UPIRSOs is any incident, experience, outcome or new information that meets all of the following 3 criteria:

      i. Is unexpected
      ii. Is related or possibly related to participation in the research , and
      iii. Indicates that subjects or others are at a greater risk or harm (including physical, psychological, economic or social harm) that was previously known own or recognized

For more information on reporting requirements see HRPP policies:

1. MHC_RP0121 – Reporting Adverse Events and Unanticipated Problem Involving Risks to Subjects or Other (UPIRSO)
2. MHC_RP0122 – Protocol Deviations, Violations and Exceptions in Human Subjects Research
3. MHC_RP0113 – Changes to Currently Approved Human Subject Research

Continuing review

All active expedited or full board (non-exempt) studies must be reviewed at least once a year. Investigators must submit a continuing review (CR) application at least one month prior to the study expiration date. The investigator must provide a progress report indicating the status of the study since the start of study (e.g. enrolling new subjects, enrollment closed/data analysis only, closed/final report). If the study is complete, a final report must also be submitted to the IRB in the form of a continuing review application. The requirement for continuing review does not apply to research determined to be exempt from IRB review.

How do I submit a continuing review?

Complete the "Continuing Review Form" through the eProtocol System. Ensure that any documents or supporting documents for changes being submitted for review are provided in the attachments section of the application. This may include, but is not limited to, annual DSMB or DMC report, informed consent form(s).

Modifications to previously approved research can be included with the continuing review application. Simply identify what change(s) is (are) being submitted for review in the continuing review application in eProtocol.

It is important that CR application be submitted to allow sufficient time for IRB review before the expiration date. Research activities must stop if approval has expired and cannot be resumed until the IRB reviews and approve the CR, and, failure to meet continuing review obligations may be grounds for suspension or termination of the research.

For additional information see HRPP policy: MHC_RP0112 – Continuing Review of Human Subjects Research

Administrative closures due to lapse in IRB approval

When IRB approval of an ongoing research project lapses, the investigator has 14 days from the expiration date to complete the continuing review application. Human subjects research activities may resume only after the investigator is notified of IRB approval.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. If this occurs, the IRB will "Administratively Close" the study. You will be notified of this action. If you wish to continue the research one your project has been administratively closed, you will be required to submit a new initial application to the IRB.

If the IRB approval for a research study lapses (expires), federal regulations and IRB policy do not allow researchers to continue ongoing research for the project until IRB approval has been restored. Continuation is considered a violation of federal regulations. Once the study expires all research activity must cease including but not limited to: enrollment of new subjects, recruitment, advertisement, interventions, interactions, data collection and data analysis.

During the cease period, if you believe that any participants would be harmed by stopping research activities you must immediately submit to the MHC IRB a list of participants for whom stopping the research activities would cause harm along with the written explanation. This notification should be made by email to hrpp@mclaren.org.

Concluding your research

A research project is closed when subject enrollment is completed, subjects have completed research related interventions/interaction, collection of PHI is completed, and data analysis is completed. Once a study is closed, no further research activity (including interactions with subjects and data) may occur and the researcher is no longer required to submit yearly continuing review applications.

How do I close out a study? - Researchers must notify the IRB that a study is complete by submitting a "Final Form" through the eProtocol System. Investigators will be asked to provide information regarding the reason for closure of the study, a summary of study enrollment, and information regarding data storage. As with all submissions to the IRB, it is important to ensure that all requested documents are attached to the application; as well as a copy of the application which has been signed by the principal investigator...

It is not necessary to submit a "Final Form" for exempt studies, as they will be administratively closed on the proposed end date provided in the eProtocol application

What if I am doing a research projects involving reviewing charts/records?

For studies where there will be a review of records but subjects will not be consented, *a waiver of consent and PHI Authorization* (if involving medical records) must be granted by the IRB. The investigator must include protocol-specific justifications for waiving consent and/or PHI Authorization. It is important to note that Health Insurance Portability and Accountability Act (HIPAA) regulations may apply for review of medical records.

Most chart review studies are retrospective versus prospective*. It is critical that you understand the difference, as this will influence how a protocol is written:

Retrospective vs. Prospective Research

PROSPECTIVE STUDIES - A study designed to follow groups of subjects for an extended period of time with defined outcomes. Data that is **not in existence prior to the date the proposed research is submitted to the IRB** for review is considered prospective data.

RETROSPECTIVE STUDIES - Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews, surveys, or

measurements. The IRB considers data retrospective when it exists **prior to** date of the initial IRB application submission.

What if I am doing a case study or case series or quality improvement project?

The MHC HRPP has specific guidelines regarding projects that involve a case study or case series. A guidance document is available on our website to assist you, "Guidance on Case Reports/Case Series":
http://www.mclarenhealthplan.org/Uploads/Public/Documents/Corporate/irbcasereports.pdf

What if I want to utilize a Humanitarian Use Device?

Humanitarian use devices are a special class of device approved by the FDA for use in a rare condition (manifesting in fewer than 4,000 persons per year). Under FDA regulations, humanitarian use devices (HUDs) must be overseen by an IRB even though HUDs are usually not research.

For more information on HUDs, the IRB's role, and investigator requirements, please reference the following guidance from the FDA, as well as MHC HRPP policy:

1. FDA "Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" found at http://www.fda.gov/RegulatoryInformation/Guidances/ucm110194.htm

2. HRPP policy MHC_RP0120 Submission of an Application for Humanitarian Use Device"

To apply for use of an HUD, an initial HUD application must be submitted via eProtocol, along with any and all applicable documents. Physicians will need to submit the appropriate continuing review application if use of the HUD is expected to continue past the current IRB approval expiration date. Modifications to the approved HUD project, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval. The physician must a modification application to the IRB. A Final Report Form" must be submitted to the IRB at the time of HUD closure...

What are the requirements if I want to sponsor and/or initiate a study as a principal investigator?

A Sponsor Investigator (SI) is anyone who functions as the PI of a given study and holds an Investigational New Drug (IND) or an Investigational Device Exemption (IDE). Such studies may be referred to as Investigator-Initiated studies.

An investigator-initiated study does not always involve drugs or devices. If the study involves drugs, devices, or biologics the SI is held accountable for all the roles and responsibilities of a PI. The Food and Drug Administration (FDA) also requires that the SI follow the FDA regulations for sponsors. Sponsor-specific regulations can be found on the FDA website.

Questions to consider:

Does my study need an IND?

In general, an Investigational New Drug (IND) application is required when the primary intent of any clinical research study is to develop information that proposes the use or evaluation for safety and/or effectiveness of an unapproved drug. Please note: in research, "off-label use" of a lawfully marketed drug would be considered an unapproved drug.

A checklist has been created to assist you, "Does My Study Need an IND can be found on our website: http://www.mclaren.org/uploads/Public/Documents/Corporate/IND_Determination_Worksheet.pdf

IND application procedures:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362743.htm

Does my study need an IDE?

An Investigational Device Exemption (IDE) allows an investigational device (i.e. a device that is the subject of a clinical study to be used in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application; or a Premarket Notification [510(k)] submission to Food and Drug Administration (FDA)). Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)'s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

IDE Application Procedures:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm

IRB Requirements

Prior to approving a protocol that involves a sponsor-investigator, the IRB must be satisfied that the sponsor-investigator is knowledgeable about his/her responsibilities and has adequate policies and procedures in place to comply with the FDA regulatory requirements.

Sponsor-Investigator Requirements

A sponsor-investigator assumes all responsibilities required by the FDA of the sponsor and the investigator, including those related to record keeping and prompt reporting of safety reports to the FDA. These responsibilities include:

- Selection of research staff qualified by training and experience
- Commitment to personally conduct or supervise the investigation according to the research plan
- Selection of study monitor(s) qualified to monitor the progress of the project

• Maintenance of accurate, complete and current records, including correspondence with the FDA, monitor and IRB, records on shipment and disposition of devices, and records of participants' case histories and exposure to the device
• Completion of regulatory filings, including amendments (supplemental applications)
• Timely submission to IRB:
- Reporting of Adverse Events and UPIRSO: see MHC policy – MHC_RP0121
- Continuing (annually or less if required by the IRB)
- Final Report (within 30 days of completion or termination of investigation)

For further information on the FDA requirements, see Title 21 Code of Federal Regulations part 812 , particularly sections:

21 CFR 812.40 General responsibilities of sponsors
21 CFR 812.100 General responsibilities of investigators
21 CFR 812.110 Specific responsibilities of investigators
21 CFR 812.140 Records
21 CFR 812.145 Inspections
21 CFR 812.150 Reports

For additional guidance:

1. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm
2. http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046702.htm#resofinvforsig
3. Guidance for Clinical Investigators, Sponsors and IRBs – Investigational New Drug Applications: Determining Whether Human Research Studies Can Be Conducted Without an IND http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf

Guidance for Clinical Investigators, Sponsors and IRBs - IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf

What if I want to include subjects from vulnerable populations in my study?

You may not involve any individuals of the following populations as subjects in your research, unless it is indicated in your application. Inclusion of subjects in these populations have specific regulatory implications that the MHC IRB must address.

- Adults who lack the capacity to provide legally effective consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

If a study subject becomes vulnerable during the course of the study, you must immediately notify the IRB.

Populations which are not federally protected under 45 CFR 46 –subpart B, C and D, but may be vulnerable
The concept of justice and respect for persons should be thoroughly considered when

including a population at increased risk of coercion or undue influence. The researcher should consider whether the principle of justice is met in including these populations; and that appropriate safeguards have been put into place to minimize the risk of coercion or undue influence.
The National Bioethics Advisory Commission (NBAC) identifies the following six categories of subject vulnerability:
• Cognitive or communicative vulnerability
• Institutional vulnerability
• Deferential vulnerability
• Medical vulnerability
• Economic vulnerability
• Social vulnerability

For additional information see HRPP policy: MHC_RP0116 – Vulnerable Subjects in Research

How many study subject can I enroll in a study?

Investigators must provide an estimate of the number of participants to be enrolled in the study at the time of initial submission to the IRB. Investigators may not enroll more participants than the number specified in the application currently approved by the IRB. A modification to increase enrollment must be review and approved by the IRB before more participants can be enrolled.

Subject Status Definitions

Enrolled participants McLaren defines enrolled as "consented and screened, with eligibility verified".

Screened participants: individuals who have given informed consent and participated in screening procedures to determine eligibility. Note that informed consent is required before any data can be collected for screening purposes. A screening process where persons are simply informed of inclusion/exclusion criteria and allowed to self-identify as eligible for enrollment does not require informed consent because no data about the individuals are collected.

Screen failures: individuals who have given informed consent and participated only in screening procedures to determine eligibility, but who were determined to be ineligible to take part in the study.

Withdrawals: individuals who have given informed consent and participated in some study procedures, but who withdrew or were withdrawn from the study.

How do I write a Protocol?

A research protocol is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project. The research protocol should provide IRB members and reviewers with sufficient information to conduct a substantive review. If a separate sponsor's protocol exists, please submit it.

Sponsor Investigator may need to create a new protocol. "Protocol Templates", including one for a chart review, can be found on our website: http://www.mclaren.org/Main/Research-Templates1.aspx
Please note: The templates contain instructions on completion with example language, and should be revised as necessary for you project.

Protocol development assistance, covering a wide-range of therapeutic areas, is available through the McLaren Center for Research & Innovation. For additional guidance and information, please complete a request form found at
http://www.mclaren.org/Main/Research-Resource-Center1.aspx

The Consent Document and the Consenting Process

How do I create an informed consent or assent document?

Informed consent documents must be written at 10th grade level (or below), and in a language the subject will understand. An "Informed Consent Template" has been created to assist with the creation of an informed consent document: http://www.mclaren.org/Main/Research-Templates1.aspx

Informed consent documents must include all required elements of informed consent disclosure. Additional elements may be required, depending on your study. For instance, information regarding the Genetic Information Nondiscrimination Act (GINA) must be included in the consent form if genetic testing will occur as part of the research. Please ensure you read through the consent template thoroughly to ensure all appropriate elements required for your study are included in the informed consent document you provide to the IRB.

Can I request a "waiver or alteration" of informed consent?

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent under one of two set of conditions:

1. Most common set of conditions for a waiver or alteration
   a. The research involves no more than minimal risk to the participants;
   b. The waiver or alteration will not adversely affect the rights and welfare of the participants;
   c. The research cannot practicably be carried out without the waiver or alteration;

d. Whenever appropriate, the participants will be provided with additional pertinent information after participation; and,
e. The research is not FDA-regulated.

2. Less common set of conditions for a waiver or alteration
   a. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs; and,
   b. The research could not practicably be carried out without the waiver or alteration

For examples of waiver of informed consent requirements:
http://www.mclarenhealthplan.org/uploads/Public/Documents/waiverofinformedconsentrequirements.pdf

Can I request a "waiver of documentation" of informed consent?

The IRB may waive the requirement for you to obtain a signed consent form, for some or all subjects, under one of two sets of conditions:

1. Condition 1
   a. The research presents no more than minimal risk of harm to subjects;
   b. The research involves no procedures for which written consent is normally required outside of the research context (for example, non-sensitive surveys, questionnaires, and interviews);
   c. The oral or written information to be communicated to subjects includes all required and appropriate additional elements of consent disclosure;
   d. The IRB has determined whether the subjects should be provided written information.

2. Condition 2
   a. The only record linking the subject and the research will be the consent document;
   b. The primary risk will be potential harm resulting from a breach of confidentiality;
   c. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (for example, domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers);
   d. The research is not FDA-regulated;
   e. The oral or written information to be communicated to subjects includes all required and appropriate additional elements of consent disclosure;
   f. The IRB has determined whether subjects should be provided written information.

For examples of waiver of documentation of informed consent requirements:
http://www.mclaren.org/uploads/Public/Documents/waiverofdocumentationconsent.pdf

Are there guidelines to obtaining and documenting the consent process?

Obtaining informed consent from participants fulfills the ethical requirement of "respect for persons" discussed in the Belmont Report. Potential subjects should have all the information necessary regarding the study, including the purpose, procedures, risks, and benefits, prior to agreeing to be a part of the study. However, consent is a process, not a signature on a form. The consent process starts during the recruitment phase. Once the consent form is signed, consent continues through ongoing communication with the subject throughout the life of the study. Subjects should be reminded of their requirements, procedures being done, risks to expect, etc. to ensure that they continually have the knowledge necessary to determine if they want to continue in the study. Unless waived by the IRB, consent from subjects must be obtained freely, without coercion and/or undue influence.

Researchers must be aware of any real or perceived power differential between researchers and potential subjects (such as doctor/patient, employer/employee, or teacher/student relationships), in which case(s) the recruitment and consent process must be modified accordingly (such as relying on a trained independent third-party on the research staff to recruit and consent subjects).

Parental permission is required for all human research involving minors (in Michigan this is any person under the age of 18) unless waived by the IRB. In addition, minor assent must be obtained from subjects unless waived by the IRB. When the minor reaches the age of majority (age 18) they should be consent as an adult to continue

To make sure you cover all the necessary key aspects of consenting a subject, utilize a consenting checklist. A template can be found at http://www.mclaren.org/Uploads/Public/Documents/Corporate/HRPP-Consenting-Process.pdf. Likewise, if you don't want to use the checklist, you can document the information on a progress note.

When consenting subjects, be sure to use a valid consent. A valid consent is one that has the IRB stamp on the footer of the page. The footer includes the approval period for which the consent is valid to be used. We recommend that you date the revisions of your consent documents to ensure that only the most recent IRB-approved consent is used.

<u>Documenting written informed consent</u>

The following are requirements for written consent documents:

- The subject or representative signs and dates the consent document in their own handwriting
- The individual obtaining consent signs and dates the consent document
- Whenever required by the IRB, the subject's or a 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 must be provided to the subject

Documenting short form written informed consent

The following are requirements for approved short form consent documents:

- The subject or representative signs and dates the consent document
- The individual obtaining consent signs and dates the consent document and the summary
- The witness to the oral presentation signs and dates the consent document and the summary
- A copy of the signed and dated consent document is provided to the subject

For additional information see HRPP policy MHC_RP0115 – Obtaining Informed Consent from Research Subjects

Can I use investigational drugs or devices in an emergency?

Situations exist when use of an unapproved drug or device is necessary to prevent a life-threatening situation or death. The FDA has defined this as "emergency use" and has guidance available.

Emergency use of an unapproved drug or biologic in a life-threatening situation, without prior IRB review, is "research" as defined by FDA; and the individual receiving 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 receiving 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

If the situation arises, contact the HRPP Office or IRB Chair immediately to discuss the situation. If there is no time to make this contact, see policy "MHC_RP0128 Emergency Use of Investigational Drugs and Devices" for the regulatory criteria allowing such a use, and ensure these criteria are followed. You will need to submit an "Application for Emergency Use" to the IRB within five days. This application can be found at: http://www.mclaren.org/Main/Research-Guidance1.aspx

What if I need assistance from another McLaren Health Care department?

Investigators must identify any department (e.g. Medical Records, Pharmacy, Laboratory, Nursing, Finance, Radiology, Surgery, etc.) of a subsidiary hospital that will be affected by their research and obtain the Department Manager/Director's written approval. This can be documented by completing a separate "Project Impact Statement" for each department impacted.

This form can be found at: http://www.mclaren.org/Main/Research-IRB-Forms1.aspx

What are the Internal Revenue Service (IRS) reporting requirements for compensating subjects?

It is not necessary to compensate subjects who participate in research. However, paying research subjects in exchange for their participation is a common and, in general, acceptable practice. Payment for participation should be just and fair (e.g. current market value). Proposals to the IRB regarding subject compensation should indicate and justify monetary and non-monetary compensation. If compensation is included as part of the protocol, a description and justification of non-payment, partial payment, or proration must also be included.

Payment to subjects for research participation is subject to IRS reporting requirements. Tax information must be reported for subject payments over $600 per year, while payments of less than or equal to $600 per year to subjects are exempt from IRS 1099 reporting requirements. The $600 threshold encompasses the cumulative amount a subject receives from all UA studies in a single calendar year. It is the responsibility of the principal investigator to obtain subjects' names, social security numbers (SSN), addresses, and payment amounts, and include that information as an attachment to the check request for reimbursement of the subject payment. This information should be kept separately from the study documents and in a secure location. No other information about the study should appear with the reimbursement documentation.

How to adequately protect your subjects, records, institution, and the investigator

1. **Maintain data privacy, confidentiality and security**
   HIPAA guarantees certain rights of privacy to all patients, including research subjects. Privacy and confidentiality of information is important to minimize the risk to research subjects involved. A breach in privacy, confidentiality, or security affects not only the subjects but also the institution, investigator, and the research itself. The institution could potentially incur legal and financial repercussions.

   Whether information is kept in electronic, digital, or paper format, it must be secured through administrative, physical, and technical protections and must be accessible only to appropriate persons. Assessment of the adequacy of the administrative, physical, and technical protections should include consideration of the sensitivity of the data. PHI should always be stored in locked areas, desks, and cabinets. Unless sponsor required, ePHI is to be deleted when it is no longer needed.

   The investigator is responsible for maintaining the privacy, confidentiality, and security of research subjects' data for as long as the investigator is in possession of such data. This includes only allowing access of research information only to those individuals who are approved by the MHC IRB to participate in the conduct of the study.

DO NOT:

1. Release research data to others (including other researchers or students) without first obtaining MHC IRB approval.
2. Store coding information with research files.
3. Use portable device for storing PHI (personal laptops , hand held devices, cell phones, thumb drives, and jump drives)

For more information see MHC Corporate policies:

1. MHC_CC0124 – Email Use
2. MHC_CC0106 –Acceptable Use of Technology Resources

2. **Maintain storage of records, data and specimens**
An investigator must retain a hard copy or electronic version of the submission, as well as the IRB notification letters, as part of their regulatory documentation. These materials may be maintained through eProtocol (all final and validated versions are on the ”Event History” section of the eProtocol application), on a secured drive, or via hard copy binder or filing system.

   The Office of Research Compliance and Quality Improvement can provide guidance on what other regulatory documentation is required as part of PI files and how best to maintain it.

3. **Ensure retention of Records - What to do with your data when you are finished**
Maintain your research records, including signed and dated consent documents, for at least seven years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least seven years after completion of the research. If your research is sponsored, contact the sponsor before disposing of human records. For institutional requirement on research record retention, reference HRPP policy: MHC_RP0114 – IRB Documentation and Research Record Retention.

4. **Proper establishment and operation of a repository** is a specific research project on its own. It must have its own IRB approval, in addition to the IRB approvals required for each research project using data and/or specimens from the repository. Subjects may be consented directly into the repository, or they may allow their information from another study to be submitted (when documented as an optional activity on a study-specific consent document). In addition, investigators can seek permission to obtain leftover clinical specimens for submission into the repository.

5. **Comply with the protocol, HRPP policies, applicable Federal regulations and laws**
Failure to follow the regulations governing human research; requirements or determinations of the IRB; or institutional policies, constitutes noncompliance. This definition may include action of any McLaren employee or agent, such as investigators, research staff, IRB members, IRB staff, employees or institutional officials.

Noncompliance is different from protocol deviations that occur during the course of clinical research. Very rarely, a protocol deviation may be considered noncompliance, when the deviation compromises the rights and welfare of subjects.

All reports of alleged noncompliance or inappropriate involvement of human subjects in research may come to the attention of the IRB from different sources and by various means. Alleged noncompliance reports may come from an IRB member, an investigator, a subject or subject's family member, institutional personnel, institutional committees, etc. Reports of alleged noncompliance or inappropriate involvement of humans in research are investigated by IRB, Office of Human Research or FDA when appropriate.

Important Definitions and Actions Taken by the MHC IRB:

Non-Compliance
Failure to follow the regulations, or the requirements or determinations of the IRB.

Serious Non-Compliance
Non-compliance that adversely affects the rights or welfare of subjects

Continuing Non-Compliance
A pattern of noncompliance that indicates a deficiency likely to result in further non-compliance, or circumstance in which an investigator fails to cooperate with investigation or correcting non-compliance

Suspension of a Study by the IRB
In cases of Serious Adverse Events (SAEs), Unanticipated Problems Involving Risks to subjects or others, researcher noncompliance, or protocol violations reported to the IRB, the IRB may suspend a study to ensure subject safety.

Termination of a Study by the IRB
Upon investigation of any SAE, UPIRSO, noncompliance, or protocol violations, the convened IRB may vote to terminate a study. A PI can address the issues that caused a termination via modification or protocol violation/exception report, as appropriate, in eProtocol unless the IRB specifically requires that the PI submit a new study.

Additional information can be found in the following HRPP policies:
MHC_RP0123 – Complains and Non-Compliance in Human Subject Research
MHC_RP0111 – Study Suspension, Termination and Investigator Hold
MHC_RP0124 – Reporting to Regulatory Agencies and Institutional Officials

What are the ClinicalTrials.Gov requirements?

Investigators must register clinical trials/investigation with a clinical trials registry that is electronically searchable and accessible to the public at no charge. The site for registration is maintained by the National Library of Medicine on www.clinicaltrials.gov. Under the HRPP policy, a **clinical investigation** is defined as, "any experiment that involves a test article and one or more human subjects.

Investigational drug is one for which the PI or a sponsor has filed an IND application or an approved drug that is being studied for an unapproved or approval use in controlled, randomized or blinded clinical trial.

Investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

Which McLaren Health Care "clinical trials" need to be registered on http://www.clinicaltrials.gov:

- Trials of Drugs/Biologics: Controlled, clinical investigations of a product subject to FDA regulations. This includes preliminary studies or phase I trials to be published in an ICMJE journal.
- Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.
- More data elements are required than under prior federal law, and these new requirements include:
    - Primary and secondary outcome measures;
    - Start date;
    - Target number of subjects; and
    - Adverse events.

For trials that are already registered, these new data fields, as well as the previous data fields, must be updated when there are changes to the study.
(* An "ongoing" trial has enrolled one or more subjects and the final subject has not been examined or received an intervention for the purpose of collecting data on the primary outcome).

What are the requirements for updating clinical trial registrations?

1. Unless there have been no changes, registration information must be updated no less than once every 12 months.
2. If recruitment status for the study changes (ex., recruitment suspended), the registration must be updated within 30 days.
3. If the trial is complete (whether concluded or terminated prior to conclusion), registration must be updated within 30 days.

Timing of Registration at ClinicalTrials.Gov
For new clinical trials, submission requirements are triggered by enrollment. The PI or sponsor must submit required information no later than 21 days after the first participant is enrolled.

For ongoing clinical trials already registered, new information must be posted. A trial that was enrolling subjects as of September 27, 2007 (even one which does not involve a "serious or life-threatening disease or

condition") must be registered and updated at least annually (see details below).

International Committee of MEDICAL JOURNAL EDITORS recommendations for registration
The ICMJE policy on registration of clinical trials has been revised to broaden the definition of clinical trials to include preliminary studies or phase I studies (Clinical Trial Registration JAMA 298; 93-4, 2007). The ICMJE has adopted the World Health Organization's definition of clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health related interventions to evaluate the effects on health outcomes." Health outcomes include any biomedical or health-related measures including pharmacokinetic measures and adverse events. However, the ICMJE states "Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration." The ICMJE's Frequently Asked Questions about Clinical Trials Registration states, "Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal."

The ICMJE policy applies to all trials that began enrollment on or after July 1, 2008.

Penalties for Failure to Register
There are now penalties for responsible parties who fail to register applicable clinical trials or who submit false or misleading information. Civil monetary penalties are allowed under FDA regulations. Civil penalties for investigator sponsors can range up to $10,000/day (see, Food and Drug Administration Amendments Act of 2007 (FDAAA Law)). For federally-funded trials, the penalties could include withholding or recovery of grant funds.

Where Can I Get Help?

Human Research Protections Program

HRPP staff holds office hours to help researchers, including graduate students and residents, who are preparing Institutional Review Board (IRB) submissions and exemption requests. Sessions are intended to help researchers, students, and their advisors navigate eProtocol (electronic IRB submission system) and learn about policies and review procedures.

Date: Mon, Wed, Fri
Time: 1:30pm - 4:30pm
Location: HRPP Office

PROCESS
No appointment is necessary. Please contact Markeda Richards at (248) 484-4950 or (248) 484-4952 or via email at Markeda.Richards@mclaren.org for questions or more information.

Human Research Protections Program
2701 Cambridge Ct., Suite 110
Auburn Hills, Michigan 48326
Tel: (248) 484-4950
Fax: (248) 276-9732
Email: hrpp@mclaren.org

McLaren Center for Research and Innovation

The McLaren Center for Research and Innovation offers researchers the following resources for the conduct of research:

1. **Protocol Development**
2. **Contracts and Budgets**
3. **Statistical Analysis**

PROCESS

1. Researchers interested in the resources must complete the appropriate request form
2. All completed forms must be emailed to clinicaltrialsprogram@mclaren.org or faxed to (248) 276-9731
3. The McLaren Center for Research and Innovation staff will contact the researchers and provide additional information about the requested resource.

Protocol Development

If you are interested in using the services of a protocol writer for your research study, please complete the Protocol Development Request Form found at: http://www.mclaren.org/Main/Research-Resource-Center1.aspx

Contracts and Budgets

If you need assistance with review and negotiations of budgets and contracts, please complete the Contracts & Budgets Form found at: http://www.mclaren.org/Main/Research-Resource-Center1.aspx

Statistical Analysis

If you need help with statistical analysis for your research study it is recommended that you contact us during the protocol development stage and also before submission to the IRB. Please complete the Statistical Analysis Request Form found at: http://www.mclaren.org/Main/Research-Resource-Center1.aspx.

Contact Information: All request forms must be emailed or faxed to the McLaren Center for Research and Innovation. Email MCRI@mclaren.org, Fax # (248) 276-9731. Address: 2701 Cambridge Ct. Suite 110, Auburn Hills, Michigan 48326.

APPENDECIES

Appendix A-1 - Additional Requirements for DHHS Regulated Research

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]

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

Appendix A-2 - 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.
        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.

[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

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:
        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.

[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

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 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.

[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

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 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.

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

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.
    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.

[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

Appendix B - 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 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 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 should inform a subject when medical care is needed for recurrent 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 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 written application to the IRB, the investigator 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 should supply a copy of the updated Investigator's Brochure to the IRB.
   c. During the trial the investigator should provide to the IRB all documents subject to review.

5. Compliance with Protocol
    a. The investigator 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 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. The sponsor or sponsor-investigator should include a description of the manufacturing, handling, and storage in accordance with applicable good manufacturing practice (GMP).
    b. Responsibility for investigational product accountability at the trial site rests with the investigator.
    c. Where required, the investigator should assign some or all of the investigator'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.
    d. The investigator and/or a pharmacist or other appropriate individual, who is designated by the investigator, 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.
    e. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
    f. The investigator should ensure that the investigational product are used only in accordance with the approved protocol.
    g. The investigator, or a person designated by the investigator, 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.
    h. 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 authorized 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 authorized 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 authorized 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 authorized 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 authorized 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 authorized 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 authorized representative, and by the person who conducted the informed consent discussion.
i. If a subject is unable to read or if a legally authorized 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 authorized representative, and after the subject or the subject's legally authorized 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 authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized 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 authorized 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 authorized 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 authorized 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 authorized 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 authorized representative (e.g., children, or incompetent patients), 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 authorized 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. (See "CHECKLIST: COGNITIVELY IMPAIRED ADULTS (HRP-417)" for full requirements related to adults who lack capacity to provide legally effective consent.)
o. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally authorized representative, if present, should be requested. When prior consent

of the subject is not possible, and the subject's legally authorized 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 authorized representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested (see HRPP policy MHC_RP0119 for full requirements related to emergency use.)

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 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 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 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.
    g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator 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 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 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 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 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 should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports