

Investigators Acting as Sponsors for Research

I. Policy Statement:

The purpose of this policy is to outline the requirements and review process for research studies where the Investigator will also serve as the Sponsor (also known as "Sponsor-Investigator (SI) initiated research). As defined in FDA regulations (21 CFR 312.3 and 812.3(o)), a Sponsor-Investigator is an individual who both initiates and conducts a Clinical Investigation, and under whose immediate direction a Test Article (i.e., an investigational drug, device, or biologic) is administered, dispensed, or used. The requirements of a Sponsor-Investigator include both those applicable to an Investigator and those applicable to a Sponsor.

This policy applies to any individual within the Trinity Health West Region who initiates a Clinical Investigation involving a Test Article where the individual is acting as both the Investigator and the Sponsor (i.e., is the holder of the IND or IDE and therefore assumes the duties of the Sponsor of the Clinical Investigation under the applicable FDA regulations); or is responsible for filing or receiving exempt notification from the FDA that an IND or other filing is not required. This also includes any Clinical Investigation involving patients.

II. Definitions:

Clinical Investigation: any experiment that involves a Test Article and one or more Human Subjects and that may or may not be subject to requirement for prior submission to the FDA under section 505(i) or 520(g) of the act, but the results of which are intended to be submitted later to or held for inspection by the FDA as part of an application for research or marketing permit. The term does not include experiences that are subject to non-clinical laboratory studies. Clinical trial, trial, clinical study are synonymous terms.

Human Subject: an individual who is or becomes a participant in research, either as a recipient of the Test Article or as a control subject. A Human Subject may be either a healthy human, or a patient. Subject, human subject, and research participant are synonymous terms.

Human Subjects Protection Program (HRPP): a comprehensive system designed to ensure the protection of the rights and welfare of subjects in Human Research. The HRPP is comprised of institutional leadership (Institutional Officials); Research Operations including individual investigators and research coordinators; Integrity –HIPAA and Billing; Research Compliance, which includes the Institutional Review Board (IRB), Conflict of Interest, Scientific Misconduct and other compliance activities; investigators and their study staff; and relevant Research Committees.

Investigational Device: A device that has not been approved by the FDA that is the object of a Clinical Investigation designed to evaluate its safety or effectiveness.

Investigational Device Exemption (IDE): An FDA-approval of the application for an exemption that permits an Investigational Device to be shipped and used in a Clinical Investigation.

Investigational New Drug: A drug or biologic that is the object of a Clinical Investigation. A drug may be considered "new" even if it has been previously approved by the FDA, if the Clinical Investigation seeks a change in the proposed use, formulation, route of administration, or labeling of the drug. The terms investigational drug and investigational new drug are synonymous.

Investigational New Drug Application (IND): The application submitted to the FDA which permits an Investigational Drug to be shipped and used in a Clinical Investigation. **Investigator:** An individual who conducts a Clinical Investigation and under whose immediate direction the Test Article is administered, dispensed, or used.

Medicare Coverage Analyses: This is a required documented analyses for all qualified clinical trials involving interventions (treatments) detailing which items and services are or may be invoiced to the patient insurer(s) or Sponsor. (Note: In this policy, there is not a sponsor/commercial company). For more information go to National Coverage Determination (NCD) for Routine Costs in Clinical Trials.

Non-Significant Risk Device: An Investigational Device that does not meet one or more of the criteria for a Significant Risk Device.

Protocol: is a formal document that is versioned, authored by the Sponsor-Investigator and possible collaborators that describes how a Clinical Investigation will be conducted includes the objective(s), design, methodology (inclusion/exclusion criteria, risks monitoring plans), statistical considerations and organization of a Clinical Investigation, and ensures the safety of the research subjects and integrity of the data collected.

Regional Health Ministry (RHM): includes the hospitals and the locations on the header of this document.

Significant Risk Device: An Investigational Device that may present a potential for serious risk to the health, safety, or welfare of a subject; and (1) is intended as an implant; (2) is used in supporting or sustaining human life; (3) is of substantial importance in diagnosing, curing, mitigating or treating a disease, or otherwise preventing impairment of human health; (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Sponsor: A person (or entity) who takes responsibility for and initiates a Clinical Investigation of a Test Article. The Sponsor may be an individual, a company, a governmental agency, academic institution, private organization, or other organization. The Sponsor does not actually conduct the Clinical Investigation unless the Sponsor is a Sponsor-Investigator.

Sponsor-Investigator: An individual who both initiates and actually conducts, alone or with others, a Clinical Investigation, i.e., under whose immediate direction the Test Article is administered, dispensed, or used involving a subject. The Sponsor-Investigator must be an individual.

Sub-Investigator: Any individual member of the research team other than the Principal Investigator.

Test Article: means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the Food and Drug Cosmetic Act.

III. **Equipment:** None

IV. **Procedure:**

Role and Responsibility of the Sponsor Investigator

Qualifications:

A. The investigator must comply with the following:

1. Have had previous experience conducting prospective, interventional, randomized controlled trials (Clinical Investigations) at one or more RHM's within the Trinity Health West Region or elsewhere.
2. Complete and submit Good Clinical Practice (GCP) training record.
3. Be in good standing and have no record of serious and/or continuing non-compliance in the conduct of research.
4. Complete and submit a Financial Conflict of Interest Disclosure Form annually, at the time of any changes, and upon each submission to the IRB. *Exclusion: A resident, student or fellow (or other trainee) is **not** eligible to hold the position of a Sponsor-Investigator; however, such an individual may be permitted to participate on the research team as a Sub-Investigator*

B. Responsibilities

In addition to the requirements of 21 CFR 312 and 21 CFR 812, investigators who hold an IND, IDE, PMA or 510K must also meet all regulatory requirements pertaining to Sponsors, appearing in other Food and Drug Administration parts, as applicable to the Test Article used in the research and,

- 21 CFR part 54 for requirements related to financial disclosures by clinical investigators, and,
- 21 CFR part 11 Electronic Records, Electronic Signatures

Links to the FDA guidance as well as a complete list of FDA Regulations are located at the end of this policy under the subheading **References**.

The Sponsor-Investigator is responsible for ensuring that the Clinical Investigation is conducted according to:

- sound research design and generally acceptable scientific methods
- all terms of contracts and/or signed agreement(s)
- the obligations specified in the signed Form FDA 1572, if applicable
- the Clinical Investigation plan (otherwise known as the Protocol) as approved by the IRB; and
- all applicable regulations and laws

Specific responsibilities include:

1. Ensuring institutional review process is followed.
2. Selecting qualified study team personnel, including a research coordinator, as defined by the Job Description, who has appropriate training and expertise to assist in the conduct of the proposed research according to regulatory requirements. This coordinator would need to be familiar with the RHM's processes for subject registration/enrollment, tracking visits to ancillary departments, and proper billing procedures for study-related services as they occur.
3. Providing study team member(s) with the necessary information and training to conduct the Clinical Investigation. Training should include methods detailed in the Protocol including but not limited to, obtaining consent, process of reporting adverse events, data collection and data

- monitoring plan. Evidence of the required education and training for all study team members must be submitted to the IRB.
4. Prior to initiation of the clinical investigation, a Medicare Coverage Analyses (MCA) will need to document research charges, standard of care and non-covered standard of care charges and confirm that according to Centers for Medicare and Medicaid it is a qualifying trial. The MCA will document whom or what entity will bear the costs that will be incurred during the clinical investigation such as through a subject's insurance and what will be paid for as part of the research. This is required by Centers for Medicare and Medicaid and must be signed by the Sponsor-Investigator. Proper tracking, coding and billing milestones will need to be documented to ensure timely and accurate billing to the payor, the study subject, or another funding mechanism, as determined in the research budget.
 5. Personally, conducting or supervising the proposed Clinical Investigation, including all of the following:
 - a. Conducting the Clinical Investigation in accordance with agreements, contracts, the Protocol, as filed with the FDA and IRB and any other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and the RHM where the Clinical Investigation is being conducted.
 - b. Supervising the use of the Test Article at their site and administering the Test Article only to subjects under the PI's personal supervision or under the supervision of a person whom the PI has formally delegated in the delegation log,
 - c. Obtaining the legally effective informed consent of the subject or the subject's legally authorized representative prior to the administration of a Test Article.
 - d. Protecting the rights, safety, and welfare of subjects.
 - e. Understanding FDA guidance on FDA expectations regarding supervision and task delegation to other research team members.
 6. Ensuring IRB approval is obtained before the clinical investigation activities begin, and again prior to the expiration of continuing review approval.
 7. Preparing, submitting and maintaining an IND or IDE application to FDA, and submitting the FDA approval letter to the IRB as part of the submission.
 8. Registering and maintaining the Clinical Investigation on clinicaltrials.gov that includes obtaining the NCT number prior to beginning the Clinical Investigation. Following IRB approval, a copy of the approved consent form must be posted on clinicaltrials.gov.
 9. Ensuring compliance with all FDA labeling requirements, as applicable.
 10. Maintaining adequate records of the disposition of the Test Article, including dates, quantity, and use by subjects; return of the unused supplies of the Test Article to the manufacturer or other disposition of unused supplies, and complying with any other applicable record-keeping and retention requirements for the Test Article, as set forth by the FDA.
 11. The Sponsor-Investigator and the institution are required to permit and facilitate monitoring and auditing, at reasonable times, by funding agencies, federal and state regulatory agencies, and others as appropriate.
 12. Fulfilling all the requirements of a Sponsor, ensuring proper monitoring of the Clinical Investigation in accordance with the plan documented in the protocol and submitted to the IRB.
 13. Ensuring prompt reporting of any unanticipated problem involving risk to subjects or others to the IRB, appropriate Institutional Officials and State and Federal regulatory agencies as appropriate in keeping with the IRB's policy on Unanticipated Problem and Adverse Event Reporting.

Review and Approval Process

A. Institutional Review

Reviews by the following members of the Human Subject Protection Program (HRPP) need to occur at each RHM where the clinical investigation will be conducted. The criteria evaluated must include, but is not limited to, Clinical Investigation objectives, sound scientific methods and study design, resources (people, drug/device acquisition etc.), costs (budget plans), plans for clinical investigation management (including data safety monitoring) and other relevant aspects. The proposed Protocol must have sufficient detail for reviewers (internal and those from FDA) to have an exact indication of the work proposed and contain background with references to support the objectives of contribution of unknown knowledge in the literature. (Refer to THWR Protocol Template). An institutional review will include, but is not limited to, the following:

1. Institutional official (IO) review and acknowledgment.
2. Legal counsel review (contracts, risk and insurance aspects).
3. Scientific and Feasibility review by the designated THWR Research Feasibility Committee.
4. Research operations review (budget, resources, Medicare Cost Analyses).
5. Privacy and security review, as applicable.
6. IRB review.

Each of these is detailed below and may not flow sequentially but will each be completed in accordance with the THWR research review processes.

B. Institutional and Federal Wide Assurance Considerations

Each Regional Health Ministry has designated an Institutional Official. Under an FWA, an institution commits to HHS that it will comply with the requirements set forth in 45 CFR part 46, as well as the Terms of Assurance.

The Sponsor-Investigator of the planned Clinical Investigation will need to present the proposed Protocol, to the local IO that includes addressing resources needed to perform the research as well as any costs detailed in a documented budget and identify risks to subjects, or others or to the RHM where the research will be conducted. The IO should acknowledge awareness of the planned research before it is reviewed by a Scientific Committee, the Institutional Review Board, Legal, and the Food and Drug Administration. The IO may request additional information by or from other internal or external resources prior to acknowledgement.

Any exceptions to this policy are at the full discretion of the Institutional Official and will be documented in the applicable research compliance file and the relevant IRB notified.

C. Legal, Insurance and Risk Management Assessment

Legal counsel will be consulted, and the appropriate agreements must be filed and signed by appropriate parties prior to the commencement of any Clinical Investigation. The type of agreement (or agreements) required will depend on the nature of the proposed research. Potential agreements needed for the proposed Clinical Investigation may include:

1. Contracts for drug, device, and/or biologic procurement.
2. Collaboration agreements for research involving non-employed colleagues, including contracted physicians or P.C. groups.
3. Data Use Agreements and/or Business Associate Agreements.
4. Material Transfer Agreements, and
5. Other contractual agreements deemed appropriate or necessary by legal counsel.

Legal counsel will engage Insurance and Risk Management, as appropriate, to assess whether the proposed research involves extenuating circumstances that may require additional coverage or insurance types to sufficiently cover the institution. Requests for contract review and preparation must be submitted to the RHM's legal counsel in accordance with the Trinity Health-West Region Leadership Policies on Contracts.

D. **Scientific Review**

The proposed Protocol that specifies the details of the Clinical Investigation must be formally reviewed by an independent scientific committee or board that has the experience and expertise to determine feasibility and scientific rigor of the proposed research. The committee is comprised of designated individual from all THWR ministries. at each local RHM to have institutional delegated. The scientific review occurs prior to Institutional Review Board consideration.

E. **Research Operation Review**

The research operational leader(s) at THWR sites is responsible for providing assistance in determining appropriate resources, risks, costs, and other operational factors, including but not limited to the following:

1. **Billing Considerations:** The Sponsor-Investigator will prepare an MCA in collaboration with the research coordinator or operation leader. the following billing aspects must be considered:
 - a. Follow peer-reviewed guidelines as to timing of procedures such as biopsies, scans and cardiac tests.
 - b. A **Phase I clinical trial** requires consultation with the Institutional Official and the Medicare contractor to determine coverage of the treatments and procedures to be used.
2. **Study Budget and Funding:**
 - a. Responsible for identifying sufficient funds to enable conduct of the research from sources that may include federal or foundation grants, pharmaceutical collaborators, and/or philanthropic funds.
 - b. Obtain prior written authorization from the FDA to charge for an Investigational Test Article as applicable.
 - c. Consult the Research Operations Director/Leader at the RHM where the research will be conducted as early as possible in Protocol development to obtain estimates for applicable costs including:
 - i. Research nurse/research coordinator/data manager effort.
 - ii. Personnel costs for coordination, monitoring and auditing of external sites, as applicable.
 - iii. Cost of statistical analysis.
 - iv. Credentialing or other processes for personnel necessary for conduct of the clinical investigation.
 - v. Specialized staff required for the clinical investigation (e.g., a technician with a special certification).
 - vi. Cost of having the Test Article manufactured, shipped, dispensed and stored.
 - vii. Cost of inspections/audits for compliance with Good Manufacturing Practices (GMP), if applicable.
 - viii. Cost of contracting with and monitoring the conduct of the research at all sites.
 - ix. Expenses for use of a CRO, if applicable; and
 - x. Expenses for an external Data and Safety Monitoring Board.

F. Privacy and Security Assessment

Collection of data, retention of records and maintenance of records will need to be sequestered as required by FDA regulations. If statistical analyses are being performed by an outside/external entity, it will be necessary to determine that privacy and confidentiality of the records are maintained as per HIPAA and the local THWR ministry policies. A Business Associate Agreement or Data Use Agreement may be needed depending on the proposed use of business partners.

G. Investigational Pharmacy and/or Supply Chain

It is incumbent upon the Sponsor-Investigator to meet with investigational pharmacy and the involved THWR supply chain manager to determine the procedures for Test Article procurement, dispensing, delivery, use and storage requirements. If a Test Article is being procured, it will be necessary to determine an appropriate channel of receipt and accountability within supply chain, investigational pharmacy, or other functional area within the THWR ministry.

Federal Government Requirements

A. Food and Drug Administration

The intent and nature of the Clinical Investigation will determine what governmental filings need to occur. The Sponsor-Investigator must determine if the proposed research will require an Investigational New Drug (IND) application and/or Investigational Device Exemption (IDE) and submit to the FDA accordingly. The Sponsor-Investigator is responsible for not only initial filing, but also on-going submissions, annual reports or other FDA regulated documents that are required for the research. Such filings include but not limited to: IND, IDE, PMA, 510K and determination of exemption.

Receipt of an exempt notification from the FDA that an IND or other applicable FDA filing will be required prior to IRB review. Any FDA notifications will need to be included in the IRB submission.

B. ClinicalTrials.gov

ClinicalTrials.gov is a database of privately and publicly funded Clinical Investigations conducted around the world. The Sponsor-Investigator must file the Clinical Investigation information on the FDA website, obtain an NCT number and maintain the filing through the life of the research at www.clinicaltrials.gov.

Human Subject Protection Review: THWR IRB and Privacy Board

A reviewing IRB is responsible for those duties set forth in, 21 C.F.R. Parts 312 (including 21 C.F.R. § 312.40), 21 CFR 812 and Parts 50 and 56. Those duties include, but are not limited to:

1. Determining if the Sponsor-Investigator has the medical expertise, qualifications, training, support, and facilities necessary to conduct the research that protects the human subjects, fulfills the scientific purpose of the Protocol and meets federal, state and local laws and regulations. If necessary, additional staff or an outside consultant may be required
2. Determining if there is an adequate and effective Data and Safety Monitoring Board or Plan. An outside Data Safety and Monitoring Board may be required or requested by the IRB.
3. If using an Investigational Device, determining if it meets the FDA definition of Significant Risk by considering the proposed use of the Investigational Device as well as any Protocol related procedures and tests in making their determination.

4. Ensuring Investigators who assume Sponsor functions are knowledgeable about the regulatory and institutional requirements involved.

IRB review conducted more frequently than the yearly standard may also be a requirement set by the IRB. Please note that a consent document will not be issued by the IRB for a proposed Clinical Investigation without the NCT number issued from www.clinicaltrials.gov.

- Appropriate contracts signed
- Scientific review is complete
- Medicare Coverage Analyses is complete and signed
- Receipt of written notification from the Institutional Review Board and Privacy Board of Record.

Please note that a consent document will not be issued by the IRB for a proposed Clinical Investigation without the NCT number issued from www.clinicaltrials.gov.

V. Ministry Specific Related Addendums, Procedures, and/or Policies:

- A. Saint Agnes Medical Center: None
- B. Saint Alphonsus Health System: None

VI. Additional Approval: Not applicable.

VII. References

For sponsor-investigator guidance when applying to the FDA for an IND, refer to Information for Sponsor Investigators Submitting Investigational New Drug Applications (INDs)

Clinical investigators either conduct a clinical trial or are the responsible party of a team of investigators. See 21 CFR 312.3 and 812.3(i). The clinical investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator's care. See 21 CFR 312.60 and 812.100. For further information, refer to "Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects"

Refer to 21 CFR part 54 for general requirements related to financial disclosures by clinical investigators and "Guidance for Industry - Financial Disclosure by Clinical Investigators".

For more information concerning electronic records and part 11 requirements, refer to 21 CFR part 11 and "Guidance for Industry: Part 11, Electronic Records, Electronic Signatures — Scope and Application".

Applicable Regulations:

List of Regulations: In addition to the requirements of 21 CFR 312 and 21 CFR 812, investigators who hold an IND or IDE must also meet all regulatory requirements pertaining to sponsors, appearing in other FDA parts, as applicable, as listed but may not be limited to:

For Drugs or Devices:

- 21 CFR 11 (Electronic records and electronic signature)
- 21 CFR 54 (Financial Disclosure by Clinical Investigators)

For Drugs and Biologics:

- 21 CFR 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General)
- 21 CFR 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals)
- 21 CFR 312 (Investigational New Drug Application)
- 21 CFR 314 (Drugs for Human Use)
- 21 CFR 320 (Bioavailability and Bioequivalence Requirements)
- 21 CFR 330 (Over the Counter (OTC) Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded)
- 21 CFR 601 (Biologics Licensing)

For Devices:

- 21 CFR 807 (Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices)
- 21 CFR 812 (Investigational Device Exemptions)
- 21 CFR 814 (Premarket Approval of Medical Devices)
- 21 CFR 820 (Quality System Regulation)
- 21 CFR 860 (Medical Device Classification Procedures)

Centers for Medicare and Medicaid:

- National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1)