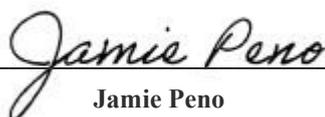


 <b>DIVISION OF RESEARCH &amp; INNOVATION</b> Research Integrity & Compliance		<b>Institutional Review Board</b> <b>Standard Operating Procedures</b>	
<b>Title:</b> FDA Regulated Research			
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<b>Date</b>	<b>Section</b>	<b>Author</b>	

**PURPOSE**

The purpose of this Standard Operating Procedure (SOP) is to describe the IRB oversight, to outline the responsibilities of Principal Investigators when participating in or leading FDA Regulated Research, and to describe the information that must be provided to the IRB regarding the oversight, operations, and procedures which will be used during the conduct of an FDA Regulated research study.

**SCOPE**

This SOP delineates systematic process activities and functions for compliance with the US Department of Health and Human Service, Office for Human Research Protections (OHRP), the Food and Drug Administration, Common Rule requirements, and University of North Texas (UNT) requirements for the management, coordination, and operation of the Institutional Review Board program and research that falls within the jurisdiction of the UNT IRB. It applies to all staff members whom are engaged in the operations and support of the Institutional Review Board, and to all UNT Researchers performing human subjects research.

**DEFINITIONS/ ABBREVIATIONS**

**1. Definitions**

- 1.1 *Biologic*: Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other

- technologies. In general, the term "drugs" includes therapeutic biological products.
- 1.2 *Clinical Investigation*: Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]
- 1.3 *Dietary Supplement*: A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. [21 U.S.C. 321(ff)]
- 1.4 *Emergency Use*: Emergency use is defined as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21 CFR 56.102(d)] Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating. Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.
- 1.5 *Humanitarian Use Device (HUD)*: A Humanitarian Use Device is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.
- 1.6 *Investigational Drug*: Investigational or experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.
- 1.7 *IND*: IND means an investigational new drug application in accordance with 21 CFR Part 312.
- 1.8 *IDE*: IDE means an investigational device exemption in accordance with 21 CFR 812.
- 1.9 *In Vitro Diagnostic Product (IVD)*: In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]
- 1.10 *Non-Significant Risk (NSR) Device*: A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.
- 1.11 *Researcher*: Any individual performing various tasks related to the conduct of human subjects research activities, including but not limited to obtaining informed consent from subjects, collecting and analyzing data, interacting with subjects, and communicating with the IRB.
- 1.12 *Significant Risk (SR) Device*: Significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [21 CFR 812.3(m)]

## **2. Abbreviations**

- 2.1 FWA- Federal Wide Assurance
- 2.2 IAA- IRB Authorization Agreement
- 2.3 IDE- Investigational device exemption in accordance with 21 CFR 812.
- 2.4 IND- Investigational new drug application in accordance with 21 CFR Part 312.
- 2.5 IRB- Institutional Review Board
- 2.6 OHRP- Office for Human Research Protections
- 2.7 PI- Principal Investigator
- 2.8 RIC- Research Integrity and Compliance
- 2.9 SOP/SOPs - Standard Operating Procedure(s)
- 2.10 SR- Significant Risk Device

## **RESPONSIBILITIES**

This SOP is applicable to all members of Research Integrity and Compliance and Institutional Review Board members who are involved in record keeping, reviewing, or approving research studies for the Institutional Review Board program. This SOP is also applicable to all UNT Researchers performing human subjects research under the oversight of the UNT Institutional Review Board.

## **PROCEDURE**

### **1. Investigator responsibilities include the following:**

- 1.1 The investigator holds additional responsibilities when conducting an investigation subject to FDA regulations. These responsibilities include, but are not limited to, the following:
  - 1.1.1 Indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.
  - 1.1.2 Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the FDA or IRB.
  - 1.1.3 Personally conducting or supervising the investigation. When study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
  - 1.1.4 Maintaining a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's

- CV on file and/or training conducted by the investigator or sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
- 1.1.5 Protecting the rights, safety, and welfare of subjects under their care during an investigation, including:
    - 1.1.5.1 Informing subjects that the test article is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met.
    - 1.1.5.2 Providing or arranging for reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention.
    - 1.1.5.3 Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
    - 1.1.5.4 Adhering to the protocol so that study subjects are not exposed to unreasonable risks.
    - 1.1.5.5 As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.
  - 1.1.6 Reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
  - 1.1.7 Maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA.
    - 1.1.7.1 These records include, but are not limited to:
      - 1.1.7.1.1 Correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA;
      - 1.1.7.1.2 Drug and device accountability records;
      - 1.1.7.1.3 Case histories; consent forms; and
      - 1.1.7.1.4 Documentation that consent was obtained prior to any participation in the study.
    - 1.1.7.2 Records must be obtained for a minimum 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. For clinical investigations of medical devices, required records must be maintained for a period of 2 years after the latter of the following two dates:
      - 1.1.7.2.1 The date on which the investigation is terminated or completed; or
      - 1.1.7.2.2 The date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
    - 1.1.7.3 Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
  - 1.1.8 Controlling test articles according to FDA regulations and the Controlled Substances Act, if applicable.

- 1.2 For research reviewed by the UNT IRB, the investigator proposing the investigation is required to provide a plan, to be evaluated by the IRB, that includes storage, security, and dispensing of any test article.
  - 1.2.1 The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB for acceptability.
  - 1.2.2 Investigational drugs and devices must be labeled in accordance with federal and state standards.
  - 1.2.3 All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device, and the disposition of remaining devices at the conclusion of the investigation.
- 1.3 If applicable, the investigator shall provide all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
- 1.4 The investigator is required permit inspection of research records by the sponsor, sponsor representatives, The Department of Research and Innovation and Research Integrity and Compliance representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.
- 1.5 For emergency use of test articles, Principal Investigators are asked to contact the UNT IRB immediately and prior to use of the test article. Principal Investigators must report emergency use of test articles immediately, but no later than **2** working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
- 1.6 Researchers requesting to use investigational drugs under compassionate use should contact the IRB to discuss if your study is appropriate for compassionate use, the method to submit an appropriate plan, and the schedule for treating and monitoring the participant. The plan must always include monitoring to detect any possible problems arising from the use of the drug.
- 1.7 To request IRB approval for single patient expanded access, investigators should contact the IRB office to discuss if your study is appropriate. You must also submit the following:
  - 1.7.1 A completed application and any additional documentation noted within it;
  - 1.7.2 A copy of the LOA from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval;
  - 1.7.3 A copy of the information submitted to the FDA (and FDA approval, if available);
  - 1.7.4 A copy of the Investigator's Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational drug;
  - 1.7.5 A copy of the plan for treating and monitoring the patient; and
  - 1.7.6 A copy of the draft informed consent document.
- 1.8 Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research include, but are not limited to
  - 1.8.1 Prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate

apparent immediate hazard to the subject (in which case it must be promptly reported);

1.8.2 Reporting of unanticipated problems, noncompliance, complaints, and other reportable information; and

1.8.3 Continuing review and study closure.

1.9 Copies of any submissions or follow-up submissions to the FDA must be submitted to the UNT IRB within 5 business days of the date of submission to the FDA.

## **2. Use of Regulated Drugs or Devices in Research**

2.1 For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug or device under FDA regulations, the investigator must indicate on the IRB application whether an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the Principal Investigator. Documentation of the IND/IDE could be a:

2.1.1 Industry sponsored study with IND/IDE number indicated on the protocol;

2.1.2 Communication with/from FDA;

2.1.3 Communication with/from industry sponsor; or

2.1.4 Other document and/or communication verifying the IND/IDE.

2.2 For investigational devices, the study may be exempt from IDE requirements (IDE-exempt) or, in the case of Non-Significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a device study is identified as IDE-exempt or NSR, then the Principal Investigator should include documentation with the submission providing the basis for IDE-exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the device as used in the study is IDE-exempt or NSR, documentation of that determination must be provided.

## **3. Use of Dietary Supplements in Research**

3.1 Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

3.2 Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose).

3.3 Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply.

3.4 Whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. This is determined by the IRB.

3.4.1 If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required.

3.4.2 However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

3.5 The Principal Investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify

whether the research requires an IND.

- 3.5.1 Applications should provide detail consistent with that expected on a drug protocol and consistent with the level of risk associated or anticipated with the research.
- 3.5.2 At a minimum, the research plan should provide the following information regarding the supplement:
  - 3.5.2.1 Name;
  - 3.5.2.2 Manufacturer;
  - 3.5.2.3 Formulation;
  - 3.5.2.4 Dosage;
  - 3.5.2.5 Method/Route of administration;
  - 3.5.2.6 Mechanism of action;
  - 3.5.2.7 Known drug interactions;
  - 3.5.2.8 Risk profile;
  - 3.5.2.9 IND number (or justification for why an IND is unnecessary);
  - 3.5.2.10 Documentation of approval for use in humans; and
  - 3.5.2.11 Documentation or certification of quality or purity.
- 3.5.3 There should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return.
- 3.5.4 A plan for Data and Safety Monitoring must be included.

#### **4. IRB Responsibilities**

- 4.1 FDA guidance and regulations will be followed to determine if an IND necessary. Similarly, FDA guidance regulations will be followed to determine if an IDE is necessary.
- 4.2 Unless the conditions that permit an emergency use exemption, under FDA Guidance, are satisfied, UNT IRB approval must be obtained prior to initiating research activities.
- 4.3 UNT IRB staff determine which FDA regulations, if any, apply to a research study during pre-review of the IRB application materials provided by the researcher, in the absence of specific information from the FDA. The assessment may require obtaining additional information from the researcher, the sponsor, and/or the FDA.
- 4.4 Researchers who are using a drug, medical device, biologic, supplement, or botanical must provide the IRB with the information necessary to conduct a review.
- 4.5 UNT IRB staff conduct a pre-review of the application materials provided by the researcher. The FDA-relevant purpose of the pre-review is to:
  - 4.5.1 Determine whether FDA regulations apply to the research, following the procedures described above and, if yes, which FDA regulations.
  - 4.5.2 Determine the level of IRB review, by a full convened IRB, or eligibility for expedited (“minimal risk”) review.
    - 4.5.2.1 The existence of, or apparent need for, an IND or IDE disqualifies the study for expedited review.
  - 4.5.3 The FDA requires sponsors and sponsor-investigators to determine whether an IND or IDE is required for a study. If the IRB believes that the study requires an IND or IDE but the researcher and/or sponsor do not, the IRB has the authority to require the researcher and/or sponsor to provide or obtain confirmation from the FDA that an IND or IDE is not required. The FDA expects the IRB to confirm any IND or IDE before the study begins. When possible, this confirmation is obtained by HSD staff during the pre-review process. It consists of obtaining documentation from the researcher or

- sponsor that:
  - 4.5.3.1 Is from the sponsor, FDA, or a multi-site coordinating center;
  - 4.5.3.2 Refers to the specific research; and
  - 4.5.3.3 Provides the IND or IDE number assigned by the FDA.
- 4.6 For studies with an investigational device, the IRB must determine whether the use of the device involves “significant risk” or “non-significant risk”. The risk determination is specific to the use of the device in the proposed study.
  - 4.6.1 The researcher is responsible for providing the IRB with any information relevant to this determination, including a copy of the FDA’s determination (if one has been made).
  - 4.6.2 The sponsor is required by FDA regulations to provide the IRB with its risk assessment and rationale.
- 4.7 The FDA does not routinely make a risk assessment except in connection with an IDE application from the sponsor.
  - 4.7.1 If the sponsor believes that the use of the device is “non-significant risk”, then an IDE application is not required by the FDA and there will be no FDA determination.
  - 4.7.2 If the researcher has submitted an IDE application to the FDA, then approval of the IDE by the FDA indicates that the FDA considers the device to be significant risk.
  - 4.7.3 When the IRB believes that an FDA risk determination is important to obtain, it may be possible for the researcher to consult with the FDA. However, it may be necessary for the sponsor to submit an IDE application to the FDA in order to obtain a risk determination. The IRB should carefully consider whether there are other sources of information about the risk and whether the additional information gained from an FDA determination is worth the considerable time and effort to prepare an IDE application and have it reviewed by the FDA.
  - 4.7.4 When the FDA has already made a risk determination:
    - 4.7.4.1 If the determination was “significant risk”:
      - 4.7.4.1.1 The FDA’s decision is final and the IRB’s determination must concur.
    - 4.7.4.2 If the determination was “non-significant risk”:
      - 4.7.4.2.1 The IRB may choose to concur with the FDA or it may override the FDA’s determination with a “significant risk” determination. When the review is being done by the expedited process, the expedited reviewer(s) may concur but if they believe the determination might more appropriately be significant risk, the review should be transferred to the full convened IRB.
- 4.8 The IRB’s decisions are based on some or all of the following materials:
  - 4.8.1 Risk determination already made for this study;
  - 4.8.2 Risk determination for other uses of the device;
  - 4.8.3 Information in the database maintained by the device division of the FDA;
  - 4.8.4 Sponsor’s risk assessment and rationale;
  - 4.8.5 Researcher’s risk assessment and rationale;
  - 4.8.6 Nature and description of the device, including its inherent risks-
  - 4.8.7 Description of procedures and tests that are required because of the device; For example, the IRB must consider the potential harm caused by a surgical procedure necessary to implant a device as well as the potential harm caused

- by the device itself;
- 4.8.8 Subject population and selection criteria. The use of a device may have more potential for harm in certain subject populations than in others – for example, subject populations comprised of frail elderly individuals with significant health issues;
- 4.8.9 Reports of any prior investigations conducted with the device;
- 4.8.10 Review of this device and study by other IRBs; and
- 4.8.11 The risk determination interacts with the requirement for an IDE. If the IRB determines that the device is “significant risk”, the study must have an IDE application approved by the FDA and documented for the IRB.
- 4.9 The FDA has additional requirements for consent processes and forms. The IRB must confirm that the requirements have been met. The IRB does not approve the research until any missing elements have been provided. The requirements are:
  - 4.9.1 A statement indicating that the FDA may review subject medical records and research records which identify the subjects;
  - 4.9.2 For applicable clinical trials: A statement informing subjects that the clinical trial has been registered with the ClinicalTrials.gov database, and that some research data will be submitted to the database. The FDA regulation (21 CFR 50.25(c)) specifying this requirement provides the exact statement that must be used, without revision; and
  - 4.9.3 The IRB reviews the Investigator Brochure to ensure that the risk information in the consent form conforms to the information in the Brochure. For device studies, the IRB includes a consideration of the risks of implants, the possible need to remove them, and how removal would be managed and funded.
- 4.10 FDA allows a waiver of consent based on the minimal risk criteria but does not allow for a waiver of consent for public service and demonstration projects (i.e., the criteria described at 45 CFR 46.116(c)).
  - 4.10.1 The FDA allows a waiver of documentation of consent, but in more limited circumstances than is allowed by the HHS (“Common Rule”) regulations.
  - 4.10.2 There are two important FDA requirements.
    - 4.10.2.1 The FDA requires all electronic consent processes to meet certain regulatory requirements (reference 8.11), Most of which pertain to the nature and security of the electronic system.
    - 4.10.2.2 When the subject’s signature is not personally witnessed by a member of the study team, the e-signature must be accompanied by some method to verify the identity of the consent form signer.
- 4.11 Depending upon the item and the risks associated with its use, the UNT IRB may require information and documentation about the manufacture of the item.
- 4.12 FDA regulations require sponsors and researchers to provide adequate control, tracking, and handling of investigational items. The IRB must review the plans. The plan, as outlined in the IRB application materials, is assessed for the presence of the following elements of control:
  - 4.12.1 Provide the investigational item only to participants under the researcher’s direct personal supervision or under the supervision of a co-investigator who is directly responsible to the researcher;
  - 4.12.2 Maintain accurate, complete, and current records about the use of the item, including records of receipt, use, or disposition of the item. This typically includes dates, names, identification numbers such as lot numbers or code numbers, and (for drugs) amount dispensed; and
  - 4.12.3 The IRB has the authority to require that the research use of investigational

drugs be managed through a pharmacy service.

- 4.13 IRB approval is required before the investigational test articles are used. Standard procedures for IRB submissions, and organizational approvals are to be followed. The UNT IRB will consider reliance upon an external IRB under an IRB Authorization Agreement for test article protocols on a case-by-case basis when an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the [untirb@unt.edu](mailto:untirb@unt.edu) to discuss IRB Authorization Agreements.

## **REFERENCES**

1. US Department of Health and Human Service, Office for Human Research Protections (OHRP)
2. 45 CFR 46
3. 21 CFR 312.8
4. 21 CFR 812.25

## **APPENDICES**

1. IRB SOPs