

7.0 Drugs and Devices in Research

7.1 Drug Policy

All drugs, agents and/or biologics used in human subjects research under the purview of Pennington Biomedical Research Center IRB shall be stored, handled, and dispensed in compliance with regulations or requirements of the FDA, the Louisiana Board of Pharmacy (LABP), federal, state and other laws and regulations, and the policies and procedures of the HRPP. Furthermore, if research is conducted on Pennington Biomedical Research Center premises, such research shall be conducted in accordance with applicable institution and medical staff policies and guidelines.

All drugs, agents and/or biologics used in human subjects research requires approval from government regulatory agencies to use investigational drugs and devices in research. For organizations in the US, this means complying with requirements of the US FDA. For organizations outside the US, the approval to use investigational drugs and devices comes from the relevant authority in that country.

Pennington Biomedical Research Center Pharmacy provides administrative and clinical services to Investigators and research staff involved in drug-related research conducted at Pennington Biomedical facility under the purview of Pennington Biomedical Research Center's IRB. Furthermore, a Pennington Biomedical research pharmacist may be consulted by the IRB to have complete information about all IRB approved research that takes place at the facility.

Regardless of whether Investigators conduct drug studies for inpatients or outpatients, the institution's policy requires that the IRB review and approve all drug research involving human subjects prior to initiation of the study and prior to enrollment of subjects. When an IND is required by regulation or by IRB determination, the IRB staff ensures that research involving an investigational drug does not commence until a valid IND is in place. This includes recruiting, obtaining consent and screening participants for a specific study that is subject to the IND.

In general, the IND regulations in part 312 require that human research studies be conducted under an IND if **all** of the following conditions exist:

- The research involves a drug as that term is defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(g)(1)).
- The research is a clinical investigation as defined in the IND regulations (21 CFR 312.3).
- The clinical investigation is not otherwise exempt from the IND requirements in part 312.

If the investigational drug requires an IND, the IRB staff will verify the IND number by requiring the sponsor's protocol or the FDA correspondence. The pharmacist will review any study that involves an investigational drug.

If the IRB determines that an IND is needed, the Investigator/sponsor must submit an IND application to the FDA and provide documentation of the outcome of the FDA determination (IND number) to the IRB before the IRB gives approval to enroll subjects in the study.

When the IRB determines that an IND may be required, the Investigator/sponsor must consult with the FDA. See [FDA Guidance for Industry: Investigational New Drug Applications \(INDs\) - Determining Whether Human Research Studies Can Be Conducted Without an IND, Section VIII. Process for Addressing Inquiries Concerning the Application of IND Requirements.](#)

If the FDA determines that the IND is exempt, the Investigator will receive a letter to that effect which must be uploaded into IRB Manager. If the FDA requires an IND application, all documentation from the FDA and from the sponsor/Investigator of the IND must be uploaded into IRB Manager.

Regulations & Guidelines: FDA 21 CFR 11; 21 CFR 54; 21 CFR 210; 21 CFR 211; 21 CFR 312; 21 CFR 314; 21 CFR 320; 21 CFR 330; 21 CFR 601; 21 CFR 807; 21 CFR 812; 21 CFR 814; 21 CFR 820; 21 CFR 860

7.2 Definitions

Administer: Means the direct application of a drug to the body of a research subject by injecting, inhalation, ingestion, or any other means. (LA R.S. 37:1164).

Agents: are chemical agents that affect the function of living things.

Biologic: a substance made from a living organism or its products and used in the prevention, diagnosis, or treatment of certain health conditions.

Biological Products: are subsets of drugs used for the treatment, prevention or cure of disease in humans. FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Biological products, like other drugs, can be studied in clinical trials involving humans subjects under an IND in accordance with the regulations at 21 CFR 312.

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 FDA under section 505 of the Federal Food, Drug, and Cosmetic Act the FDA Act) (21 U.S.C. 355) or to, or held for inspection by the Food and Drug Administration FDA) as part of an application for a research or marketing permit. (21 CFR 50.3)

Dietary Supplement: is defined by Dietary Supplement Health and Education Act of 1994 (DSHEA), as a product (other than tobacco) intended to supplement the diet that bears or contains one or more dietary ingredients. 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.-Dietary supplements are taken by mouth and can be found in many forms such as tablets, capsules, softgels, liquids, gelcaps, or powders.

- When a lawfully marketed dietary supplement is being studied for its effects on **diseases** (i.e., to cure, treat, mitigate, prevent, or diagnose **disease** including its associated symptoms) it is an investigational new drug and is subject to the 21 CFR 312 IND requirements. However, Investigators may request an exemption from 21 CFR 312 directly from the FDA.
- When a lawfully marketed dietary supplement is being studied for its dietary supplement use (i.e., structure and/or function claims), it is not an investigational new drug and is not subject to the 21 CFR 312 IND requirements. Structure and function claims are statements that describe the effect a dietary supplement may have on the structure or function of the human body.

Dispense: means the interpretation, evaluation, and implementation of a prescription drug order, including the preparation and delivery of a drug or device to a patient or patient's agent in a suitable container appropriately labeled for subsequent administration to, or use by, a patient. Dispense necessarily includes a transfer of possession of a drug or device to the patient or the patient's agent. (LA R.S. 37:1164). Louisiana law requires that dispensing may only be done by a licensed pharmacist or a physician who is registered with the board as a dispensing physician. (LA R.S. 37:1201).

Distribute or Distribution: means the delivery of a drug or device other than by administering or dispensing.

Drug: means: a) any substance recognized in the official compendium, or supplement thereto, designated by the Louisiana Board of Pharmacy or other appropriate jurisdiction) for use in the diagnosis, cure, mitigation, treatment or prevention of diseases in humans, b) any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans, or c) any substance other

than food intended to affect the structure or any function of the body of humans. (LA-R.S. 37:1164).

GRAS: refers to a product containing substances generally recognized as safe. Substances designated as GRAS for use in food are generally not approved as drug products. A clinical investigation of a GRAS substance that is intended to evaluate the product's ability to diagnose, cure, mitigate, treat, or prevent disease requires an IND under part 312, unless the substance to be studied is also a lawfully marketed drug and the clinical investigation meets the criteria for exemption under 21 CFR 312.2(b).

[FDA Guidance for Clinical Investigators, Sponsors, and IRB: Investigational New Drug Applications \(INDs\) – Determining Whether Human Research Studies Can Be Conducted Without an IND](#)

Investigational Drug: means a new drug or biological that is used in research. It also includes a biologic used *in vitro* for diagnostic purposes. The FDA considers the term investigational new drug or investigational drug to be synonymous with investigational drug (FDA 21 CFR 312.2). However, for purposes of this document, an investigational drug includes the following:

- An approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.
- Those new drugs for which the Investigator or a sponsor has filed an IND application (FDA 21 CFR 312) which are exempt from pre-marketing approval requirements and may be lawfully shipped for use in clinical investigations in human subjects.

A drug that is lawfully marketed in the U.S. that may still be considered investigational and required that an IND be filed if the proposed use of such a drug involves a controlled study aimed towards seeking a significant change in labeling, advertising, route of administration, dosage level, dose regimen, or other factor that affects the risks associated with the use of the product (FDA 21 CFR 312.3 (b)). The clinical investigation of a drug product that is not lawfully marketed in the United States requires submission of an Investigational New Drug (IND) Application to the FDA, unless exempt according to 21 CFR 312.2.

Investigational New Drug Application or “IND”: refers to either an investigational new drug application or to a new drug that is used in clinical investigations. IND is synonymous with Notice of Claimed Investigational Exemption for a New Drug (FDA 21 CFR 312).

Off-Label Use: means the use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. In general, research involving off-label use requires an IND or IDE (Investigational Device Exemption, if using a device) application.

Regulations & Guidelines: [FDA “Off-Label and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet](#)

Test Article: Is any drug including a biological for human use), medical device for human use, human additive, color additive, electronic product, or any other article subject to FDA regulation (FDA 21 CFR 50.3(j); 21 CFR 56.102 (l)).

7.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the EPA or the Food Safety and Inspection Service of the U.S. DOA (FDA 21 CFR 56.104 (d)).

7.4 IND Requirements

The Investigator must indicate on the initial IRB application whether the research involves investigational drugs. If so, the Investigator must indicate if there is an IND for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND could be:

- Industry sponsored protocol with IND.
- Letter from FDA.
- Letter from industry sponsor.

If the research involves drugs and there is no IND, the Investigator must provide a rationale why it is not required.

The IRB staff or the IRB will determine:

- Whether there is an IND and if so, whether there is appropriate supporting documentation.

- If the research involves drugs or devices with no IND, and whether the research meets the criteria below.

7.4.1 IND Exemption

In general, Investigational New Drug (IND) regulations (21CFR312) apply in human research studies that involve use of a drug (as defined in the Food, Drug, and Cosmetic

Act (FD&C Act)) in a clinical investigation (as defined in 21CFR312.3) unless otherwise exempt from IND requirements.

Clinical investigations of lawfully marketed drug or biologic are exempt from IND requirements if **all** of the six criteria below are met:

- i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
- ii. it is not intended to support a significant change in the advertising for the product;
- iii. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
- v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
- vi. it does not intend to invoke 21 CFR 50.24.

The three most commonly occurring scenarios when clinical investigations may be exempted from the IND application requirements refer to:

1. certain limited situations of clinical investigations with approved marketed drugs;
2. bioavailability or bioequivalence studies; and
3. clinical investigations involving radioactive drugs considered safe for certain research uses.

For each of these and few other scenarios, the specific criteria for exemption must be met (21 CFR 312.2(b)).

The following are also exempt from the IND requirements: a) a clinical investigation involving use of a placebo if the investigation does not otherwise require submission

of an IND; and b) a drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

- It involves one or more of the following: a) Blood grouping serum, b) Reagent red blood cells or c) Anti-human globulin;
- It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
- It is shipped in compliance with 21 CFR 312.160.

Regulations & Guidelines: [FDA Guidance for Clinical Investigators, Sponsors, and IRB: Investigational New Drug Applications \(INDs\) – Determining Whether Human Research Studies Can Be Conducted Without an IND](#)

7.4.2 Responsibilities

This section describes the responsibilities and related responsibilities for handling investigational drugs or unlicensed test articles with respect to pharmacy, inventory control, reporting and documentation.

Regulations & Guidelines: FDA 21 CFR 312.61; 21 CFR 312.62; 21 CFR 312.69

7.4.2.1 Investigator Responsibilities - IND Determination

The Investigator is responsible for submitting sufficient information to the IRB to ensure proper IND determination. Required information may include, but is not limited to the following:

- Investigator's Brochure
- Package insert
- Summary of prior use/investigations
- FDA correspondence
- Plan for receipt, storage, control, labeling, and dispensing of drug
- A copy of any available supporting documentation (e.g., letter from the sponsor or FDA, other basis for determination) supporting claim that an IND is not required.

7.4.2.2 Investigator Responsibilities - Control of the Investigational Drug

An Investigator conducting a clinical investigation under an IND application is responsible for ensuring that the investigation is conducted according to the signed Investigator's statement Form 1572, the investigational plan, and the applicable Investigator's and sponsor's responsibilities including provisions for disqualification of clinical Investigators (21CFR 312.50-312.70). In addition, an Investigator is responsible for ensuring that the research is conducted according to Pennington Biomedical policies and procedures and must protect the rights, safety, and welfare of subjects under the Investigator's care and the control of drugs under investigation.

For Pennington Biomedical Research Center inpatients and outpatients, investigational drugs for research studies must be dispensed by the Pennington Biomedical research pharmacy. If a licensed Investigator by the Louisiana Board of Pharmacy requests to have control of the investigational drug agent or biologic then the Investigator must submit for IRB approval a plan for the distribution, storage, dispensing, accountability and destruction or return of drug at completion of the study for the investigational drug products.

An Investigator is expected to administer the drug only to subjects under the Investigator's personal supervision or under the supervision of a subordinate research staff responsible to the Investigator. The Investigator must not supply the investigational drug to any person not authorized to receive it. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

- **Dispensing to inpatients:** For participants in the inpatient unit of Pennington Biomedical Research Center, the Investigator must use the research pharmacy as the coordinating and control center for the research drug. As the coordinating and control center, the research pharmacy assumes the responsibility for maintaining records of the drugs delivered to the research pharmacy, inventory of the drug, dispensing of drugs to research subjects, and then return to the sponsor or disposition of unused product. The Pennington Biomedical research pharmacy will store and dispense the

investigational drug as specified by the sponsor and in accordance with applicable regulatory requirements.

Pennington Biomedical's research pharmacy may initiate or adjust drug therapy and/or order laboratory tests associated with a research protocol when requested to do so by the Investigator. Any pharmacist participating in such a protocol must be trained and deemed competent to participate by the Investigator or his/her designee). Specific details on the adjustment of drug therapy or ordering of laboratory tests should be reviewed during the protocol initiation visit.

When Pennington Biomedical research pharmacy is the coordinating and control center for the research drug, the research pharmacy will store the returned dispensed investigational drug in a designated return area when a study protocol requires the subject to return the empty investigational drug container or any amount of the unused investigational drug. However, it is the responsibility of the Investigator or Investigator staff to deliver the returned dispensed investigational drug to research pharmacy when subjects leave the dispensed investigational drug in the outpatient clinic.

In coordinating the control of the research drug, the Investigator will forward a copy of the complete research protocol, a copy of the Investigator's drug brochure, research pharmacy manual, ordering procedures, any special storage, handling or preparation requirements, and any pertinent dispensing information to the research pharmacist.

A cost estimate should be obtained from research pharmacy during the initial stages of budget development. A pharmacy fee will be applied to all research involving investigational drugs. The research pharmacy will prepare a cost estimate of pharmacy fees after review of the above material.

- **Dispensing Controlled Substances:** controlled substances must be securely stored and must be dispensed by a duly licensed pharmacist.
- **Dispensing to Outpatients:** If a licensed Investigator by the Louisiana Board of Pharmacy requests to have control of the investigational drug agent or biologic then the Investigator must submit for IRB approval a plan for the distribution, storage, dispensing, accountability and destruction or return of drug at completion of the study for the investigational drug products.
 - **Drug Accountability Record** - The Investigator must maintain records of the product's delivery to the study 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, and the unique code numbers assigned to the investigational products and trial subjects. The Investigator should maintain records that document adequately that the subjects will provide the doses specified by the protocol and reconcile all investigational products received from the sponsor. The investigational drug supply is subject to audit by the IRB.

In regard to the use by each subject, Investigators should maintain drug accountability records that document adequately which subjects received the drug; when the subjects received the drug; the specific dosage the subjects received; and any returned amount of the dispensed investigational drug.

- **Drug Storage** - Investigational products should be stored as specified by the Sponsor and in accordance with applicable regulatory requirements. Storage guidelines, include:
 - Storage area is large enough for the supply of study drug.
 - Storage area can be locked.
 - Investigational drug is stored separately from other compounds.
 - Non-dispensed drug is stored separately from returned dispensed drug.
 - If the study protocol requires the subject to return the empty investigational drug container or any amount of the unused investigational drug, it is the Investigators responsibility to store the returned dispensed Investigational drug separately from the non-dispensed investigational drug.
 - It is the responsibility of the Investigator to deliver the returned dispensed investigational drug to the research pharmacy if it is the coordinating and control center for the research drug.
 - Inventory control procedures are used.
 - Any environmental controls are maintained.
 - Access is limited to study staff.
 - Controlled substances are not allowed to be stored outside Pennington Biomedical Research Center research pharmacy.
- **Drug Labeling for Investigational Drugs** - The following labeling requirements are required for investigational new drugs:

- The immediate package of an investigational new drug intended for human use shall bear a label with the statement, *Caution: New Drug – Limited by Federal or U.S. law* to investigational use (FDA 21 CFR 312.6).
 - The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular way and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated (FDA 21 CFR 312.6).
 - Participant Identifier
 - Protocol number or name
 - Strength of drug
 - Dose
 - Directions for use or administration
 - Quantity dispensed
- **Drug Labeling for Drugs:** Louisiana rules and Pennington Biomedical Research Center require that all drugs dispensed shall contain a medication label with the following:
- Pharmacy name, address and phone number
 - Prescription number
 - Name of prescriber
 - Patient's name
 - Date dispensed
 - Drug name and strength
 - Directions for use or administration
 - Pharmacist's name or initials
 - Auxiliary labels, if applicable
 - Indication that it is an investigational drug, if applicable
- **Drug Administration** – Investigational drugs shall be administered in accordance with any applicable federal or state laws and regulations and in accordance with any policies or procedures set forth by Pennington Biomedical Research Center. An informed consent document signed and dated by the subject and the Investigator must be in place before administering the drug.

A person licensed within State of Louisiana and so authorized by their professional scope of practice shall administer an investigational drug to a subject. An Investigator may designate the responsibility of administering the drug only after the designee has been given and has demonstrated an understanding of basic information about the drug according to the

protocol. This education and delegation of responsibility must be documented.

Regulations & Guidelines: FDA 21 CFR 312.61

- The Investigator shall report all unanticipated problem involving risks to subjects or others to the IRB according to the procedures outlined in section 8 and all protocol violations and protocol deviations see section 9.0 (FDA 21 CFR 312.64). For research involving investigational new drugs:
 - The Investigator is required to inform research pharmacy that the IRB has approved the protocol through submission of the IRB approval letters.
 - The Investigator must inform the IRB and pharmacy when a study involving investigational drugs has been terminated by the sponsor.
 - The Investigator will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.
 - The Investigator will insure the investigational products are manufactured, handled and stored in accordance with applicable good manufacturing practice.
 - Where allowed or required, the Investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator.
 - The Investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants.
 - Investigators should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.
 - The Investigator will maintain the following:
 - Current curriculum vitae (CV)
 - Protocol
 - Records of receipt and disposition of drugs

- List of any co-Investigators with their CV
 - Certification that all physicians, dentists, physician's assistants, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and
 - Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the Investigator considers that the event is not related to the drug. All unexpected, serious adverse effects shall be reported immediately to the IRB in the manner defined by the protocol and this document.
 - IRB letters of approval.
 - Other documents as outlined in the human subject protection program standard operating procedures.
- Investigator-sponsor or Investigator-initiated studies – When an Investigator files an IND or IDE, the Investigator is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations.

An individual or group of individuals or organization is considered a sponsor for an investigation if they hold the IND or IDE.

The research plan asks the Investigator if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed and will comply with the regulatory responsibility of a sponsor.

The sponsor or the Investigator has responsibilities which includes the following:

- Selecting qualified Investigators
- Providing Investigators with the information they need to conduct the investigation properly
- Ensuring proper monitoring of the investigation
- Ensuring that the FDA, any reviewing IRB, and all participating Investigators are promptly informed of significant new information about an investigation.

Additionally, if the IND or IDE product will be manufactured or produced at Pennington Biomedical Research Center, the PI must submit documentation that:

- The product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.

- The IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

The GMP plan has been reviewed by pharmacy, risk management, legal, and compliance issues prior to IRB review. After these offices have reviewed, the GMP plan has been approved by the institutional official. The IRB will periodically conduct random audits of PIs holding an IND or IDE as part of ongoing research compliance efforts.

7.4.2.3 IRB

The IRB will review the research using the same criteria it would use in considering approval of any research involving an FDA-regulated product (FDA 21 CFR 56.111).

All test articles that are dispensed by a pharmacist and administered in a capsule or in a tablet form will be reviewed by the convened board to ensure the safety of the product is reviewed by IRB members with appropriate expertise. Test articles include: drug, biological product for human use, medical device for human use and human food additives.

7.4.3 Expanded Access of Investigational Drugs

FDA regulations allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics. Pennington Biomedical Research Center is not a treatment facility, due to these constraints; this institution will not take part in expanded access of investigational drugs.

7.4.4 Emergency Waiver of IND

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an Investigational Drug to be used in an emergency situation that does not allow time for submission of an IND. Pennington Biomedical Research Center is not a treatment facility and does not treat patients in an emergency.

7.4.5 Waiver of Informed Consent for Planned Emergency Research

Pennington Biomedical Research Center is a research facility, not a treatment facility; therefore a waiver of informed consent for planned emergency research will not apply to any research completed at this institution.

7.5 Investigational Devices in Research

7.5.1 Policy

Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations found at 21 CFR 812 and other applicable FDA regulations.

The following procedures describe the use of investigational devices in research under the purview of the institution's IRB.

Regulations & Guidelines: FDA 21 CFR 812.00; 21 CFR 812.110; 21 CFR 812.140
(a)

7.5.2 Definitions

Adverse Device Effect or "ADE": is any adverse event or adverse effect caused by or associated with the use of a device that is unanticipated and has not been included in the protocol or the Investigator's Brochure.

Device: is an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related test article, including a component part, or accessory which is a) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans, or b) intended to affect the structure or any function of the body, and which does not achieve any of its primary intended purposes through chemical action within or on the body, and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Investigational Device: as defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR 812.3 (g)). Investigational devices include transitional devices (21 CFR 812.3 (r)) that are objects of investigations. However, for the purposes of this document, an investigational device may be an approved device that is being studied for an unapproved use or efficacy.

Investigational Device Exemption ("IDE"): is an FDA-approval of the application for an exemption that permits an unmarked device to be shipped for the purpose of doing research on the device (See 21 CFR 812.1 and 812.2 for the scope and applicability).

Non-Significant Risk Device or NSR Device: is an investigational device other than a significant risk device.

Significant Risk Device "SR Device": is an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a human subject;
- 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 human subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presented a potential for serious risk to the health, safety, or welfare of a human subject;
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a human subject.

7.5.3 IDE Requirements

Clinical investigations of devices are subject to the Investigational Device Exemption (IDE) regulations at 21 CFR 812. An approved IDE permits a device that is not approved (via premarket authorization (PMA)) or cleared to market (via 510K) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk devices must have an IDE issued by FDA before they can be shipped. Non-significant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a non-significant risk device.

Research with devices falls into three (3) categories:

- Investigations of significant risk devices to determine safety and effectiveness of the device
- Investigations of non-significant risk devices to determine the safety and effectiveness of the device
- Investigations exempted under the regulations

Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure (45 CFR 46.110 and 21 CFR 56.110).

The Investigator must indicate on the initial IRB Application whether the research involves investigational drugs or devices. If so, the Investigator must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND/IDE could be a:

- Industry sponsored protocol with IND/IDE;

- Letter from the FDA; and
- Letter from industry sponsor

The sponsor is responsible for making the initial risk determination, SR or NSR, and presenting it to the IRB. If the sponsor has determined that a device study is NSR, the IRB will review the sponsor's determination. If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB will inform the Investigator and, where appropriate, the sponsor. The IRB will document its SR/NSR determination in the IRB meeting minutes.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as non-significant risk, then the Investigator must provide an explanation of the determination. If the FDA has determined that the study is non-significant risk, documentation of that determination must be provided. If the research involves drugs or devices and there is no IND/IDE, the Investigator must provide a rationale why it is not required. The IRB staff will confirm the validity of the IDE number.

Regulations & Guidelines: 21CFR 812; FDA Guidance: IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed (2013)

7.5.4 Determination of the Safety and Effectiveness of a Device

The device fulfills the requirements for an abbreviated IDE.

- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR 812.5.
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
- The sponsor ensures that each Investigator participating in an investigation of the device obtains from each subject under the Investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);

- The sponsor ensures that participating Investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

7.5.5 Exempted IDE Investigations

For devices, an IDE is not necessary if:

- The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
- The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
- The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10 (c) and if the testing:
 - Is noninvasive;
 - Does not require an invasive sampling procedure that presents significant risk;
 - Does not by design or intention introduce energy into a subject; and
 - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
- The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
- The research involves a device intended solely for veterinary use;
- The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5 (c); and/or
- The research involves a custom device as defined in 21 CFR 812.3 (b), unless the device is being used to determine safety or effectiveness for commercial distribution.

7.5.6 Responsibilities

7.5.6.1 Principal Investigator

The Investigator is responsible for ensuring that the research is conducted according to all regulatory guidelines, this document, and institutional policies and procedures. The Investigator must obtain approval from the IRB before initiating any research activities or enrolling any subjects in the research.

The Investigator proposing the device research will be required to provide a plan to be evaluated by the IRB that includes storage, security, and dispensing of the device. Elements of a sound control plan include the following:

- **Storage:** All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI's control. 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.
- **Reporting:** The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 8.
- **New Device Requirements:** For research involving investigational new drugs:
 - If a device is considered a NSR device by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
 - If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining.
 - The PI will maintain the following:
 - Current curriculum vitae CV;
 - Protocol of the study;
 - Records of receipt and disposition of devices;
 - List of any co-Investigators with their CV;
 - Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation;

- Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All adverse device effects are reportable;
 - IRB letters of approval.
 - Device training; and
 - Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.
- **Logs:**
 - The device accountability log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation; and
 - After use, the Investigator must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation
 - **Reporting:** The Investigator will submit to the sponsor and to the 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;
 - **Investigator-Sponsor or Investigator-Initiated Studies:** When a PI files an IND or IDE; the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the Sponsor, as described in the FDA regulations.

An individual or group of individuals or medical center is considered a sponsor for an investigation if they hold the IND or IDE. At Pennington Biomedical these studies are typically called “Investigator initiated studies” when they involve the use an investigational drug or device or use an approved drug or device for investigational purposes.

The research plan asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to *affirm* that he/she has reviewed the **Guidance Document on Requirements of Un-sponsored/Investigator-Initiated Research** and will comply with the regulatory responsibilities of a sponsor.

The sponsors’ or the Investigator as a sponsor responsibilities includes the following:

- Selecting qualified Investigators;

- Providing Investigators with the information they need to conduct the investigation properly;
- Ensuring proper monitoring of the investigation; and
- Ensuring that the FDA, any reviewing IRBs and all participating Investigators are promptly informed of significant new information about an investigation.

Additionally, if the IND or IDE product will be manufactured or produced at Pennington Biomedical Research Center, the PI must submit documentation that: The product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.

The GMP plan has been reviewed by pharmacy, risk management, legal, and compliance issues prior to IRB review. After these offices have reviewed, the GMP plan has been approved by the institutional official. The IRB will periodically conduct random audits of PIs holding an IND or IDE as part of ongoing research compliance efforts.

7.5.6.2 IRB

The IRB will review the research involving investigational devices in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).

- Control plan;
- Unless the FDA has already made a risk determination for the study, the IRB will review NSR Device studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. NSR Device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If the study that has been submitted as non-significant risk is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained;
- The IRB will not review protocols involving SR devices under expedited review;
- The IRB determines whether or not the device is a significant risk device.

- The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR device/SR device; and
- If the FDA has already made the SR device or NSR device determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.
- If the IRB makes a NSR determination, the IRB will confirm whether the test article met the requirements for an abbreviated IDE

7.5.7 Emergency Use of Unapproved Medical Devices

An unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the FDA Act (21 U.S.C. 360 (e)).

Pennington Biomedical Research Center is not a treatment facility; this institution does not conduct the emergency use of unapproved medical devices.

7.5.8 Humanitarian Use Devices (HUD)

Pennington Biomedical Research Center is not a treatment facility; this institution does not conduct research using humanitarian use devices.