I. Purpose

a. This policy outlines the regulatory and institutional requirements regarding use of drugs in an investigational manner (to include approved and investigational drugs, vitamins, biologics, and neutraceuticals) in human subjects research. Investigational drug research involves the use of a non-approved, non-marketed investigational drug or investigational use of an approved marketed product in a clinical protocol.

b. Faculty and physicians at Georgia Regents University may be involved in doing research on investigational drugs in one of two situations: 1) A multi-center clinical trial where the sponsor and medical director for the study have secured Food and Drug Administration (FDA) approval for such research; or 2) a local principal investigator has initiated such research and applied and received both FDA approval and licensure for conducting the research at GRU. In both cases, GRU Institutional Review Board (IRB) (to include an approved commercial IRB) review and approval of the protocol must occur before the research begins.

II. Definition(s)

a. Clinical Investigation – Any experiment that involves a test article (in this case – drug or biological drug) and one or more human subjects (participants) and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding non-clinical laboratory studies.

The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part [21 CFR 56.102(c)].

b. Investigational “Agents” – 1) Drugs, vitamins, biologics, and neutraceuticals that are in clinical evaluation, for which a sponsor or PI has filed an Investigational new Drug (IND) Application with the FDA, has not been released by the FDA for general use, and is not available through regular channels of interstate commerce, but has been granted approval to use for research or humanitarian purposes by the FDA; 2) FDA approved drugs, biologics, and neutraceuticals which are used in a non-FDA approved manner under a study protocol (i.e., change in therapeutic indication, dosage, route of administration); and 3) any drug, biologic, and neutraceutical that is deemed “investigational” by the FDA. For all Charlie Norwood Veterans Administration Medical Center (JDD VAMC) research, any approved drug, biologic, and neutraceutical that is being studied in a controlled, randomized, or blinded clinical trial is also considered an “investigational drug” VHA Handbook 1200.5 14(b).
Investigational Drug Research

c.  **Investigational New Drug** – A new drug or biological drug that is used in a clinical investigation. The term also includes a biological agent that is used in vitro for diagnostic purposes. The term investigational drug and investigational new drug are deemed to be synonymous for purposes of this part [see 21 CFR 312.3(b)].

d.  **IND** – an investigational new drug application. The term IND is synonymous with “Notice of Claimed Investigational Exemption for a New Drug” [see 21 CFR 312(b)].

e.  **Investigational Pharmacist** – Pharmacist at a study site or institution where the research involving the investigational drug is being conducted. The Investigational Pharmacist will ultimately dispense the investigational drug pursuant to authorized orders for investigational drugs stored in the Research Pharmacy.

f.  **Phases for an IND** – An IND may be submitted for one or more phases of investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general, the phases are conducted sequentially, they may overlap.

- **Phase 1** includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer participants (subjects). These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug’s pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects (participants) and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20-80 [21 CFR 312.21(a)(1)].

  Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes [21 CFR 312.21(a)(2)].

- **Phase 2** includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects (participants).

- **Phase 3** studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician
Investigational Drug Research labeling. Phase 3 studies usually include from several hundred to several thousand subjects (participants) [21 CFR 312.21(c)].

g. **Treatment Use of an Investigational Agent** – Use of an investigational drug, vitamin, biologic, or neutraceutical with a person or group of persons with a serious or debilitating condition where there are no other treatment options available.

III. **IND Determination**

According to 21 CFR 312.20(a) “A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 21 CFR 312.2(a).” Based on federal regulations found at 21 CFR 312.2, the IND regulations apply in the following way:

(a) “Applicability. Except as provided in this section, this part applies to all clinical investigation of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)” (21 CFR 312.2a).

However, the following are exemptions to the requirements for an IND as found in 21 CFR 312.2:

(b) Exemptions. a. “(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:”
   i. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug,”
   ii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product,”
   iii. The investigation does not involve a route of administration or dosage level or use in a patient 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. The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
   v. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
Investigational Drug Research

b. (2)
   i. A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b) (2) (ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 21 CFR 312.160.
   ii. In accordance with paragraph (b) (2) (i) of this section the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.”

“(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 21 CFR 312.160.”

“(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b) (1) of this section.”

“(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.”

“(6) A clinical investigation involving an exception from informed consent under 21 CFR 50.24 of this chapter is not exempt from the requirements of this part.”

c. Bioavailability Studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of 21 CFR 320.31.”

d. Unlabeled Indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.”

**Obtaining an IND**

If an IND number and date is not provided on the protocol and/or in the eIRB application, and the study involves the use of an investigational drug (see Definitions), the PI will be contacted to clarify if an application for an IND has been submitted to the FDA.

If the PI does not intend to submit an IND, a written explanation of why an IND is not required must be submitted to the IRB. This explanation should include the criteria for exemption and why the project meets the criteria. A letter from the FDA should accompany this explanation.

If the FDA has determined that an IND is not required, then documentation will be required and the FDA’s determination will be documented in the IRB protocol file. If an IND is required, IRB approval will not be granted until an IND number and the date that it was obtained is provided to the IRB Committee.

According to the VHA Handbook, “…an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or on earlier notification by FDA that the clinical investigation may begin.”

Version Date: 1.8.14
Investigational Drug Research

Investigator-held IND Studies

For studies in which the investigator is the IND holder and assumes sponsor responsibilities, the following procedure should be followed:

a) The PI will include in the protocol submission the following parts written to the specifications identified Title 21—Food and Drugs, Chapter 1—Food and Drugs Administration, DHHS, Subchapter D—Drugs for Human Use, Part 312 – Investigational New Drug Application Subpart D, responsibility of the investigator

b) The PI must send a copy of all correspondence to and from the FDA in the initial submission, including investigator reports. A letter from the FDA regarding the IND status (including exemption) is also required for IRB approval.

c) The IRB will ensure that at initial and continuing review, these elements are in compliance with:

- § 312.50 - General responsibilities of sponsors.
- § 312.52 - Transfer of obligations to a contract research organization.
- § 312.53 - Selecting investigators and monitors.
- § 312.54 - Emergency research under 50.24 of this chapter.
- § 312.55 - Informing investigators.
- § 312.56 - Review of ongoing investigations.
- § 312.57 - Recordkeeping and record retention.
- § 312.58 - Inspection of sponsor's records and reports.
- § 312.59 - Disposition of unused supply of investigational drug.
- § 312.60 - General responsibilities of investigators.
- § 312.61 - Control of the investigational drug.
- § 312.62 - Investigator recordkeeping and record retention.
- § 312.64 - Investigator reports.
- § 312.66 - Assurance of IRB review.
- § 312.68 - Inspection of investigator's records and reports.
- § 312.69 - Handling of controlled substances.

§ 312.70 - Disqualification of a clinical investigator

d) Investigators must contact the IRB Office to schedule a meeting to confirm that the PI is knowledgeable on the requirements associated with 21 CFR §312. Investigational New Drug Application

e) Investigators assuming sponsor responsibilities are also responsible for registering the study in the Clinical Trials Registry, Clinicaltrials.gov.

Version Date: 1.8.14
IV. **IRB Review and Approval of Investigational Drug Studies**

All investigational drug studies must be reviewed and approved by a GRU IRB, or an approved commercial IRB, prior to starting the research. Research that requires an IND will be reviewed as follows:

- A project that meets the criteria for Expedited Review will be evaluated by the IRB Chair or his/her designee. This individual will confirm that the IND number and information provided by the researcher is valid.
- A project that meets the criteria for Full Board Review will be reviewed by the IRB Chair of the committee that will be reviewing the proposal. The IRB Chair will assign reviewers, based on scientific expertise (e.g., M.D., D.O., Pharm.D. or other clinically relevant credentials).
- Should further input be required, a consultant with the appropriate expertise and experience with the pharmaceuticals associated with the IND will be requested to further review the submission and (1) provide written comments, or (2) attend the IRB meeting and give an oral report of his/her findings.

IRB review will include the following:

- Receipt and confirmation of a valid IND# with date and letter from the FDA or a letter from the FDA stating that an IND# is not required [21 CFR 312.2(b)].
- Receipt and review of the Investigational Drug Brochure and, if applicable, the Package Insert.
- Review of a detailed plan for monitoring the data and safety of all participants enrolled in the study (see HIC Policy: “Data and Safety Monitoring in Research”).

Once approved, the PI must provide a copy of the approval notice to the investigational pharmacist, if the investigational drug is to be dispensed form there. All studies involving investigational drugs at VAMC are dispensed by the VAMC pharmacist. If requested, a copy of the approval memo may be sent directly to the VA investigational pharmacy from the IRB.

V. **Drug Dispensing and Accountability**

All investigational agents including placebo(s) used in clinical research studies must be labeled, stored, and dispensed according to federal, state, and institutional policies and regulations. The PI is responsible for maintaining adequate and accurate records regarding drug dispensing and accountability. All medications must be shipped to and dispensed by the GR Medical Center, Department of Pharmacy, Investigational Drug Service/Clinical Research Pharmacy, unless the study is conducted at a non-GR Medical Center location for which IRB approval was attained.

The GR Medical Center, Department of Pharmacy, Investigational Drug Service/Clinical Research Pharmacy is responsible for the receipt, dispensing, accountability and record keeping for all investigational drugs used in research studies involving humans at GR Medical Center, including Georgia War Veterans Nursing Home (GWVN). It may also be utilized for those purposes for other GRU investigational drug studies.

Version Date: 1.8.14
Investigational Drug Research

Please note that the GR Medical Center Clinical Research Pharmacy does charge for their services. For more information, call (706) 721-0802.

Only the principal investigator or co-investigators listed as key personnel on the research protocol may prescribe investigational drugs.

Only appropriately credentialed professionals may dispense investigational drugs provided they are adequately trained and the drug information is available to them. Training records should be maintained in the study binder in the research office.

If a research subject misses an appointment and the investigational medication was dispensed to the research team member from the Clinical Research Pharmacy, the medication must be returned to the Clinical Research Pharmacy immediately.

If a research subject returns investigational medication (packets, bottles, tablets, capsules, etc.), that was dispensed from the Clinical Research Pharmacy, return the investigational drug to the Clinical Research Pharmacy upon receipt from the research subject.

**Prescribing**

Prior to prescribing an investigational drug, the PI must ensure that full informed consent was obtained and the process fully documented in the research or medical record (in Computerized Patient Record System for VA studies). Adequate time must be taken to guarantee full patient understanding of the administration of the drug, any risks, the existence of alternative therapies, and potential effects on the health of the participant.

If the participant is unable to give consent because he/she is unconscious or has been judged incompetent by a court, has a psychiatric disorder, is incapable of comprehending the significance of such action or of exercising appropriate judgment, the consent of the patient’s guardian or next of kin will be obtained in accordance with institutional requirements, regulations, and state law regarding Legally Authorized Representative. A copy of this informed consent form must be forwarded to the Investigational Pharmacy at the VAMC. For non-GR Medical Center sites, an informed consent verification system may be used in lieu of the investigational pharmacy receiving a copy of each informed consent, if appropriate.

The PI should provide the Clinical Research Pharmacist or designee with a list of names, signatures, page numbers, and phone numbers of those who have been approved to prescribe the investigational drug in the IRB application. This list must also be given to the Clinical Research Pharmacist, if the investigational drug is dispensed from the GR Clinical Research Pharmacy.

**Dispensing**

Investigational Drugs will only be dispensed by the Clinical Research pharmacist when a written order authorized by the PI or designated sub-investigator has been received in the investigational pharmacy. The prescription must contain the name of the research participant,
Investigational Drug Research

medical record/social security number, date, number and quantities of the prescribed drug, and complete directions for use.
The prescription will be labeled in accordance to state and federal regulations. The label must indicate that the drug is intended for “INVESTIGATIONAL USE”.

The investigational pharmacist will not dispense the investigational drug until all required documents are received from the PI. The person administering the investigational drug must verify that the research participant has signed an informed consent document prior to dispensing the investigational drug.

For studies that do not utilize the Clinical Research Pharmacy, only authorized individuals, per Georgia Code O.C.G.A. 26-3-10, under the supervision of the principal investigator or authorized provider may dispense investigational drugs.

Administration

The person(s) that have been designated to administer the investigational drug must be trained prior to giving the investigational drug, by the PI or sponsor in processes and procedures appropriate to the specific protocol. All questions should be directed to the PI, sub-investigator, pharmacist, or sponsor.

Storage

All investigational drugs must be stored according to institutional policy. At the VAMC, the Chief of the Pharmacy Section will designate a separate storage area for investigational drugs in the pharmacy apart from the regular drugs stored and under conditions specified by the manufacturer and secured. For studies not conducted at the GR Medical Center, the investigational drug may be kept under lock and key in the PI’s office or other site utilizing secure storage conditions specified by the manufacturer.

Drug Accountability

A complete record of each drug will be maintained by the PI or his/her designee or the Clinical Research Pharmacist and shall include the following:

- Name of Drug
- Manufacturer
- Quantity received
- Quantity dispensed
- Remaining balance
- Expiration date
- Lot number
- Date of authority to use
- Patient’s name or Identifiers
- Patient’s number
- Authorized investigator and designated person who prescribes the drug
Investigational Drug Research

All entries into the drug accountability log must be initialed by the pharmacist, PI, or his/her designee.

Disposal
When the investigational drug order is discontinued, all unused investigational drug must be returned to the Clinical Research pharmacy (for studies in which the investigational drug was dispensed from the Clinical Research Pharmacy), returned to the sponsor following the sponsor’s specific instructions, or destroyed according to the sponsor’s directions or institutional policies. If the PI is acting as the sponsor, the drug should be disposed of according to policies of the investigational pharmacy within the institution.

Records
Drug accountability records for studies shall be returned to the PI when the study is terminated, for studies involving investigational drugs dispensed from the Clinical Research Pharmacy. Drug accountability records should be kept in the research binder for at least 2 years after the drug has become commercially available, or longer, if requested by the sponsor.

Expanded Use (Treatment Use) of Investigational Drug or Biologic
The treatment Investigational New Drug Application (IND) [21 CFR312.34 and 312.35] is a mechanism for providing eligible patients with investigational drugs for treatment of serious and life-threatening illnesses for which there is no satisfactory alternative treatment. A treatment IND may be granted after data has been collected to show that the drug may be effective and does not have unreasonable risks. Because data related to safety and side-effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

Four requirements must be met before a treatment IND can be issued: (1) the drug is intended to treat a serious or immediately life-threatening disease; (2) there is no satisfactory alternative treatment available; (3) the drug is already under investigation or trials have been completed; and (4) the trial sponsor is actively pursuing marketing approval.

When a physician wishes to use an investigational drug or biologic for treatment purposes in a non-emergent situation and the patient meets the criteria set forth in the FDA regulations for a treatment IND, a prospective research protocol must be submitted to the IRB for review and approval and an informed consent must be obtained prior to the use of those drugs or biologics.

An exception to the requirement for the prior review and approval of the IRB exists when investigational drugs or biologics are required for emergency situations to save a patient’s life. This type of situation is covered by the IRB policy: “Emergency Use”.

Version Date: 1.8.14