INVESTIGATIONAL DRUGS AND SUPPLIES

1. REASON FOR ISSUE. This Veterans Health Administration (VHA) Handbook provides specific direction and procedures related to the appropriate handling of investigational drugs and supplies.

2. SUMMARY OF MAJOR CHANGES. This VHA Handbook contains additional information regarding:

a. Responsibilities,

b. Expanded access to Investigational Drugs; and

c. Identification of specific areas of reference.

3. RELATED DIRECTIVE. VHA Directive 1058 and VHA Directive 1108 (to be published).

4. RESPONSIBLE OFFICE. The Office of Patient Care Services, Pharmacy Benefits Management Services (10P4P), is responsible for the contents of this Handbook. Questions may be addressed to 202-461-7326.

5. RESCISSIONS. VHA Handbook 1108.04, dated October 14, 2005, is rescinded.

6. RECERTIFICATION. This VHA Handbook is scheduled for recertification on/or before the last working day of February 2017.

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Under Secretary for Health

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1. PURPOSE

This Veterans Health Administration (VHA) Handbook provides specific procedures related to the appropriate management of investigational drugs and supplies.

2. DEFINITIONS

a. **Adverse Event (AE).** An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research (see VHA Handbooks 1200.05 and 1058.01).

b. **Affiliated Institution.** An affiliated institution is an academic institution that has a relationship for the purpose of education, research, or enhanced patient care with a Department of Veterans Affairs (VA) medical facility documented by a formal Affiliation Agreement in conformance with VA requirements (also referred to as "academic affiliate").

c. **Authorized Prescriber.** An authorized prescriber is a prescriber authorized to prescribe the investigational drug or supply for a specific clinical investigation at the site. The prescriber may be the Principal Investigator (PI), Local Site Investigator (LSI), Co-PI or Investigator. Co-PIs must be approved by the Institutional Review Board (IRB) and the Research and Development (R&D) Committee, and listed on the United States (U.S.) Food and Drug Administration (FDA) Form 1572, Statement of Investigator, and VA Form 10-9012, Investigational Drug Information Record, as applicable.

d. **Blinded (Blinded Study).** A blinded study design is one comparing two or more interventions in which the research personnel, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects.

e. **Centralized Dispensing Protocol.** A centralized dispensing protocol is a protocol that requires dispensing of the investigational drug(s) and possibly concurrent or comparator medications from a single centralized pharmacy, directly to the study participants.

f. **Clinical Investigation.** For FDA related studies, the FDA considers the term clinical investigation to mean any experiment that involves a test article and one or more human subjects, that:

(1) Meets the requirements for prior submission to the FDA under §§ 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (Title 21United States Code (U.S.C.) 355(i) and 21 U.S.C. 360j(g));

(2) Does not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic 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 (Title 21 Code of Federal Regulations (CFR) 56.102(c));

(3) Is not covered under an Investigational New Drug (IND); or

(4) Involves an approved drug that is already in use by VA (e.g., comparative effectiveness studies).

g. **Clinical Trial.** A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related intervention to evaluate the effects on health outcomes.

h. **Comparator Drug.** A comparator drug is an agent that the investigational drug is being compared to in a clinical trial. A comparator drug may be the current standard of care for the disease state being studied.

i. **Control Group.** A control group is the standard by which experimental observations are evaluated. In many clinical trials, one group of patients is given an experimental drug or treatment, while the control group is given either usual care for the illness or a placebo.

j. **Cooperative Study.** A cooperative study is a project or program of research at two or more health care facilities which utilizes a common protocol. A cooperative study is often referred to as a multi-center study.

k. **Double-blinded Study.** A study is referred to as double-blind if both the researcher and the participants are not aware of which treatment each participant is receiving.

l. **Expanded Access.** Expanded access refers to any of the FDA procedures that distribute experimental drugs to participants who are failing on currently available treatments for their condition, and also are unable to participate in ongoing clinical trials.

m. **Experimental Drug.** An experimental drug is a substance that has been tested in a laboratory and has received approval from the FDA to be tested on people.

n. **Human Research Protections Program (HRPP).** A HRPP is a comprehensive system to ensure the protection of human subjects participating in research. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research (see Handbook 1200.05). At a local VA facility, the HRPP consists of a variety of individuals and committees including, but not limited to:

(1) The VA facility Director;

(2) The Associate Chief of Staff (ACOS) for R&D;

(3) The Administrative Officer (AO) for R&D;

(4) The Research Compliance Officer (RCO);

(5) The R&D Committee;

(6) The IRB staff;

(7) Other committees or subcommittees addressing human subjects protection (e.g., Subcommittee on Research Safety (SRS), Institutional Bio-safety Committee, Radiation Safety Committee, Radioactive Drug Research Committee, Conflict of Interest Committee);

(8) Investigators;

(9) Research staff;

(10) Health and safety staff (e.g., Bio-safety Officer, Radiation Safety Officer); and

(11) Research pharmacy staff.

o. **Institutional Review Board (IRB).** An IRB is a board, committee, or other group formally designated by an institution to review, approve, require modification of, disapprove, and conduct continuing oversight of human research in accordance with 38 CFR Part 16 and other applicable VA and Federal requirements (see VHA Handbook 1200.05). ***NOTE:*** *The Central IRB is another IRB located centrally in VHA.*

p. **Investigational Brochure (IB).** The IB is a comprehensive document summarizing all known information about an investigational agent.

(1) This includes all basic chemistry, pharmacology, toxicology, pre-clinical and clinical data to date, and summaries of clinical trials and adverse experiences with the investigational agent.

(2) The sponsor is responsible for keeping the IB updated on a regular basis.

(3) The IB is usually considered proprietary information of the sponsor and as such the use and distribution of the IB is limited to the study teams.

q. **Investigational Drug.** An investigational drug is a chemical or biological drug that is used in a clinical investigation.

(1) An investigational drug can be:

(a) A new chemical compound, which has not been approved by the FDA, or

(b) An approved drug that is being studied for an approved or unapproved use, dose, dosage form, administration schedule, or under an IND application, in a clinical investigation. This includes: prescription drugs, over-the-counter drugs, nutritional supplements, herbal preparations, and legend items used for the diagnosis, treatment, cure, mitigation or prevention of disease and meeting the above definition. ***NOTE:*** *A physician may use a marketed drug in an unapproved manner in an individual patient without requiring a clinical study protocol or obtaining an IND for therapeutic, rather than investigational purposes (Title 21 CFR*

§ 312.2[d]) (see VA's Off Label Drug Use Guidance at: http://vaww.pbm.va.gov/directive/Guidance%20Off%20Label%20Prescribing.pdf). This is an internal Web site and is not available to the public. The Veterans Integrated Service Network (VISN) Therapeutics Management Committee, the Chief of Staff, or the medical facility Director may apply more stringent controls regarding such drug usage.

(2) Concurrent medications, comparators, or rescue medications used in the investigational trial that are not the drug(s) being studied are not defined as investigational drugs, unless they are not commercially approved or not available through commercial channels. ***NOTE:*** *The preceding definitions also apply to drugs used for animal research that are stored in and/or supplied through pharmacy.*

r. **Investigational New Drug (IND) Application**. An IND application is an application to the FDA that allows an investigational drug or biological product to be studied in humans. An IND application must be in effect prior to shipment and administration of investigational drugs or biological products (see 21 CFR 312).

s. **Investigational Supply.** An investigational supply is any medical or surgical product listed in the VA National Drug File that is being used in a study. These products are identified as VA Class IN-000, and are not subject to co-payment.

t. **Office of Research and Development (ORD).** The ORD is responsible for:

(1) Serving as the primary VHA office responsible for the development of policies related to the conduct of research and VHA's research program;

(2) Allocating appropriated Medical and Prosthetic Research funds; and

(3) Developing and implementing educational programs in support of VHA's research mission (see http://www.research.va.gov/programs/default.cfm).

u. **Office of Research Oversight (ORO).** ORO is responsible for:

(1) Serving as the primary VHA office in advising the Under Secretary for Health.

(2) Exercising oversight concerning all matters of research compliance and assurance, including human subject protections, laboratory animal welfare, research safety, research laboratory security, research information security, research misconduct, debarment for research impropriety, and other matters that the Under Secretary for Health may assign.

(3) Developing and conducting RCO education programs as directed by the Under Secretary for Health.

v. **Open-Label.** Open-label refers to when both the researchers and participants know the identity of the drugs or treatments being administered.

w. **Principal Investigator (PI).** A PI is the individual who is accountable for the proposal, protocol, performance, and culmination of a research or development project. For multi-center (cooperative) clinical trials, there is a LSI at each location who is accountable for all aspects of conduct of the study at the local site. ***NOTE:*** *The terms PI and LSI are considered equivalent for the remainder of this Handbook.*

x. **Repass or Retest Date.** A repass or retest date is the date assigned by the manufacturer after which the drug substances need to be examined to ensure that they are within suitable specifications for use in the manufacture of a drug product. ***NOTE:*** *The repass or retest dates are often used to denote the last date on which an investigational drug should be administered without additional testing to confirm potency and to extend the retest date.*

y. **Research Compliance Officer (RCO).** The RCO is an individual whose primary responsibility is to review research projects relative to requirements for the protection of human subjects, laboratory animal welfare, research safety, research laboratory security, research information protection, and other areas under the jurisdiction of ORO. ***NOTE:*** *Guidance and materials related to RCO responsibilities are provided on ORO's Web site at: http://www.va.gov/oro/* .

z. **Serious Adverse Event (SAE).** A local SAE in human research is an AE that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.

aa. **Sponsor.** For FDA studies, the FDA considers a sponsor to be the entity that takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, or private organization. The sponsor does not actually conduct the investigation, unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of their own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators (21 CFR 312.3 and 21 CFR 812.3).

bb. **Test Article.** A test article is any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug and Cosmetic Act or under §§ 351 and 354 through 360F of the Public Health Service Act (42 U.S.C. 262 and 21 U.S.C. 360hh-360ss; and 21 CFR Section 50.3(j)).

cc. **Unblinding or Breaking the Blind.** Unblinding or "Breaking the Blind" is the formal process of revealing the true identity of the treatment assignment or investigational drug in a double-blinded study.

dd. **Usual Care.** Usual care is medical or other treatment and services that a research subject would receive if not participating in the research study (e.g., the chemotherapy an oncology patient would receive whether or not the patient was participating in a research study).

ee. **VA Research.** VA research is research approved by the R&D Committee and conducted by VA Investigators including PIs, Co-PIs, and LSIs. These activities are performed on VA time (serving on compensated, without compensation (WOC), or Intergovernmental Personnel Act (IPA) appointments), utilizing VA resources (e.g., equipment), or on VA property including space leased to, and used by VA. The research may be funded by VA, by other sponsors, or be unfunded.

3. SCOPE

The Investigational Drug agenda is a major component of VHA's clinical research program and the protections of human subjects in research. Clinical investigations may be local or multicenter in design. In all instances the facility, the investigator, and the clinical investigations comply with all applicable VA regulations, VHA Handbooks, VHA policies, FDA regulations and local medical facility policies.

4. RESPONSIBILITIES OF THE FACILITY DIRECTOR

The facility Director, or designee, is responsible for ensuring:

a. There is a HRPP, in order to conduct research involving humans.

b. Clinical investigations using investigational drugs and/or supplies are being carried out, and there are written policies and procedures that provide adequate safeguards are in place to protect the subject, staff, and facility.

c. The quality of the study.

d. All clinical investigations using investigational drugs and/or supplies are compliant with all applicable laws, regulations, and VA and VHA policies.

e. That before research is initiated, the clinical investigation:

(1) Is conducted by properly qualified investigators;

(2) Has approval of the IRB of Record and the R&D Committee of the medical facility where the study is conducted; and

(3) Meets all requirements of VHA Handbook 1200.01.

f. The subject or the subject's legally-authorized representative is given all required information regarding the research study during the informed consent process. Informed consent must be obtained from the subject, or the subject's legally-authorized representative in accordance with VHA Handbook 1200.05 and FDA regulations found in 21 CFR Part 50.

g. Consideration is given to include a representative from the investigational pharmacy or Pharmacy Service as either an ex-officio non-voting member or voting member of the IRB or R&D Committee.

h. All investigational drugs and supplies required by a clinical trial protocol, being used under an IND, are provided by the study sponsor.

i. Concurrent, comparator, or rescue medications that are required and supplied by the study sponsor and used for study-related purposes are recorded by the dispensing investigational pharmacy as part of the study treatment.

j. These medications (subpar. 4i) are stored in accordance with subparagraph 10b. If the study sponsor does not provide these medications and medical care appropriations are utilized for their purchase, the cost of the medication must be reimbursed from the research funds; unless the study drugs are determined to be "usual care," as outlined in subparagraph 6c.

k. Medications supplied or procured for an investigational study are identified in the drug file as a study medication.

(1) Entries must start with "INV" in order for them to be recognized as investigational both locally and in national reports. If the medication is already listed in the drug file, a second entry in the drug file clearly identifying the medication as a study medication or supply is required.

(2) The appropriate drug class from the National Drug File is to be selected when entering the drug to ensure the proper electronic order checks for allergies; in addition, the proper Drug Enforcement Agency (DEA) Special Handling drug code (I) needs to be designated to ensure that no co-pay is assessed.

l. That Pharmacy Service has a specific policy or standard operating procedure in place that specifically addresses investigational drug control and management.

NOTE: *The Investigational Drug Pharmacist, or the Pharmacy Automated Data Processing Applications Coordinator (ADPAC), may be contacted regarding questions relating to the entry of research medications.*

m. All investigational drug and supply management remain under the direction of the facility Chief of Pharmacy (see par. 10).

5. FINANCIAL RESPONSIBILITIES OF RESEARCH SERVICE

a. Research service must work with the Pharmacy service liaison to ensure that Pharmacy Service receives appropriate reimbursement for required supplies and services (VHA Handbook 1200.01). This reimbursement must be in writing and agreed to by the PI before the protocol is completed and submitted.

b. When the sponsor of the research does not provide the protocol medication and medical care appropriations are utilized for their purchase, the amount must be reimbursed from either the research appropriation or other research funding source.

c. If the study is sponsored by VA and the research appropriation is used to fund the study, then the research appropriation that the facility receives would be used to reimburse the pharmacy service.

6. ROLES AND RESPONSIBILITIES OF THE STUDY SPONSOR

All investigational drugs and supplies required by a clinical trial protocol being studied under an IND must be provided by the study sponsor. However, there are clinical investigations where drugs and supplies, that are part of the study, are not being used under an IND. The requirement for the sponsor to provide the drugs and/or supplies is dependent on the situation and the usual clinical care of patients in these investigations.

a. If the drugs and/or supplies are not part of usual care for the condition or disease state under study, then the sponsor must either provide the drugs and supplies or provide for procurement of these drugs and supplies using research funds.

b. In those instances when the sponsor does not provide the protocol medications and medical care appropriations are utilized for their purchase, that amount must be reimbursed from the research appropriation.

c. If the drugs and/or supplies are part of the usual care for the condition or disease state and would likely be prescribed for the study subjects (e.g., had they not met all study enrollment requirements, declined to be in the study, or there was no study taking place) then the study sponsor is not required to supply the drugs and/or supplies or provide funding; and medical appropriations can be utilized. Drugs in this category are subject to any restrictions and prior authorizations required for regular clinical care. This does not preclude the sponsor from providing the drugs, supplies or funding.

7. ROLES AND RESPONSIBILITIES OF THE INVESTIGATOR

a The PI or LSI must provide the Pharmacy Service with the following:

(1) Written approval letter signed by the ACOS for R&D that all relevant approvals have been obtained and that the study may be initiated at the site (VHA Handbook 1200.01);

(2) An IRB approval letter;

(3) A copy of the approved study protocol;

(4) A copy of VA Form 10-9012, when appropriate;

(5) An IB, when appropriate;

(6) Any sponsor-provided documents relating to the storage, preparation, dispensing, and accountability of the investigation products;

(7) Protocol revisions, amendments, and updates after IRB approval and after the IRB approved the amendment;

(8) Updates and changes to authorized prescribers after IRB approval;

(9) Documentation of IRB continuing review approval;

(10) Notice if clinical investigation is suspended or terminated by the IRB, R&D Committee, FDA, or other oversight group (e.g., ORO or the study sponsor); and

(11) Notice of when the study is closed.

b. The PI or LSI must provide Pharmacy Service and/or the Research Service Investigational Pharmacy, investigational drug information on each patient receiving an investigational drug through the electronic medical record or other locally-approved means. This documentation is to include allergies, toxicities, or adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements (herbals, nutriceuticals).

c. The PI or LSI must place the completed VA Form 10-9012, or electronic equivalent, in the subject's medical record.

8. ROLES AND RESPONSIBILITIES OF THE FACILITY CHIEF OF PHARMACY

The Chief of Pharmacy Services, or designee (e.g., Research Service Investigational Pharmacist), is responsible for the receipt, storage, security, labeling, dispensing, and disposition of all investigational drugs and supplies used in clinical investigations, and for ensuring that:

a. There is adequate pharmacy staffing and resources to safely conduct investigational drug studies in compliance with all rules and regulations. If there is insufficient staff or resources to support investigational drug studies, they are not to be conducted until the situation is rectified. ***NOTE:*** *Resource models need to consider pharmacist time and associated costs. These costs may include, but are not limited to: pharmacist time for protocol review, study initiation activities, supply ordering, sponsor monitoring, drug accountability, storage monitoring, subject randomization, drug preparation/compounding/admixing, dispensing, drug and supply returns and study closure; space and equipment (e.g., room temperature, storage, refrigerator or freezer space and temperature monitoring); the destruction or return of unused medication or supplies; and plans for the inclusion of non-VA subjects or subjects continuing on study medications after completion of the study protocol.*

b. All research pharmacy staff having direct responsibilities for the management, dispensing and oversight of investigational drugs and biologicals, complete all Human Subject Protection Training requirements and have an approved Scope of Practice according to VHA Handbook 1200.05.

c. Pharmacy staff who only assist in the research pharmacy or the research pharmacist by preparing or compounding an investigational drug (e.g., intravenous (IV) admixture) according

to local Pharmacy Service standard operating procedures, and are performing within their usual scope of duties, do not need to complete the Human Subject Protection training.

d. A local pharmacy standard operating procedure is developed which provides written instruction for the processing and dispensing of investigational drugs and/or supplies to ensure compliance with the study protocol and all Human Subject Protection requirements for each study or group of similar studies.

e. The receipt, maintenance, review, and compliance with study protocol documents and approvals are accomplished in all instances.

f. The investigational drug study has received initial approval and funding, prior to ordering, receipt, storage, or dispensing of investigational drugs.

g. Documentation of approved clinical investigations using investigational drugs or supplies and commercial drugs are maintained. For example:

(1) Ensuring that a VA Form 10-1086, Research Consent Form, dated and signed by both the subject and the individual conducting the consent process is received for each subject, prior to dispensing to the subject for the first time.

(2) Maintaining a real time investigational drug log or accountability record of all transactions involving receipt, storage, dispensing, and disposition of unused stocks of investigational drugs, unless this responsibility has been authorized in writing to the PI as outlined in subparagraph 10c.

(3) The study protocol documents and Investigational Drug Accountability maintained by the Pharmacy Service are research records, and are to be maintained according to VHA Records Control Schedule (RCS) 10-1. In some cases, FDA regulations or sponsor requirements mandate record retention for a specified period after New Drug Application approval, or discontinuation of the IND (21 CFR Sec. 312.62). Records are to be retained according to the longest requirement at the time. Records are not to be destroyed until approval by the sponsor has been received. All documents and correspondence provided by the PI (see par. 6.) are to be maintained with protocol records.

h. Representative(s) who become members (either voting or nonvoting) of the local R&D Committee or IRB of Record meet all VA, VHA, and local educational requirements for R&D Committee or IRB members, respectively.

9. STUDY PROTOCOL DOCUMENTS AND APPROVALS

a. Documentation of a properly-approved clinical investigation includes:

(1) Written approval letter signed by the ACOS for R&D that all relevant approvals have been obtained and that the study may be initiated (VHA Handbook 1200.01);

(2) An IRB of record approval letter;

(3) A copy of VA Form 10-9012,when appropriate;

(4) A copy of the approved protocol; and

(5) Drug accountability records.

b. The documentation of approved-clinical investigations using investigational drugs or supplies and commercial drugs includes:

(1) Maintaining a file of all studies involving drugs;

(2) Approvals by the IRB and R&D committees;

(3) Any sponsor-related correspondence to the investigator, specific to the drug(s); and

(4) All correspondence from the FDA (and other authorities) specific to the investigational drug(s).

c. The Pharmacy Service Investigational drug records are to be made available to the RCO, ORO, ORD, and other auditors as required to ensure compliance with VHA policies.

d. Clinical investigations conducted as part of a "Cooperative Research Agreement" (clinical trial research agreements with another Federal agency) require review by the Pharmacy and Therapeutics (P&T) Committee in addition to the IRB. The local P&T Committee (or the VISN Therapeutics Management Committee), must review the "Cooperative Research Agreement" to ensure that all medication benefits and costs associated with the clinical trial are realized.

10. INVESTIGATIONAL DRUG AND SUPPLY MANAGEMENT

All investigational drug and supply management must remain under the direction of the Chief of Pharmacy Services.

a. **Receipt**

(1) Regardless of the source, all investigational and sponsor supplied drugs must be delivered to the Pharmacy Service or Research Service Investigational Pharmacy for receipt, storage, security, labeling, distribution, dispensing, and disposition.

(2) Investigational drugs are not to be obtained from other facilities or PIs without an approved Letter of Understanding (LOU) (see App. A), and adherence to protocol procedures and FDA requirements. An LOU can exist between a university affiliate or a VA affiliate and the VA Medical facility (or a parent VA Medical facility and its affiliated satellite clinics).

(3) Detailed information as to how drugs are to be dispensed and accounted for must be clearly stated in the Investigational Drug LOU.

b. **Storage and Accountability**

(1) Investigational drugs and supplies must be securely stored in the pharmacy; they must be kept separate from all non-investigational drugs and supplies; and they must be clearly identified as to which study they are assigned. ***NOTE:*** *Storage does not require a separate locked area within pharmacy, unless the medication has specific storage requirements as identified in subparagraph 10b(5).*

(2) Investigational drugs must be stored according to the study sponsor's requirements (room temperature, refrigerated, in freezer, etc.) and routinely monitored.

(3) An investigational drug log or an accountability record, authorized by the facility and/or study sponsor, must be maintained and contain the following information:

(a) Name of the drug, dosage form, and strength;

(b) Manufacturer or other supply source;

(c) Date of receipt of the drug;

(d) Quantity received;

(e) Expiration, retest, or repass date;

(f) Control, lot number, or other identification (ID) number;

(g) Name of LSI;

(h) Protocol name or number;

(i) Name of subject or other subject identifier for individuals receiving the medication;

(j) Quantity dispensed;

(k) Balance of drug currently available (when amenable to protocol design); and

(l) Recorder's initials.

NOTE: *When documentation by the clinical investigation sponsor demonstrates that the expiration date and control number (or lot number) of the medication(s) are monitored centrally, (to maintain blinding procedures or ensure continued stability) this information does not need to be maintained on the investigational drug log.*

(4) All electronic drug accountability records must be FDA compliant (see 21 CFR Part 11).

(5) Clinical investigations involving controlled substances must meet the same storage and accountability requirements as outlined for routine patient care and in accordance with applicable

laws, regulations, and VA policies. In addition to the storage requirements for non-controlled study medications, the following requirements and detailed information must be kept for a controlled substance study drugs:

(a) Controlled substance review and inventory requirements as specified in VHA Handbook 1108.01;

(b) Monthly unannounced inspection as specified in VHA Handbook 1108.02;

(c) All controlled substance dispensing;

(d) Controlled substances returned (including drugs drawn up, but not used);

(e) All controlled substance record reconciliation;

(f) Controlled substances wasted; and

(g) Controlled substance use, categorized by investigator and/or prescriber.

(6) A final entry is made when drug therapy for the entire study (at the site) has ended. This entry documents the date of termination of the use of the drug, the quantity remaining, the action taken to dispose of the balance on hand, and the agent or individual responsible for drug destruction or return.

(7) Investigational drug or supply returns and destruction need to follow the requirements as outlined in the study protocol.

c. **Storage Outside of Pharmacy Service.** ***NOTE:*** *The storage of investigational drugs outside of the Pharmacy Service needs to be discouraged when a pharmacy is located within the facility.*

(1) The Chief of Pharmacy Services, or designee, and/or Research Service Investigational Pharmacist may delegate, in writing, the custody of investigational drugs stored outside the pharmacy to the PI.

(2) This Delegation of Custody document is an agreement on the specific procedure that the PI is required to follow and must include the following:

(a) The drug storage location;

(b) The name of the investigator responsible for the storage and dispensing; and

(c) The Signature of the PI.

(3) The Delegation of Custody document must be maintained in the pharmacy.

(4) The Investigational Drug Pharmacist, or designee, must verify that the storage location meets all storage and security requirements.

(5) Access to this storage area is to be restricted to authorized study personnel only.

(6) The PI must ensure that a real-time drug dispensing log of all dispensing is maintained. This dispensing log provides a method for Pharmacy Service to inspect the investigational drug inventory and track all dispensing from the storage location.

(7) The PI must comply with all dispensing and documentation requirements and the dispensing log must be made accessible to the investigational drug pharmacist upon request.

(8) Distribution to other locations such as Community-Based Outpatient Clinics (CBOC) may only occur from the main pharmacy and only if the CBOC or other site is an approved research location. All investigational drugs must remain under the direction of Pharmacy Service.

(9) Investigational drugs mailed directly to the subject through centralized dispensing protocols do not need to go through the local Pharmacy Service or the Research Service Investigational Pharmacy.

d. **Dispensing**

(1) Investigational drugs and supplies can only be dispensed directly to the patient, the legally-authorized representative, or authorized-study personnel.

(2) Investigational drugs and supplies may be dispensed only after a provider, who is authorized to prescribe the drug, has submitted a proper written or electronic order.

(3) Investigational drug prescriptions may be entered into the Computerized Patient Record System (CPRS) by an Investigational Drug Pharmacist at the VA medical facility.

(4) The initial order or prescription for each new subject on an investigational protocol must be accompanied by a signed informed consent or written assurance, by the provider, that the signed consent is available for viewing and printing in the electronic medical record. ***NOTE:*** *Pharmacy does not need to physically have a copy of the consent if it can be viewed in the electronic medical record. If there is not a physical copy of the consent maintained in pharmacy there must be a mechanism by which the pharmacist can document that the signed consent was seen before dispensing to the subject for the first time.*

(5) The investigational drugs and/or supplies must be prepared, labeled, and dispensed according to the study protocol requirements and VA regulations.

(6) In addition to the generally-required prescription label information and appropriate auxiliary caution or warning labels, all investigational drug labels must include the following legend:

"CAUTION – NEW DRUG: LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE."

(7) If compounding or admixing of the investigational drug is required by the study protocol, applicable United States Pharmacopoeia Standards and Good Clinical Practices (GCP) must be followed.

(8) In blinded studies, pharmacists are required to maintain the study blind to ensure scientific integrity. However, in rare emergency situations the blinded study must be broken for reasons of subject safety. The decision to break the blind must be made by the subjects treating physician after consultation with the PI or LSI, and in accordance with the procedures for un-blinding in the approved protocol or the protocol's standard operating procedures.

(a) In all cases the study sponsor, PI, and the Chief of Pharmacy Service and/or Investigational Drug Pharmacist must agree on the proper procedures and required documentation for unblinding. This procedure must provide a mechanism where the blind can be broken at any time (e.g., 24-hours per day, 7-days per week, and 365-days per year).

(b) If the Investigational Drug Pharmacist is not part of the initial unblinding process, the investigational pharmacy must be notified as soon as possible of the unblinding event.

e. **Drug and Supply Returns**

(1) In accordance with Federal regulations, sponsors generally require the subject to return unused clinical investigation drugs and empty containers.

(2) Clinical investigational drugs and supplies returned by subjects may not be re-dispensed.

(3) Clinical investigational drugs and containers returned by subjects are to be stored separately from study supplies that have not been dispensed.

(4) Returned supplies are either to be returned to the sponsor (at the sponsor's expense) or destroyed according to local medical facility policies and as permitted by the sponsor.

11. FORMS FOR USE WITH INVESTIGATIONAL DRUG PROTOCOLS

a. **VA Form 10-1086, Research Consent Form.** VA Form 10-1086 must be completed in accordance with VHA Handbook 1200.05 and bear the appropriate signatures as required by the IRB and sponsor. This form is to be reviewed for each subject, by the Pharmacy Service or Investigational Drug Pharmacy designee, prior to dispensing to the subject for the first time.

b. **VA Form 10-9012, Investigational Drug Information Record.** VA Form 10-9012 must be provided to the pharmacy by the PI prior to the time of first dispensing of the investigational drug. Once on file, additional copies are required only if the form requires revision.

(1) VA Form 10-9012 informs the authorized prescribers and other clinical personnel of the side effects and any known antidote of the investigational agent, as well as who the designated

contact person is for questions. VA Form 10-9012 is required on all investigational agents where a drug manufacture's package insert in not available.

(2) VA Form 10-9012, or an electronic equivalent, must be placed in the subject's medical record by the PI or LSI.

12. CO-PAYMENTS

a. Title 38 U.S.C. 1722A, Co-Payment for Medications, and 38 CFR § 17.110, Co-Payment for Medications, state that VA medication co-payments must be waived if the medication is provided to the subject as part of a VHA-approved research protocol. This waiver applies whether or not the sponsor of the investigational study provides the medication. Neither dispensed supplies nor investigational supplies are subject to co-payment.

b. Co-payment eligible subjects, participating in 38 U.S.C. 7303 third-party funded VHA-approved research projects are not to be charged a co-payment for inpatient or outpatient medications provided through an investigational drug study. However, these individuals are still subject to appropriate co-payment for VHA-provided medications for non-research medical care.

13. EXPANDED ACCESS TO INVESTIGATIONAL DRUGS

a. The FDA has established "Expanded Access to Investigational Drugs for Treatment Use" regulations. Therefore, in certain instances an investigational drug may be authorized for individual or widespread treatment. The use of a drug under this regulation is considered a treatment use and not research.

b. All FDA regulations for emergency use of a test article must be complied with, including but not limited to, obtaining informed consent from the subject or the subject's legally-authorized representative, unless the study falls under FDA regulations for an exception from informed consent (21 CFR 50.23[a]).

c. There are three categories of Expanded Access under FDA regulations, they are:

(1) Individual Patients including for Emergency Use (21 CFR 312.310);

(2) Intermediate Size Populations (21 CFR 312.315); and

(3) Treatment IND or Treatment Protocols (21 CFR 312.320).

d. Requests for use for individual patients in an emergency setting must adhere to the FDA rules regarding Emergency Use of a Test Article (21 CFR 56.102[d]). FDA regulations describe specific instances when an investigational drug or biologic may be used on a human subject when there is not sufficient time to obtain IRB approval.

e. The Pharmacy Service may receive the investigational drug and the treating physician may treat the patient without prior IRB approval, when:

(1). The physician determines that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) The FDA determines that the patient cannot obtain the drug under another IND or protocol. The treating physician must notify the IRB within 5 days of the first use in the patient.

f. Requests for use under categories for Intermediate Size Populations and Treatment INDs must go through all the required reviews as with any other clinical investigation before the investigational drug can be obtained and provided to the patient(s). ***NOTE:*** *Additional information about expanded access and FDA contact information can be obtained by referring to 21 CFR 312.300) (http://edocket.access.gpo.gov/2009/pdf/E9-19005.pdf) and the FDA Web site (www.FDA.gov).*

g. Since, within VA, emergency use of a test article is not considered to be research, the patient is not a research subject, the emergency care cannot be claimed as research, and the outcome of such care cannot be included in any report of research activity subject to 38 CFR Part 16.

h. Use of an investigational drug from an outside source for a hospitalized patient who is a research subject at another health care facility may be permitted to ensure the patient's well-being. In this instance:

(1) The Pharmacy must obtain the drug and dispense in accordance with FDA regulations;

(2) The study PI from the other health care facility must be contacted prior to dispensing by the patient's treating clinician at the VA facility;

(3) The patient's treating clinician at the VA facility must determine whether it is in the subject's best interest and well-being to continue receiving the investigational drug; and

(4) The patient's clinician must obtain from the study PI at the other health care facility; a copy of the signed informed consent, information on the protocol, and all drug-related information (see subpar. 7). This consent must be given to the VA Pharmacy Service prior to making arrangement for receiving or dispensing the investigational drug after an order is submitted.

14. VA COOPERATIVE STUDIES PROGRAM CLINICAL INVESTIGATIONS

a. In the case of a VA Cooperative Study employing investigational drugs, the Cooperative Studies Program (CSP) Clinical Research Pharmacy Coordinating Center (CRPCC) must prepare VA Form 10-9012, for the PI at the VA medical facility.

b. CSP is responsible for obtaining the investigational drug(s) or when commercially available, reimbursing the cost of the drug(s) and for distributing them to the Pharmacy Service at each authorized participating medical facility, unless the conditions of usual care as outlined in subparagraph 6 are met.

c. Pharmacy Service at each participating medical facility must designate an individual to whom the investigational drug(s) must be shipped.

d. The Pharmacy Service of each participating medical facility must maintain records on investigational drug(s) including all transactions involving receipt, dispensing, and disposition of unused drugs in accordance with paragraph 10 of this Handbook.

e. A copy of all records, describing the return or local destruction of investigational drugs associated with the protocol, must be provided to CRPCC by the Investigational Drug Pharmacist at each participating medical facility.

15. CENTRALIZED DISPENSING PROTOCOLS

a. Due to unique circumstances, it may be advisable for investigational drug dispensing to be performed centrally. In these instances, the following procedures apply:

(1) All centralized dispensing of investigational drugs must be approved by the participating R&D Committee (when applicable) and the responsible IRBs.

(2) The IRB must confirm that the dispensing pharmacy is accredited by The Joint Commission (TJC) or is in the accreditation process. The IRB must forward this confirmation to the local Investigational Drug Pharmacist.

(3) All centralized dispensing of investigational drugs must be accomplished using VA's pharmacy record system in the Veterans Health Information System and Technology Architecture (VistA). This ensures that all dispensing is in full compliance with TJC standards for patient records review (i.e., medication profile, laboratory results, adverse drug reactions, etc.) prior to dispensing.

(4) Dispensing must adhere to all VistA prescription standards (i.e., the maximum supply is 90 days).

(5) The CRPCC pharmacist performing the centralized dispensing is required to:

(a) Maintain all necessary records and correspondence;

(b) Obtain a signed copy of the informed consent prior to dispensing;

(c) Ensure that all dispensing requirements in subparagraph 10d are followed;

(d) Ensure that all dispensing activity is entered into the patient files at a centralized location using VistA software. This information must be accessible to all VA facilities using the Network Health Exchange.

NOTE: *Alternately, the centralized pharmacy, the local pharmacy, information technology, and other key personnel at the study location may jointly elect to provide remote access to the centralized dispensing pharmacist for direct VistA data entry. If this option is mutually agreed*

upon, the joint recommendation must be submitted to the R&D Committee and IRB as part of the protocol submission.

(e) Ensure that the PI and a CRPCC dispensing pharmacist, who is familiar with the protocol, are available at all times (e.g., on call 24-hours per day, 7-days per week, and 365-days per year); and

(f) Ensure that all authorized providers use the Computerized Patient Record System (CPRS) at the study site to prescribe the investigational drug.

b. The study investigators must:

(1) Ensure that all protocols are reviewed by their local R&D and IRB Committees;

(2) Ensure that the local P&T Committee has the opportunity to review the protocol prior to initiation when necessary;

(3) Ensure that all prescribing takes place using the VistA access provided to the centralized pharmacy;

(4) Annotate on the local medication profile, under Non-VA Medication, that the subject is on the investigational protocol and how to access information about the investigational drug. This information must be updated at least quarterly to reflect the current dispensing status. When dispensing from the centralized pharmacy is discontinued, the authorized provider must indicate this in the "Non-VA Medications" package and in the subject's CPRS record.

(5) Identify that the patient is to begin the investigational drug protocol and forward copies of the protocol and VA Form 10-9012, for the investigational drug to the local Investigational Drug Pharmacist for future reference; and

(6) Communicate the existence of this protocol to all pharmacist staff at the local facility.

16. REFERENCES

a. Title 38 U.S.C. 7303, and 1722A.

b. Title 38 CFR Sections 16.110, and 17.110.

c. Title 21 CFR Sections 56.102 (d), 56.104 (c), 312.2(d), and 312.62.

d. TJC Standards: Medical Management (MM).1.10, MM.4.10, MM.4.20, and MM.7.40.

e. VHA Records Control Schedule 10-1.

f. VHA Handbook 1200.05.

g. VHA Handbook 1200.01.

SAMPLE LETTER OF UNDERSTANDING (LOU)

Medical Facility Name: _____

Medical Facility Number: _____

"Protocol or Study Name"

This letter reflects the understanding between _____ (hereinafter referred to as "Department of Veterans Affairs (VA) Affiliate") and the VA Medical Facility at _____ regarding the circumstances under which the VA Affiliate agrees to provide study drug to the VA Medical Facility for the following research study _____, "_____" ("PROTOCOL or STUDY"). A copy of the Protocol, dated ___/___/___, is attached and incorporated herein by reference.

The VA Medical facility Pharmacy Service at_____ serves as a liaison between the VA Affiliate and the VA investigator and acts as the central control and distribution center for donated drugs for the STUDY. Pharmacy Service must provide guidance and information regarding study drugs as well as serving as a conduit for communications between the VA Affiliate and the Food and Drug Administration when appropriate. The VA Affiliate provides ___(Insert Drug name and strength)___ and matching placebo (hereafter referred to as **"Study Drug**") for the STUDY in accordance with the following provisions.

The VA Medical facility at _____ and the VA Affiliate have agreed upon the following operating procedures in connection with the STUDY and this Letter of Understanding:

1. Conduct of the STUDY**.** The VA Medical Facility at _____ will conduct the STUDY in accordance with the terms of Protocol and within VA guidelines with the participation of the VA Affiliate.

2. Drug Supply, Distribution, and Accountability. The VA Affiliate will supply Study Drug for the duration of the STUDY, free of charge, and will include in planning allowances for wastage that may unavoidably occur during dispensing. The VA Affiliate will provide shipment of Study Drug directly to the Pharmacy Service in accordance with the schedule agreed to by both parties. The Pharmacy Service will label and dispense Study Drug and keep all records of drug disposition. The Pharmacy Service warrants that in its processes the Study Drug shall not be adulterated or misbranded, in accordance with the Food, Drug and Cosmetic Act. Pharmacy Service agrees to use the Study Drug supplied by VA Affiliate only for the investigational purposes authorized under the Protocol. No other use of the drug will be permitted by Pharmacy Service. In the event that the Pharmacy Service has unused Study Drug at the time the STUDY is completed or terminated, the Pharmacy Service will dispose of Study Drug in accordance with operating procedures outlined by the VA Affiliate.

3. Safety Information Reporting. The local investigator is responsible for reporting adverse events with respect to Study Drug to the VA Affiliate and/or FDA in conformance with all applicable laws, rules, and regulations in effect.

a. The local investigator must provide to the VA Affiliate any information on any serious adverse event, side effect, injury, toxicity, sensitivity reaction or any unexpected incidence and the severity thereof related to the Study Drug that is associated with its "clinical" use in accordance with the Protocol. "Serious Adverse Events," as used in this context, have the meaning ascribed thereto in the Protocol. All such events deemed to be related to the Study Drug must be reported to the VA Affiliate on Protocol SAE forms within _____ business days of receipt by the local investigator.

b. It is understood and agreed that these adverse events reporting requirement provisions are based upon the VA Affiliate's respective policies and procedures and regulatory reporting requirements. Accordingly, in the event of changes to VA Affiliate's policies and procedures for adverse events reporting, the local investigator agrees to comply with such revised notification requirements as reasonably requested in writing by the VA Affiliate. This is provided that the scope and extent of activity and undertakings are not materially increased. The VA Affiliate agrees to pay all costs associated with this request.

4. Early Study Termination. The STUDY may be terminated at any time by the Institutional Review Board for safety or efficacy reasons if it is thought to be in the best interests of the patients. Either the VA or the VA Affiliate may withdraw support from the STUDY with 90 days written notice only if this agreement has been violated.

5. Patient Confidentiality. Patient confidentiality must be maintained at all times in accordance with applicable law and VA policy. Reports issued for public distribution or to the VA Affiliate will contain only aggregate data with all patient identifiers removed.

6. Selection of Participants . The VA Medical facility at _____ is responsible for all decisions concerning the selection and/or discontinuation of participants in the STUDY.

7. Record Retention. The VA Medical facility at _____ must retain all records related to the STUDY [according to VHA Records Control Schedule (RCS) 10-1] for a minimum period of 3 years from the date of the last patient follow-up. At that point the STUDY records will be evaluated for archiving.

8. Term of Agreement. This agreement shall be effective as of the date last signed below and shall expire upon completion of all activities related to the STUDY as defined by the submission of the final STUDY report to the VA Affiliate and the primary publication of the STUDY results.

9. Modification to Agreement. This agreement can only be modified in writing and would require signatures by the VA Medical facility at _____ and VA Affiliate representatives.

10. Approval. The following signatures indicate approval of the terms of this letter of understanding.

_____ _____
(Name and Signature of the PI) (Date)

_____
(Name of the VA Affiliate)

_____ _____
(Name and Signature of the VA Investigator) (Date)

_____
(Name of the VA Facility)