INVESTIGATIONAL DRUGS

1. POLICY

The Birmingham VA Medical Center (BVAMC) Human Research Protection Program (HRPP) is committed to ensuring compliance with all VA and Food and Drug Administration (FDA) regulations involving investigational drugs. This standard operating procedure (SOP) establishes procedures for investigators to follow when submitting projects proposing the use of investigational drugs that are not otherwise specified in other pertinent SOPs, such as those pertaining to initial, continuing, or expedited review, reporting requirements, and informed consent. Specifically, this SOP provides more detail pertaining to need for, exemption of, and/or verification of an FDA Investigational New Drug (IND) application and approval.

2. RESPONSIBILITIES

BVAMC Institutional Review Board (IRB) is responsible for the review and approval of all studies involving investigational drugs in accordance with VA, FDA, BVAMC SOPs and other Federal requirements including, but not limited to, VHA 1200.05, 21 CFR 56, and 21 CFR 312.2(b)(1). The IRB is also responsible for ensuring appropriate monitoring and oversight of the project in accordance with VA and FDA requirements and its own SOPs.

The IRB Administrator, in consultation with the IRB Chair, is responsible for ensuring existence of an active IND application and that the IND number is valid, if applicable.

The IRB Chair must determine whether the protocol meets one of the FDA exemptions from the requirement to have an IND, in the event that the study involving an investigational drug does not require an IND. In the event that the Chair for IRB is the PI, the Chair of R&D Committee will make this determination.

Research Compliance Officer (RCO) is responsible for auditing the requirement for and documentation of an IND at the time of their tri-annual review.

Investigators are responsible for ensuring that a research project involving the use of investigational drugs is conducted in accordance with all applicable FDA, VA, and IRB requirements. If an IND is required by the FDA, the investigator is responsible for submitting the application for the IND. If the study involving an investigational drug does not require an IND, the investigator must explain in the protocol how the study meets one of the FDA exemptions from the requirement to have an IND. Investigators are also responsible for the following:
- Submitting documentation to the BVAMC IRB Administrator of verification for drug studies that an IND application (see below) was submitted to FDA and that it is ‘active’ (i.e. FDA has not put a hold on the IND application).
- Informing the BVAMC IRB when a project involving a FDA-regulated product has been suspended, terminated or closed.
- Following all BVAMC IRB SOPs regarding requests for amendment of a project, continuing review, and reporting of adverse events and unanticipated problems.

To receive an investigational drug as defined by VHA Handbook 1108.04, in addition to FDA regulations for the conduct of research under an IND and investigator responsibilities identified in Paragraph 9 of this Handbook, the investigator must:

(1) Provide the Pharmacy Service or Research Investigational Pharmacy information on each subject receiving an investigational drug through the electronic medical record or other locally approved means. 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, i.e., herbals, nutriceuticals (see VHA Handbook 1108.04).

(2) Ensure the local Pharmacy Service or Research Service Investigational Pharmacy receives:
   (a) Documentation of IRB and any other relevant approvals;
   (b) A copy of VA Form 10-9012, Investigational Drug Information Record, when applicable;
   (c) A copy of the current approved protocol;
   (d) A copy of the informed consent form for each participating subject with all appropriate signatures;
   (e) Documentation of the IRB continuing review approval;
   (f) Copies of sponsor-related correspondence specific to the drug(s) as appropriate;
   (g) Copies of all correspondence addressed to the investigator from the FDA (and other involved authorities) specific to the investigational drug(s) as appropriate;

(3) Inform the Chief of the Pharmacy Service, the research pharmacy when applicable, and the IRB in writing when a study involving investigational drugs has been suspended, terminated, or closed;

(4) Comply with all dispensing requirements;

(5) Comply with all documentation requirements and make relevant records accessible to the investigational drug pharmacist when requested (VHA Handbook 1108.04 6.a.(4));

(6) Comply with all VHA pharmacy requirements regarding receiving, dispensing, storing, and record-keeping for investigational drugs.
   - When applicable, forwarding an updated VA Form 10-9012 to the BVAMC IRB for review and signature if there are any changes to authorized prescribers or any other information on the form.
   - Prior to dispensing an investigational drug, send to the Pharmacy Service a copy of the informed consent form, signed and dated by both the research subject and the individual conducting the consent process.
   - Informing the Chief, Pharmacy Service and the local R&D Committee when a project involving investigational drugs has been suspended, terminated, or closed.
The Pharmacy Service is responsible for the receipt, storage, security, dispensing, and disposition of all investigational drugs in accordance with sponsor, manufacturer, and/or local guidelines.

3. DEFINITIONS

- **Investigational Drug** – A chemical or biologic drug that is used in a clinical investigation. An investigational drug can be a new chemical compound, which has not been released by the FDA for general use, or an approved drug that is being studied for an approved or unapproved use, dose, dosage form, administration schedule or under an Investigational New Drug (IND) application, in a controlled, randomized, and/or blinded clinical trial. 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. Prescription drugs, over-the-counter drugs, nutritional supplements, herbal preparations, and legend items used for diagnosis or treatment and meeting the definition for an investigational drug above, are considered investigational drugs (VHA Handbook 1108.04, paragraph 2f).

- **Investigational New Drug (IND) Application** - An IND is an application to the FDA that allows an investigational drug or biological product to be studied in humans. An IND must be in effect prior to shipment and administration of investigational drug or biological products (see 21 CFR 312). An Investigator IND application is submitted by an investigator who both initiates and conducts an investigation using an investigational drug that is not otherwise exempt from IND and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population. There are two IND categories: Commercial or Research (non-commercial).

- **Test Article** – 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 Food, Drug, & Cosmetic Act or under sections 351 or 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n; 21 CFR 50.3(jj)).

4. PROCEDURES

- For submission of new projects, the investigator will follow the SOP for initial review and all appropriate paper work required on the Checklist for Submission of Research Study for Initial Review, including the VA Form 10-9012 (Investigation Drug Information Record).
- If the project involves an investigational drug, the investigator or sponsor submits one of the following: 1) documentation of the FDA’s letter clarifying the FDA’s receipt of the IND application, 2) justification for not obtaining an IND (explanation of how the
protocol meets one of the FDA exemptions from the requirement to have an IND), or 3) indication that the IND application is pending.

- Submission of FDA IND application should follow the instructions on the FDA webpage. The FDA IND application must contain information in three broad areas:
  - Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
  - Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
  - Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound—to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an IRB, and to adhere to the investigational new drug regulations.

- If the study requires an IND, the IRB Administrator, in consultation with the Chair, IRB, is responsible for ensuring existence of an active IND application and that the IND number is valid, if applicable.

- The IRB Chair (or Chair, R&D Committee in the event that the IRB Chair is the PI) will review copies of FDA correspondence submitted by the investigator, take note of the date on the FDA’s letter stating the receipt of the IND application and ensure 30 days have passed since that date before signing the final R&D Committee approval for the study to start. If the IND is not investigator-initiated (i.e. industry-sponsored), the investigator submits a statement that the sponsor’s IND is active to the BVAMC IRB Administrator. (FDA does not generally issue letters to sponsors of drug studies when the 30-day period has passed.)

- For studies using investigational drugs that do not require an IND, the Chair of the IRB must determine whether the protocol meets one of the FDA exemptions from the requirement to have an IND (as documented by the PI in the protocol). In the event that the IRB Chair is the PI, the Chair of R&D Committee will make this determination. Based on the PI’s documentation, the IRB Chair (or Chair of R&D Committee) determines if the use of the drug meets one of the following exemption criteria and confirms this determination by signing the IND review Form and the final approval letter to the PI:
  
  (1) The clinical investigation of a drug product that is lawfully marked in the United States is exempt from the requirement to obtain an IND if all of the following requirements apply:
    (a) The investigation is not intended to be reported to the 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.
(b) 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 of the product.

(c) 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.

(d) The investigation will be conducted in compliance with the requirements for IRB review and with the requirements for informed consent.

(e) The investigation is conducted in compliance with the requirements of 26 CFR 312.7 on promotion and charging for investigational drugs.

(2) A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
   • Blood grouping serum
   • Reagent red blood cells
   • Anti-human globulin

(3) The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.

(4) The diagnostic test is shipped in compliance with 21 CFR 312.160.

(5) A clinical investigation involving the use of placebo is exempt if the investigation does not otherwise require submission of an IND.

5. REFERENCES

• MCM119-20 Medication Management Policy
• Investigational Drug Information Record (10-9012)
• http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm
• 38 CFR 16, Department of Veterans Affairs, Protection of Human Subjects
• VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research
• VHA Handbook 1108.04, Investigational Drugs and Supplies
• 21 CFR 56, Food and Drug Administration, Institutional Review Boards
• 21 CFR 312, Food and Drug Administration, Investigational New Drug (IND) Application Regulations

6. ATTACHMENTS

• BVAMC IND Review Form

7. REVISIONS

SOP #21 Investigational Drugs December 1, 2010, August 8, 2011, reviewed January 1, 2018
8. **REVIEW DATE**
   January 1, 2021

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