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1 SCOPE AND APPLICABILITY

- 1.1 This standard operating procedure applies to all investigators involved with human subjects' research projects involving investigational drugs, devices, and/or biologics which are submitted to and reviewed by the VA Central IRB. This SOP also applies to VA Central IRB members and the VA Central IRB administrative staff.
- 1.2 This SOP does not include the emergency use of investigational drugs or devices. The VA Central IRB does not review any activities constituting emergency use of test articles as described in Food and Drug Administration (FDA) regulations. The VA Central IRB also does not review projects involving humanitarian use devices. These reviews are conducted by other IRBs of record for the local VA facility.
- 1.3 It is the policy of the VA Central IRB that all VA, FDA, and other requirements for the use of investigational drugs, devices, and biologics be followed in order to ensure the health and welfare of human subjects. Principal Investigator/Study Chairs (PI/SCs) and Local Site Investigators (LSIs) must provide sufficient information with their application materials or as requested for the VA Central IRB to make a determination and to ensure compliance with all VA, FDA, and other requirements.

2 DEFINITIONS

- 2.1 **Clinical Investigation.** Any experiment that involves a test article and one or more human subjects, and that either (1) must meet the requirements for prior submission to the Food and Drug Administration (FDA) under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or (2) need 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. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations 21 CFR 50.3(c) and 21 CFR 56.102(c).
- 2.2 **Investigational Device.** An investigational device is a device that is an object of an investigation. (21 CFR 812.3(g)).
- 2.3 **Investigational Device Exemption (IDE).** An application to FDA that allows an investigational significant risk device to be used in a clinical investigation to collect safety and effectiveness data. If the device is a non-significant device, it is considered to have an approved application for IDE after IRB approval is obtained. (21 CFR 812)
- 2.4 **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, 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. and VHA Handbook 1200.05)



2.5 Significant Risk Device. An investigational device that 1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; 2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health safety, or welfare of a subject; 3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3 (m))

2.6 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. (21 CFR 50.3(j))

2.7 Unanticipated Adverse Device Effect (UADE). Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))

3 RESPONSIBILITY

3.1 PI/SCs are responsible for ensuring that a research project involving the use of investigational drugs, devices, or biologics is conducted in accordance with all applicable FDA, VA, and IRB requirements. PI/SCs are also responsible for the following:

- Submitting documentation to the VA Central IRB of verification that an Investigational New Drug (IND) application was submitted to FDA for drug studies and that it is 'active' (i.e. FDA has not put a hold on the IND application); and that an Investigational Device Exemption (IDE) application has been approved by FDA for significant risk device studies
- Informing the VA Central IRB when a project involving an FDA-regulated product has been suspended, terminated, or closed
- Following all VA Central IRB SOPs regarding requests for an amendments to an approved project, continuing review approval, and required reporting of reportable events
- The receipt, storage, security, dispensing, and record keeping for the overall study of all investigational drugs and devices in accordance with sponsor, manufacturer, and/or local guidelines.

3.2 LSIs are responsible for ensuring at their local site that a research project involving the use of investigational drugs, devices, or biologics is conducted in accordance with all applicable FDA, VA and other requirements for their use, handling, accounting, and storage. In addition to meeting general requirements for conducting a study involving human research participants, LSIs are responsible for the following:

- Providing 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; this information includes allergies, toxicities, or adverse drug events related to the



investigational drug, or the potential for interactions with other drugs, foods, or dietary supplements.

- For projects involving investigational drugs as defined in FDA regulations and VHA requirements, providing the local Pharmacy Service the following:
 - Documentation of VA Central IRB approval;
 - A copy of model VA Form 10-9012, Investigational Drug Information Record, when applicable;
 - A copy of the current approved protocol;
 - A copy of the current informed consent form for each participating subject with all appropriate signatures;
 - Documentation of VA Central IRB continuing approval;
 - Copies of sponsor-related correspondence specific to the drugs as appropriate; and
 - Copies of all correspondence addressed to the investigator from the FDA and other involved authorities specific to the investigational drug as appropriate.
- When applicable, forwarding an updated VA Form 10-9012 to the VA Central IRB for review and signature if there are any changes to authorized prescribers or any other information on the form.
- Informing the Chief, Pharmacy Service, the Research Pharmacy Service when applicable, and the VA Central IRB in writing when a study involving investigational drugs has been suspended, terminated, or closed.
- Ensuring compliance with all dispensing requirements.
- Ensuring compliance with all documentation requirements and VHA Pharmacy requirements, making relevant records accessible to the investigational drug pharmacist when requested.

3.3 The VA Central IRB is responsible for reviewing all research projects involving the use of investigational drugs, devices, and biologics, in accordance with VA, FDA, and other requirements including its own SOPs. The VA Central IRB is also responsible for ensuring appropriate monitoring and oversight of the project in accordance with VA and FDA requirements and its own SOPs. In the case of investigational devices, the VA Central IRB may be required to make a "Significant Risk (SR)" or "Non-significant Risk (NSR)" device determination if applicable.

3.4 The VA Central IRB administrative staff is responsible for ensuring the existence of an active IND or an approved IDE application (for SR device studies) as applicable. It is also responsible for processing these projects and all VA Central IRB documentation in accordance with VA, FDA, and other requirements, including the VA Central IRB SOPs.

3.5 The local pharmacy services are responsible for the receipt, storage, security, dispensing, and disposition of all investigational drugs. In the case of the VA Cooperative Studies, the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CRPCC) is responsible for obtaining the investigational drug and for distributing them to the Pharmacy Service at each authorized local participating site per approved protocol.

4 PROCEDURE

4.1 Submission of New Project Applications and Receipt of the Packages by the VA Central IRB Administration Office

- 4.1.1 For new projects, the PI/SC and LSIs submit as applicable the VA Central IRB Form 108, Principal Investigator/Study Chair New Project Application, and VA Central IRB Form 104,



Local Site Investigator Application, as detailed in VA Central IRB SOP 108, Submission Requirements for VA Central IRB Review of a New Project.

- 4.1.1.1 The PI/SC and LSIs include the model VA Form 10-9012, Investigational Drug Information Record, and the site specific forms with the application packages, if applicable.
 - 4.1.1.2 If the project involves an investigational drug, the PI/SC also includes a copy of FDA's letter indicating receipt of the IND application, justification for not obtaining an IND, or confirming the status of the IND as pending.
 - 4.1.1.3 If a project involves the use of a significant risk device, the PI/SC's application must contain a copy of FDA's approval letter stating the IDE application is approved and the study can start, or the PI/SC must state that the IDE approval is pending.
 - 4.1.1.4 If a project involves the use of a non-significant risk device, the application must contain a copy of the sponsor's brief explanation of why the device is not a significant risk device.
 - 4.1.2. Upon receipt of the application package, the VA Central IRB administrative staff processes the project for review by the VA Central IRB in accordance with VA Central IRB SOP 108, VA Central IRB Meeting Preparation and Administration.
 - 4.1.3 If the study requires an IDE or an IND, the VA Central IRB administrative staff ensures the existence of the IND or IDE, as applicable, and documents the results on VA Central IRB Form 109b, Administrative Screening Checklist for PI/SC New Project Applications. Ensuring the existence of an IND or IDE is performed by reviewing copies of FDA correspondence submitted by the investigator as follows:
 - 4.1.3.1 For drug studies: A copy of the letter from the Center for Drug Evaluation and Research (CDER) stating receipt of the IND application. The VA Central IRB will take note of the date on the letter and ensure 30 days have passed since that date before allowing the study to start. In addition, the VA Central IRB obtains a statement from the study organizers that the IND is active; that is, FDA has not placed the IND application on hold. (FDA does not generally issue letters to sponsors of drug studies when the 30-day period has passed.)
 - 4.1.3.2 For significant risk device studies: A copy of the letter from the Center for Devices and Radiological Health (CDRH) approving the IDE application and stating the study can start.
- 4.2 VA Central IRB Review of New Projects Involving the Use of Investigational Drugs
- 4.2.1 The VA Central IRB will not approve a new project using an investigational drug until it ensures the IND is active and that 30 days have passed since the date of FDA's letter to the project sponsor stating that the IND application was received or an IND exemption has been



determined. Investigators are encouraged to contact the sponsor of the study prior to submitting a project to the VA Central IRB if there is a question as to whether an IND is needed.

4.2.2 If the project was submitted as a study with an IND exemption and there is no copy of FDA's letter stating an IND application was received by FDA, the VA Central IRB determines if the use of the drug meets one of the following exemption criteria:

4.2.2.1 The study involves the clinical investigation of a drug product that is lawfully marketed in the United States and all of the following requirements are met:

- 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;
- The investigation is not intended to support a significant change in the advertising for the product;
- 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;
- The investigation will be conducted in compliance with the requirements for IRB review and with the requirements for informed consent; and
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 on promotion and charging for investigational drugs.

4.2.2.3 A drug intended solely for tests in vitro or in laboratory research animals is exempt if shipped in accordance with 21 CFR 312.160.

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

4.2.2.5 A clinical investigation involving blood grouping serum, reagent red blood cells, or anti-human globulin if 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.

4.2.3 Once the VA Central IRB ensures the existence of an IND application or it determines the project is exempt, a decision is made in accordance with VA Central IRB SOP 109, Review of Projects by the Convened Board, with the results of the review communicated to the PI/SC, LSIs and the local participating facilities in accordance with VA Central IRB SOP 111, VA Central IRB Communications with Investigators and Local Participating Sites.

4.2.4 In addition to the final approval memorandum that is sent to the participating sites, copies of the local VA Form 10-9012, Investigational Drug Record, that are signed by one of the VA Central IRB Co-Chairs, are also forwarded. Copies of these forms are then forwarded by the local R&D Committee or the LSI to the local Pharmacy Service.

4.3 VA Central IRB Review of New Projects Involving the Use of Investigational Devices



- 4.3.1 If a new project is submitted to the VA Central IRB involving an investigational device that already has an IDE, the device is considered a SR device. The project is then reviewed at a convened meeting of the VA Central IRB in accordance with VA Central IRB SOP 109.
- 4.3.2 If a new project is submitted using an investigational device that is described as exempt from FDA regulation 21 CFR 812.2(c), the VA Central IRB determines if the project meets one of the following criteria for exemption from the requirement to obtain an IDE:
- 4.3.2.1 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.
- 4.3.2.2 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 and approved.
- 4.3.2.3 A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing meets **all** of the following criteria:
- It is noninvasive,
 - It does not require an invasive sampling procedure that presents significant risk,
 - It does not by design or intention introduce energy into a subject **and**
 - It is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic procedure or product.
- 4.3.2.4 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.
- 4.3.2.6 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.
- 4.3.3 If a clinical investigation is submitted using an investigational device described by the sponsor as a non-significant risk device, the VA Central IRB will make their own determination of SR or NSR. If the VA Central IRB agrees with the sponsor's NSR determination, review of the project by the IRB can continue in accordance with SOP 109, Review of Projects by the Convened Board. (However, if the IRB's determination disagrees with the sponsor's determination, the IRB follows procedures at 4.3.4.) The VA Central IRB makes their SR or NSR risk determination based on the following:
- The sponsor's brief explanation, which was provided by the investigator in the new project application, of why the device is not a significant risk device;
 - The proposed use of the device, as well as its intrinsic design and construction;
 - Reports of prior experiences and investigations;



- Comparison with devices that were previously designated SR or NSR by FDA;
- The project rationale, design, and participant selection criteria;
- Risk assessments and monitoring procedures used by a sponsor and/or investigator;
- Discussion with FDA officials if appropriate; and
- Additional information from outside consultants if appropriate.

4.3.4 Projects involving devices deemed by the sponsor to be NSR, which the VA Central IRB has determined involve the use of a SR device, are not further reviewed by the VA Central IRB. The rationale for the SR determination is documented in the minutes of the VA Central IRB meeting at which the determination was made. The VA Central IRB notifies both the PI/SC and the sponsor in writing of the results of the review and the requirement to obtain an IDE before any further review can take place.

4.4 VA Central IRB Review of Continuing Reviews, Amendments, and Other Actions. The VA Central IRB reviews all other actions regarding projects involving the use of investigational drugs, biologics and devices in accordance with the applicable VA Central IRB SOPs pertaining to those actions.

5 DOCUMENTATION REQUIREMENTS

5.1 The following are documentation requirements concerning the use of investigational drugs, devices, and biologics:

5.1.1 The VA Central IRB maintains electronic and hard copies of all required project documentation, including all FDA correspondence (IND applications and related FDA actions in accordance with VA Central IRB SOPs concerning maintenance of project files, correspondence, and meeting minutes.

5.1.2 Through the electronic medical record or other locally approved means, LSIs will provide the Pharmacy Service or Research Investigational Pharmacy with the information identified in Section 3.2, for each subject receiving an investigational drug.

6 REFERENCES

- 6.1 38 CFR 16, Department of Veterans Affairs, Protection of Human Subjects
- 6.2 VHA Handbook 1200.5, Requirements for the Protection of Human Subjects in Research
- 6.3 VHA Handbook 1108.04, Investigational Drugs and Supplies
- 6.4 21 CFR 56, FDA, Institutional Review Boards
- 6.5 21 CFR 312, FDA, Investigational New Drug (IND) Application Regulations
- 6.6 21 CFR 812, FDA, Investigational Device Exemptions (IDE) Regulations



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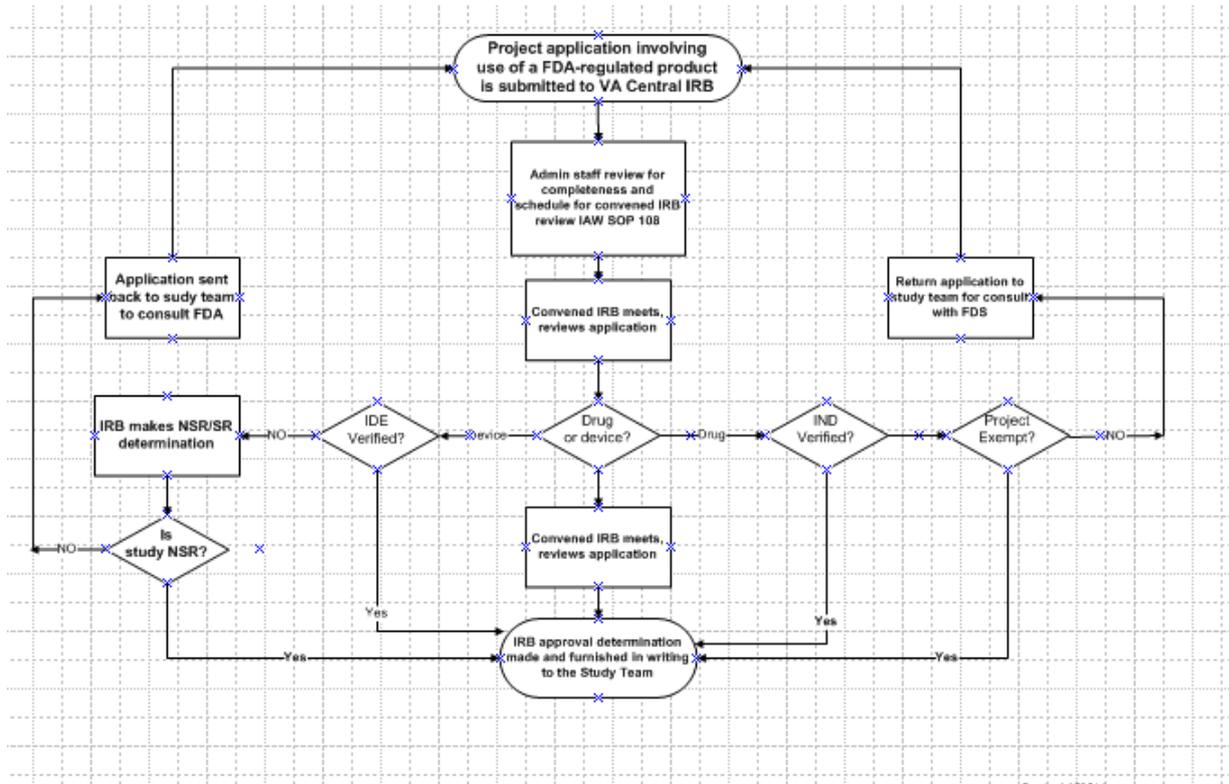
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Attachment 1: VA Central IRB SOP 117 Process Chart



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Investigational Drugs, Devices, and Biologics

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