



# Stratton VA Medical Center IRB Standard Operating Procedure: IND, IDE & Biologics in Human Research

## POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, local, and ICH guidelines in the conduct of clinical research studies involving test articles requiring IND, IDE and biologics. Written procedures are required to guide the IRB in the review of this type of research

## REFERENCES

45 CFR 46

21 CFR 50, 56, 312,812

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

## PROCEDURE

The IRB will review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by the Stratton VA Medical Center OHRP Federal Wide Assurance (FWA #00002073).

**Research Involving Investigational FDA Regulated Test Articles.** Medical products, such as drugs, biologics, and medical devices need to be proven safe and effective before the FDA can approve them for sale to and use by patients. FDA reviews the results of laboratory, animal and human clinical testing to determine if the product to be put on the market is safe and effective. New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

An approved investigational device exemption (IDE) permits device not approved by FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE (see para 3, pg 2)

All clinical research being done on FDA regulated test articles with either an IND or IDE will receive initial review at a convened IRB meeting. No claims should be made, either explicitly or implicitly, that the drug, biologic, or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic, or device.

If drugs or biologics are to be administered in the protocol, the Principal Investigator must specify the IND status on the New Protocol Submission Form.

An IND must be filed when the objective is to test the safety and efficacy of a newly developed drug for indications, marketing, labeling (or advertisement) change in indication(s), change in dosing, route of administration, patient population for whom the drug can be indicated, or any change from a (previously) approved use. Exemptions to this rule are noted in 21 CFR Part 312.2. An IND must be filed for uses of a drug other than the use of an approved drug in the course of medical practice unless the FDA exemptions are met.

If an IND/IDE is not listed or pending, the IRB staff will not accept the submission from the Principal Investigator(s) or designated contact person until the information is complete. As necessary, the IRB will review the actual IND/IDE submission from the sponsor before final protocol review. The IRB must ascertain that the IND adequately delineates the scope of the research proposed and that the submission has been completed and approved by the FDA.

**Investigator and Sponsor Responsibilities.** The interrelationship and interaction between the research sponsor (e.g., drug and device manufacturer) the clinical investigator and the IRB may be very complex. Sponsor-IRB interaction customarily occurs through the investigator who conducts the clinical study. The clinical investigator generally provides the communication link between the IRB and the sponsor. Such linkages are agreed to by the sponsors and the investigator when they sign forms FDA 1571 and FDA 1572. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The clinical investigator should be kept apprised of the discussion. Because clinical investigators work directly with the IRB, it is appropriate that they assure the sponsor that the IRB is functioning in compliance with the regulations. The IRB must notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity [21 CFR 56.109(e)]. This correspondence should be made available to the sponsor by the clinical investigator.

Under FDA regulations, the investigator in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include: (see also Investigator Responsibilities SOP)

- Obtaining IRB approval;
- Obtaining informed consent from each participant;
- Following the investigational plan;
- Complying fully with the regulations;
- Protecting the rights, welfare and safety of the subjects;
- Supervising the use and disposition of the test article according to all VA, FDA and local policies;

- Maintaining accurate, current and complete records; and
- Disclosing relevant financial information.

**The investigator will:**

- assure that the IRB will be responsible for the initial and continuing review and approval of the clinical investigation;
- promptly report to the IRB all changes in the research activity;
- promptly report all unanticipated problems involving risks to human subjects or others, and
- not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

Sponsor/Investigator - the sponsor takes responsibility for initiating the clinical investigation and holding the IND or IDE in most cases, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. A sponsor-investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The Stratton VA Medical Center infrequently allows sponsor-investigator clinical research.. Some of the responsibilities of sponsors are:

- Selecting qualified investigators;
- Providing investigators with the information they need to conduct the investigation properly;
- Ensuring proper monitoring of the investigation; and
- Ensuring that the FDA and (for devices) any reviewing IRB or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

The IRB will ascertain that there is appropriate training (verifiable) for the investigator before the initiation of the research using investigational drugs, biologicals or devices (including the storage, security and dispensing). Training can include education by the sponsor (documented) or professional training or experience of the investigator, usually associated with specialty board certification or verifiable clinical privileges and experience.

Sponsor/Investigators will be given appropriate introduction by the Research staff to the regulatory requirements for sponsorship of the above described research and the investigator will verify that he/she has received training to the IRB. Research staff will review the responsibilities with the sponsor/investigator prior to the initiation of the research. Training and orientation will include appropriate information regarding both IND and IDE related research (21 CFR 812).

For IND requiring research, the Investigator is responsible for investigational drug/biologic accountability (storage, security, dispensing, administration, return, disposition and records of accountability). The PI will delegate responsibility for drug/biologic accountability to Pharmacy Service. When the investigational drug/biologic is delivered to the PI, the PI is responsible for assuring prompt delivery of the investigational drug/biologic to Pharmacy Service.

For device related research (holding an IDE), the investigator proposing device research will be required to provide a written plan, that will be evaluated and approved by the IRB, that will include:

- a. Receipt
- b. Security of the device(s)
- c. Storage, including location, identification as RESEARCH USE ONLY, and separation from non-research clinical devices.
- d. Use (dispensing or use), including continuous inventory
- e. Return/disposition
- f. Documentation of control of device

All documentation of the above must be maintained in the Investigator's regulatory document folder.

IRB Review of Investigational Medical Devices: Investigational devices can only be used after appropriate review and approval of the protocol submission and supporting documents.

Investigators initiating or participating in research under an IDE must adhere to FDA, OHRP, and VA regulations. The Principal Investigator is responsible for the storage, security and dispensing of the device as outlined in the approved research protocol. The PI maintains records and tracking of investigational devices. All investigational medical devices must be stored in a secure location, accessible only to study personnel. The storage area must meet any conditions provided by the manufacturer related to environmental review. Investigational medical devices will be dispersed only to subjects in the approved research protocol who have signed an informed consent form and HIPAA authorization.

The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects. The investigator should maintain records that document adequately that the subjects are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

Clinical investigations of medical devices must comply with the FDA informed consent and IRB regulations [21 CFR 50 and 56, respectively]. FDA device regulations differentiate between significant risk (SR) and non-significant risk (NSR) devices. A significant risk device must have an IDE, while a non-significant risk device does not. Thus, if a clinical investigation is submitted to the IRB for a device that has an IDE, the device is considered a SR device.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR 50].

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses a SR, the IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the participant must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with the IRB's decision that a device study presents a NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study would be presented to IRB as a NSR investigation.

### **Determination of Risk Level**

Under some circumstances, the IRB must determine whether a device involves significant risk (SR) or non-significant risk (NSR) to subjects. Because NSR studies do not require an IDE, a clinical investigation involving an investigational device classified by the sponsor as NSR may be submitted to the IRB for review without an IDE. The sponsor should provide the IRB with a risk assessment and the rationale used in making its NSR risk determination. In this situation, the IRB reviews the information and makes its own independent determination that the device is SR or NSR. The IRB rationale for making the NSR/SR determination must be documented in IRB minutes.

(1) If the IRB determines that the study involves a SR device (disagrees with the assessment of the sponsor), then it would be governed by the IDE regulations at 21 CFR 812. The IRB would notify both the investigator and the sponsor of its determination, and the sponsor would need to submit an IDE application to the FDA. The study could not begin until the FDA approves the IDE and the IRB approves the study.

(2) If the IRB determines that the device is classified as NSR (concur with the assessment of the sponsor), the clinical investigation may begin once IRB approval is obtained since the submission of an IDE application to the FDA is not required. (*Note: The terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.*)

(3) If FDA agrees that a new device is substantially equivalent to a device already on the market, it can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE regulations, IRB review, and informed consent.

### **FDA IND Exemptions**

Using the Primary Reviewer Form, to be reviewed by the full IRB for full-board protocol reviews and by the IRB Chair and scientific reviewer for expedited reviews, the IRB must determine whether a study qualifies for an IND Exemption [Categories in 21 CFR 312.2(b)]

Exemption 1: The drug product is lawfully marketed in the United States. 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. 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. 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 is conducted in compliance with 21 CFR §50 and §56. The investigation is conducted in compliance with the requirements of 21 CFR §312.7.

Exemption 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.

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. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exemption 4: A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

### **FDA IDE (Device) Exemptions**

Using the Primary Reviewer Form, to be reviewed by the full IRB for full-board protocol reviews and by the IRB Chair and scientific reviewer for expedited reviews, the IRB must determine whether a study qualifies for an IDE Exemption [Criteria in 21 CFR 812.2(b)(1)]

- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR §812.5.
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR §50 and documents it, unless documentation is waived.
- The sponsor complies with the requirements of 21 CFR §812.46 with respect to monitoring investigations.

- The sponsor maintains the records required under 21 CFR §812.140(b) (4) and (5) and makes the reports required under 21 CFR §812.150(b) (1) through (3) and (5) through (10).
- The sponsor ensures that participating investigators maintain the records required by 21 CFR §812.140(a)(3)(i) and make the reports required under §812.150(a) (1), (2), (5), and (7).
- The sponsor complies with the prohibitions in 21 CFR §812.7 against promotion and other practices.

### **Adverse Events and Reporting Requirements**

Some requirements for reporting AEs are the same; regardless of what sort of test article is used (e.g. a drug or a device).

General Investigator Responsibilities for Reporting Adverse Events (AEs): FDA, VA, and DHHS regulations require prompt reporting to the IRB, FDA, OHRP, and the Office of Research Oversight (ORO) of any unanticipated problems involving risks to human subjects and others.

- (a) FDA interprets “any unanticipated problems involving risks to human subjects” to mean “...an unexpected adverse experience that is not listed in the labeling for the test article. ...including an event listed in the labeling ...that differs ...because of greater specificity or severity” (FR 28027).
- (b) FDA interprets “...and others” to mean, “...persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures developed in those trials” (FR 28027).

The Principal investigator is responsible for promptly reporting serious and unanticipated AEs to the IRB.

IRB Reports to the R&D Committee: The IRB provides notification of AEs to the R&D Committee in the IRB minutes.

Any AE information submitted to the sponsor by investigators should also be submitted to the IRB when summarizing their experience in the request for continuing review. In addition to providing prompt written notification to relevant Federal agencies, including ORO, FDA, and OHRP, of any unanticipated problems involving risks to subjects or others, the IRB should also report the resolution of those problems.

AEs and Reporting Requirements – IDEs. FDA IDE (device) reporting requirements are similar but not exactly the same as for drugs and biologics.

Investigator to Sponsor: FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect within 10 days of discovery.

Sponsor to FDA, Investigator, and IRB. The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all

reviewing IRB(s) within 10 working days of the sponsor's receipt of the information.

Expanded Access to Investigational Devices: According to the statute and FDA regulations, an unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must be contacted, as the sponsor must submit a supplement to the IDE as part of the process. The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

(1) Single Patient/Small Group Access to Investigational Devices. Allows access to a device where patient is not eligible for an ongoing clinical trial. The participant must have a serious condition/disease, with no alternative intervention available. Under some conditions, FDA may grant permission even if there is no pre-existing IDE.

- (a) Participant must have a serious condition/disease, with no alternative intervention available.
- (b) Must contact sponsor, asking to use device.
- (c) Sponsor submits IDE supplement to FDA requesting waiver, providing justification for use (may be able to do, even if no pre-existing IDE).
- (d) FDA issues response in 30 days or less (FDA must approve use).

(2) Treatment Use/IDE (21 CFR 812.36). Allows wider access to a device during the clinical trial or prior to final action on marketing application. Again, the participant must have a serious condition/disease, with no alternative intervention available.

- (a) Participant must have a serious condition/disease, with no alternative intervention available.
- (b) Must contact sponsor, asking to use device.
- (c) Sponsor submits treatment IDE supplement (pre-existing IDE required).
- (d) FDA must approve.

(3) Continued Access to Investigational Devices. Allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims. There must be a public health need for the device, as well as preliminary evidence that the device is effective.

(a) Public health need for the device.

(b) Preliminary evidence that the device is effective.

(c) No significant safety concerns identified for the proposed indication.

(d) Conducted under a formal protocol with controlled rate of enrollment.

(e) Can collect additional evidence of safety and effectiveness.

(f) May be used to address new questions regarding the investigational device, such as labeling claims.

(g) Sponsor submits IDE supplement.

(4) Access under a formal protocol. Access in a controlled rate of enrollment and with no significant safety concerns identified for the proposed indication.

IRB Findings and Determinations Where Documentation is Required by Regulation: While the regulatory agencies agree on what will be documented, the methods of documentation are not regulated. FDA guidance allows certain findings to be documented in other formats, such as reviewer checklists that are filed in the protocol files. Documentation shall be provided for the following items when appropriate:

(1) The level of risk of the research.

(2) The approval period for the research, including identification of research that warrants review more often than (at least) annually. Approvals are valid for a maximum of 365 days unless the IRB feels that potential risks are such that the review period should be for a shorter period.

(3) Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research (e.g., Cooperative Studies, or other collaborative research).

(4) Justification for waiver or alteration of informed consent, addressing each of the four (4) criteria at 38 CFR 16.116(d). (*Note: This cannot be done if a FDA test article is involved.*)

(5) Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 38 CFR 16.117(c).

(6) The special protection warranted in specific research projects on groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research. For proposals that identify the potential for enrolling subjects who could be vulnerable to coercion or undue influence, the IRB documents its consideration of additional safeguards to protect the rights and welfare of vulnerable subjects.

(7) Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special 45 CFR 46.101(i) DHHS waiver or the FDA exception at 21 CFR 50.24.

(8) Consideration of the impact of study design on risk.

(9) Consideration of provisions for safety monitoring.

(10) Determination that risks has been minimized to the extent possible.

(11) Determination of the risk level of investigational devices.

(12) The interval of continuing review is at least once per year.

(13) The interval of continuing review is appropriate to the degree of risk.

(14) Approval of research on the basis that risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects, and the importance of the knowledge that may be expected to result from research.