



# Stratton VA Medical Center IRB Standard Operating Procedure: Investigator Handbook

This document will guide Principal Investigators in their Human Research Protection Program (HRPP) responsibilities. The PI is required to read this document and acknowledge so by signing the attached Investigator Agreement. The PI is required to meet in person with the Associate Chief of Staff for Research & Development (ACOS/R&D) prior to initiating any human subjects research. A protocol specific Investigator Agreement will be signed by both the PI and the ACOS. This document must be submitted to the HRPP Coordinator before the PI initiates the project. The PI should contact the Research Office with any questions and become familiar with the more detailed IRB Standard Operating Procedures (which are available on the Research website at:

<http://visn2portal/sites/albresearch/Research%20Forms/Forms/AllItems.aspx>

Within VA, a Principal Investigator (PI) is an individual who conducts a research investigation, i.e., under whose immediate direction research is conducted, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team [VHA Handbook 1200.5 3.t]. The PI must have the appropriate training and be credentialed to conduct research involving human subjects by a program that meets all VA requirements. The investigator has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug, when applicable.

An investigator is an individual under the direction of the principal investigator (PI) who is involved in some or all aspects of the research project, including the: design of the study, conduct of the study, analysis and interpretation of the collected data, and writing of resulting manuscripts. An investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970. [VHA Handbook 1200.5 3.n] A researcher is either an investigator or a principal investigator.

The FDA considers an investigator and a principal investigator to be synonymous [VHA Handbook 1200.5 3.n].

PI shall prepare protocols giving complete descriptions of the proposed research. The PI must develop a research plan that is scientifically valid, minimizes risk to the subjects while maximizing benefits, and contains a description of the data and safety monitoring plan that includes the reporting mechanism of adverse events (AE's) to the IRB, and when required to Office of Research Oversight (ORO), VA Central Office of Research

and Development (ORD), and other Federal agencies or sponsors. The research plan must include provisions for the adequate protection of the rights and welfare of prospective subjects and ensure that pertinent laws and regulations are observed. Minimizing risks should include using procedures already required for diagnostic or treatment purposes in the protocol where possible.

The PI is responsible for obtaining initial and continuing IRB review and approval and for submitting to the IRB requests for modifications to the protocol. All proposed research involving human subjects must be reviewed and approved by the IRB and the R&D Committee prior to initiation of the research project. Research cannot begin until the PI receives final, written approval from the ACOS/R&D. The investigator is expected to know the date of the continuing review and to be aware that IRB approval for the project expires automatically when the continuing review does not occur prior to the expiration date. The PI must report progress of the research to the IRB as often and as in the manner prescribed by the IRB, but not less than once per year and submit a consent log of study subjects.

The PI is also responsible for ensuring education and training to employees conducting research (including mandated human subjects protection and good clinical practice training if applicable), and that they are aware of the regulatory requirements which affect them, are knowledgeable about the organization's ethical standards, and the supervision of delegated responsibilities (i.e., data collection, consent process, etc.), and the conduct of the research. A Scope of Practice is submitted for each member of the research team (except the PI) specific to the research-related duties and responsibilities as outlined by the PI.

## **ETHICAL PRINCIPLES**

VA research must be carried out in an ethical fashion. The basic ethical principles governing research involving human subjects are described in the following documents:

The Nuremberg Code: The modern history of human subject protections began with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles known as the Nuremberg Code. The Code is significant in that it addressed: 1) the necessity of voluntary consent on the part of the human subject, and 2) the personal responsibility of any individual "who initiates, directs, or engages in the experiment" to ensure the quality of consent.

The Declaration of Helsinki: Similar principles have been articulated and expanded in later codes, such as the World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, revised 1975, 1983, 1989, 1996, 2000). This code calls for prior approval and ongoing monitoring of research by independent ethical review committees.

The Declaration states that all subjects and controls should not receive less than the best effective therapy.

The Belmont Report: Revelations emerged in the early 1970s about the 40-year United States Public Health Service Study of Untreated Syphilis in the Negro Male at Tuskegee and other ethically questionable research. This resulted in 1974 legislation calling for regulations to protect human subjects and for a National Commission to examine ethical issues related to human subject research. The Commission's final report, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, defines the ethical principles and guidelines for the protection of human subjects. The three basic ethical principles are:

- (1) **Autonomy** by showing respect for persons by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations
- (2) **Beneficence** by weighing risks and benefits
- (3) **Justice** by the fair selection of subjects.

## **DEFINITIONS OF "RESEARCH" AND "HUMAN SUBJECT"**

### **Department of Health and Human Services (DHHS) and Department of Veterans Affairs (DVA)**

*"Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. Research subject to regulation, and similar terms is intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature [for example, Wage and Hour requirements administered by the Department of Labor, .]" Section 16.102(e)].*

*"Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) Identifiable private information. Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject."*

## **Food and Drug Administration (FDA)**

All research involving FDA regulated drugs, devices and biologics (regardless of funding source) are subject to the regulations found at Title 21CFR 50 and 56 and CFR 54, 312, 314, 600, 812, and 814 as applicable.

*Per FDA Title 21 CFR 50 and 56: Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory. An activity is FDA regulated research when:*

- 1. It involves the use of a drug (approved or unapproved), except for the use of an approved drug in the practice of medicine.*
- 2. It involves the testing of the safety or efficacy of a medical device.*
- 3. The date will be reported to or held for inspection by FDA.*

*Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. Under 21 CFR 812 this also includes an individual on whose specimen an investigational device is used.*

*Test article means 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 act or under sections 351 or 354F of the PHS ACT (21CFR50.3(j); 21 CFR 56 102(l))*

## **CONSENT PROCESS**

Investigators should understand that informed consent is a continual process throughout the participant's involvement in the research. Investigators should conduct the informed consent process in a way that meets the criteria for legally effective informed consent. (Please see Informed Consent SOP IRB-010 for detailed requirements for the Informed Consent Process.)

### **Obtaining Informed Consent.**

(1) Investigators wishing to involve human beings as subjects in research will obtain legally effective informed consent of the subject or the subject's legally authorized representative (unless an exemption is authorized by the IRB). An IRB-approved, date-stamped HIPPA authorization form signed by the participant and a "Protecting Research Subjects With Impaired Decision Making Capacity (IDMC) – IDMC Screening" form signed by the investigator or designee must be attached to all VA research consent forms (10-1086). (No subjects with IDMC may be enrolled unless prior approval has been received from the IRB.) The principal investigator must ensure the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team actually obtain and document consent. Investigators must inform the IRB of such matters as the timing of obtaining informed consent and of any waiting period (between informing the participant and obtaining the consent) that will be observed. For DHHS supported clinical trials, the DHHS approved sample consent form must be submitted (if one exists).

(2) Investigators need to be prepared to respond to subjects' concerns, complaints or requests for information. Investigators will provide contact information for concerns, complaints and requests for information on the informed consent form and will involve the IRB in complaints or requests for information, when appropriate.

(3) The investigator is responsible to notify subjects when there are significant findings that would be pertinent to a subject's continued participation. When it is anticipated that significant new findings that would be pertinent to the subject's continued participation are likely to occur during the subject's participation in the study, the investigator needs a reasonable plan to notify participants.

## **Documenting Informed Consent**

(1) Written consent form. Except when the requirement for written informed consent is waived or altered by the IRB, informed consent will be documented by the use of an IRB approved and date stamped written consent form and signed by:

(a) The subject and or the subject's legally authorized representative with date

(b) The person obtaining consent, with printed name and date.

(c) The witness (a third party whose role is to witness the subject's or the subject's legally-authorized representative's signature) with printed name and date.

Note: The person obtaining consent and the principal investigator may **not** serve as witnesses.

(2) The original signed and dated consent form must be retained in the investigator's research file under conditions of confidentiality.

(3). A copy of the signed and dated consent form must be given to the subject or the subject's legally authorized representative.

(4) The consent form must be scanned into the electronic medical record by Health Information Management Systems (HIMS).

- (5) Copy of the signed and dated consent form is to be sent to the Research Office within 5 days of obtaining signature.

If someone other than the investigator conducts the interview and obtains consent, the investigator must formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity. The investigator remains ultimately responsible, even when delegating the task of obtaining to another individual. Obtaining consent must be included in the Research Scope Of Practice of individuals who are delegated the authority to obtain consent for all protocols submitted for initial IRB review (exception: Research Scopes of Practice are not required for PIs and medical staff who are credentialed through VetPro). The individual may not begin obtaining consent until appointment, credentialing and training have been verified.

### **HIPAA Authorization**

Investigators who involve human beings as subjects in research must obtain legally effective authorization for the use and disclosure of the subject's Personal Health Information (HIPAA Authorization or waiver from the IRB). If the investigator requires a waiver or alteration of the HIPAA Authorization, the investigator must provide the IRB with information sufficient for the IRB to find that such waiver or alteration is necessary. The IRB must document its decision in its minutes.

### **Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)**

A DSMB or DMC needs to be part of the monitoring plan when required by NIH or FDA. The use of a DSMB or DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are particularly high-risk, or vulnerable populations are included. Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, the investigator will provide information to the IRB on appropriate additional safeguards to protect the rights and welfare of these subjects. If a DSMB is used, all events must be reported to the DSMB and a summary of the DSMB findings must be submitted to the IRB and other entities as required.

### **For Department of Defense-sponsored research regarding Data Monitoring:**

The appointment of a research monitor is required for research involving greater than minimal risk, although the IRB can require for a portion of the project or for studies involving no more than minimal risk if appropriate. The following conditions must be met:

- An independent research monitor shall be appointed by name
- The research monitor will have the authority to:
  - Stop a research study in progress.
  - Remove individuals from study.
  - Take any steps to protect the safety and well being of subjects until the IRB can make an assessment.

## **Screening for Impaired Decision Making Capacity**

Screening for impaired decision making capacity will be conducted during all consent interviews. Questions will be utilized to screen for understanding and ability to make an informed judgment in the subject's own best interest regarding whether or not to serve as a study volunteer. The "Protecting Research Subjects With Impaired Decision Making Capacity (IDMC) – IDMC Screening" form will be utilized for this purpose. It is first assumed that prospective subjects have decision making capacity. The IDMC form is used as a tool for screening and is not intended as a medical assessment of decision making capacity. The investigator or designee, trained in the consent process, will ask IDMC questions of the subject and will sign the form. The form will be maintained in the investigator's study file. Potential subjects who demonstrate impairment in decision making capacity will not be permitted to enroll as subjects unless the IRB has previously approved enrollment of subjects with impaired decision making capacity. In these cases a surrogate must provide consent. In cases where the prospective subject does not demonstrate sufficient decision making capacity, the practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

## **Surrogate Consent for Person Who is Incompetent or Has an Impaired Decision-making Capacity (IDMC)**

(See SOP on Impaired Decision Making Capacity for a description of individuals who can serve as a legally authorized representative and provide surrogate consent.)

1. Before an incompetent person or person with impaired decision-making capacity may be considered for participation in any VA research, the IRB must find that following conditions are met: IRB composition (IRB composition is an institutional responsibility, provided here for information only)
  - (1) The IRB must include at least one member who is an expert in the area of the research
  - (2) Consider adding a member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population
- b. Research involving persons with impaired decision-making capability (IDMC) may only be approved when the following conditions apply
  - (1) Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. This item [1. b. (1)] comes from VHA Handbook 1200.5, Requirements for the Protection of Human Subjects in Research. This item is applied as follows:

- (a) This means that persons with IDMC must be necessary to the research. If the research can produce valid results without them, then persons with IDMC should not be included. The following sentence in criteria one permits both subjects with IDMC and those who do not have IDMC to be included in the study if there is a compelling reason to do so for the scientific validity of the research. "The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects."
- (b) The notification to the IRB for any protocols that may need to include subjects with IDMC must attest to the fact that subjects with IDMC are needed in order to have a representative sample of subjects with the condition/characteristic being studied. (This can include studies with just those with IDMC or both those with IDMC and those who do not have IDMC.)
- (2) The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant
- (3) Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. The representative must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest
- c. The IRB must make a determination in writing of each of the criteria listed in (1), (2) and (3) of b. above.
- d. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives. Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.
- f. Such consent (from surrogate) may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note.
  - (1) The practitioner, in consultation with the COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
  - (2) Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-

making capacity is based on a diagnosis of mental illness. Item f. (2) comes from VHA Handbook 1200.5, Requirements for the Protection of Human Subjects in Research, July 15, 2003. This item is applied as follows: A diagnosis of mental illness per se does not indicate a determination of IDMC. The Impaired Decision Making Screening form will be used as the first part of a process to identify those potential subjects who may have IDMC. If the screener determines that the subject has capacity using the usual screening instrument, no further evaluation is necessary and is documented in the research note. If in the determination of IDMC, [as described in f. (1) above] the practitioner is not certain that the patient has decision making capacity and believes that the patient may have an Axis I DSMIV psychiatric diagnosis, the practitioner must consult with a psychiatrist or licensed psychologist to make the final determination of IDMC. In any event, if the practitioner experiences any unease with respect to the role that mental illness (in the context of an Axis I DSMIV diagnosis) may play in the IDMC, the practitioner is encouraged to consult with a psychiatrist or licensed psychologist.

## **RESOURCES**

The PI determines that the resources necessary to protect participants are present before conducting the research study and throughout the conduct of the study. The PI must provide enough specific information for the IRB to assure adequate resources are in place for human research protection, care of research participants and safety during the conduct of the study, i.e. facilities, staff, supplies, space, etc.

## **CONFLICT OF INTEREST**

A conflict of interest occurs when any arrangement, situation or action, financial or otherwise, affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings. The impact of the conflict may occur in any phase of the research from the development of the study design, to the consenting of research subjects, and to the management of the study. The conflict may also bias review of proposals, analysis of data and dissemination of research results through publications and presentations.

The PI and each member of the research team will complete a research Conflict of Interest Disclosure form as part of their application to conduct research. PIs will be familiar with and comply with the stipulations in the IRB SOP entitled: Conflict of Interest. The Conflict of Interest Administrator (ACOS/R&D) will determine whether there is an actual or potential conflict of interest that could impact a PIs current or proposed research and determine what conditions or restrictions (if any) should be imposed to manage, reduce or eliminate the conflict.

## POSTING RESEARCH NOTES INTO CPRS

A posting is not required in the medical record if the research involves no more than minimal risk and the research subject's participation involves:

1. only one encounter (i.e. healthy volunteer blood draw),
2. only the use of a questionnaire,
3. the use of previously collected biological specimens, or
4. the ability to identify a patient as a participant in a particular study places the participant at greater than minimal risk.

Investigators should document these research activities in the investigator's research case history file. All other exceptions from documentation in the medical record are at the discretion of the IRB upon request of the Principal Investigator.

**A. Research Study Initiation Note** - Once this note is signed, it will appear in the participant's EMR under "CLINICAL WARNING" in the upper right corner of the cover sheet.

Procedure:

1. Access the participant's EMR.
2. Click on the "NOTES" tab.
3. Click on "NEW NOTE".
4. Click on "RESEARCH STUDY INITIATION NOTE".
5. Enter the following required information:
  - a. Title of the research study.
  - b. Name of Principal Investigator, study coordinator, and other relevant study personnel.
  - c. The name of the individual obtaining informed consent and date informed consent was obtained.
  - d. Contact information in case of emergency or need for further information regarding protocol therapy. This should include both day-time and off-tour phone numbers.
  - e. Inclusion and exclusion criteria and documentation that the research participant meets these criteria.
  - f. A statement that the research subject had capacity to consent and comprehension of the research study or that a legally authorized representative of the patient gave consent.

**B. Research Study Progress Note** – This note is used to document each study visit, including the "enrollment visit".

1. Include the actual date that the participant was enrolled into the study (this date may or may not be identical to the date that informed consent was obtained).
2. Include all data appropriate to the study as well as a review of the participant's laboratory and clinical status indicating that the participant is still appropriate for the study.
3. Include a statement that the subject or the subject's legally authorized representative continued to comprehend and consent to the research process.

**C. Research Study Termination Note** – This note is required for all participants who have a “Research Initiation” note and is to be added as an addendum to the “Research Initiation” note. This note should:

1. be written when the participant has completed the study,
2. include the date that the participant’s study involvement ended,
3. include any other information appropriate to the study.

**D. Encounter Location-** For research studies that involve participant visits that are due to research participation only and are not part of standard care, the PI should contact HIMS to designate a specific “Research” encounter designation to be used when entering the encounter information. This is to ensure that research participants do not receive a bill from the VAMC for these visits due solely for the research.

## **WHAT TO REPORT TO THE IRB/STUDY SPONSOR**

- All amendments to, or modification of, the research proposal including the consent form must be approved by the sponsor (if applicable) and IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject. The investigator is to promptly report such changes in the protocol to eliminate hazards to the IRB. Any information collected without prior approval of the IRB and R&D Committee may not be used for research data analysis or publication.
- Serious Adverse Events (SAE) and/or Unanticipated Adverse Events (UAE) must be reported to the IRB within 5 days and other required entities as necessary. If a DSMB or DMC is used, all events must be reported to the DSMB or DMC and a summary of the DSMB or DMC findings must be reported to the IRB and other entities as required. Other AEs, as defined by the monitoring plan in the protocol, must be reported in accordance with the monitoring plan approved by the IRB and as defined in FDA regulations, or other applicable Federal regulations.
- The investigator must report all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The investigator follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
- The investigator must report adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- When a subject dies either while on study or within 30 days after ending participation, whether or not the event was related to the study, the PI must report this within 5 days to the VA IRB and hospital Performance Management.

- For reported deaths, the investigator supplies the sponsor and the IRB with any additional requested information (e.g. autopsy reports and terminal medical reports).
- Investigators and all members of the research team are required to report all non-compliance to the Research Compliance Officer (or the ACOS R&D in the absence of the Research Compliance Officer). This includes noncompliance by study personnel. (Non-Compliance refers to failure to follow medical center policies and procedures, regulatory requirements, ethical treatment of subjects, the requirements of VHA Handbook 1200.5, or the requirements or determinations of the IRB.)
- Unexpected and related adverse events regardless of whether they were on-site or off-site.
- Other information that might represent unanticipated problems involving risks to participants and others
- Investigators will immediately report to the research office when a study has been terminated and complete an IRB Continuing Review/Study Closure Request” form and check “project has terminated”.
- The Investigator is responsible to provide written reports to the sponsor and the IRB on any changed significantly affecting the conduct of the clinical trial/protocol or increasing the risk to subjects.

## PI STUDY FILES

The PI will prepare and maintain adequate and accurate study files. The Investigator Binder Checklist is a useful tool that should be followed and can be found on the Research website. Among some of the items to be maintained in the study files:

- The study protocol
- Investigator brochure
- A list of appropriately qualified persons to whom the investigator has delegated significant protocol/trial-related duties
- Correspondence with the IRB, R&D, Biosafety and Animal Research committees
- Correspondence with study sponsor
- Oversight audits and correspondence (FDA, DHHS, Compliance Officer, etc.)
- Amendments
- HIPAA Authorizations
- Consent forms and DMC plan and forms
- IND safety reports
- Serious adverse event reports
- VA Form 10-9012, Investigational Drug Information Record, where/when applicable
- A case history for each individual subject shall document that informed consent was obtained prior to participation in the study. In drug trials, case histories will record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the

investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The PI maintains records of receipt, use or description of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark, the names of all persons who received, used or disposed of each device, why and how many units of the device have been returned to the sponsor, repaired or otherwise disposed of. Records of each participants case history and exposure to the device, documents evidencing informed consent, all relevant observations,, a record of the exposure of each participant to the device including the date and time of each use and any other therapy, deviations from protocol and any other records required by the FDA.

## **INVESTIGATIONAL DRUG STUDIES**

The PI must observe polices for proper documentation, handling and use of investigational drugs, biologics, and devices as specified below per FDA 21 CFR §312, Investigational New Drug Application and 21 CFR §812, Investigational Device Exemptions:

### **A. Investigator Responsibilities for Investigational Drug Studies**

1. An investigator is responsible for:
  - Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.
  - Protecting the rights, safety, and welfare of participants under the investigator's care.
  - The control of drugs under investigation.
2. An investigator shall administer the drug only to participants under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. [21 CFR §312.61]
3. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it. [21 CFR §312.61]
4. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants. [21 CFR §312.62]
5. When appropriate, the investigator informs the subject's primary physician about the subject's participation in the clinical trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
6. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59. [21 CFR §312.62]

7. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. [21 CFR §312.62]
8. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes.
9. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
10. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. [21 CFR §312.62]
11. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under §312.33 to submit annual reports to FDA on the progress of the clinical investigations. [21 CFR §312.64]
12. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately. [21 CFR §312.64]
13. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation. [21 CFR §312.64]
14. The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study. [21 CFR §312.64]
15. An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. [21 CFR §312.66]
16. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human participants or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.
17. An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 21 CFR §312.62. [21 CFR §312.68]

18. The investigator is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
19. If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution. [21 CFR §312.69]
20. As defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR §812.3(g)). Investigational devices include transitional devices (21 CFR §812.3(r)) that are objects of investigations.
21. However, for the purposes of VHA Handbook 1200.5, an investigational device may be an approved device that is being studied for an unapproved use or efficacy. [VHA Handbook 1200.5 3.j]
22. An investigational drug is a drug or biological drug that is used in a clinical investigation. The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug. [21 CFR §312.3] A copy of the IND or IDE will be provided by the investigator to the IRB copied from the sponsor's protocol or, the sponsor's response to the investigator's specific request for the IND or IDE.
23. However, for purposes of VHA Handbook 1200.5, an Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial. [VHA Handbook 1200.5 3.k]
24. An Investigational New Drug (IND) used to refer to either an investigational new drug application or to a new drug that is used in clinical investigations. ]
25. IND is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." [VHA Handbook 1200.5 3.m]
26. See 21 CFR §312.2(a)-(b) for applicability and exemptions. [VHA Handbook 1200.5 3.m]
27. Use of investigational drugs must be conducted according to FDA IND regulations and other applicable FDA and VA regulations. [VHA Handbook 1200.5 14]
28. The use of drugs in research must be carried out in a responsible manner. [VHA Handbook 1200.5 14.a]
29. An investigational drug for clinical research use is one for which the principal investigator or a sponsor has filed an IND application. [VHA Handbook 1200.5 14.b]
30. Pursuant to these regulations an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or on earlier notification by FDA that the clinical investigation may begin (21 CFR §312.40). [VHA Handbook 1200.5 14.b]

31. For purposes of VHA Handbook 1200.5, an investigational drug is also defined as an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial. [VHA Handbook 1200.5 14.b]
32. The principal investigator is responsible for informing Pharmacy Service that IRB and Research and Development Committee approval has been obtained. [VHA Handbook 1200.5 14.c]
33. This must be through the use of VA Form 10-1223, Report of Subcommittee on Human Studies, to be sent to Pharmacy Service. [VHA Handbook 1200.5 14.c]
34. VA Form 10-9012, Investigational Drug Information Record or superseding forms must be provided to the pharmacy by the principal investigator as required in VHA Handbook 1108.04. [VHA Handbook 1200.5 14.c]
35. In addition a signed copy of VA Form 10-1086, must be sent to Pharmacy Service to document each participant's consent to participate in the study. [VHA Handbook 1200.5 14.c]
36. The principal investigator must inform the Chief, Pharmacy Service, and the Research and Development Committee when a study involving investigational drugs has been terminated. [VHA Handbook 1200.5 14.d]
37. All applicable requirements in VHA Handbook 1108.04 must be met. [VHA Handbook 1200.5 14.e]
38. FDA regulations address the treatment use of an investigational drug (not approved for marketing, but under clinical investigation for a serious or immediately life-threatening disease condition) in patients for whom no comparable or satisfactory alternative drug or other therapy is available. Use of the investigational drug for this purpose must meet all applicable FDA requirements. [VHA Handbook 1200.5 14.g]
39. The storage and security procedures for drugs used in research must follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations. [VHA Handbook 1200.5 14.a]
40. During and following a subject's participation in a trial, the investigator ensures that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the clinical trial. The investigator informs a subject when medical care is needed for other illnesses of which the investigator becomes aware.
41. The investigator follows the trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator promptly documents and explains to the sponsor any premature un-blinding.

## **B. Investigator Responsibilities for Device Studies**

1. An investigator is responsible for: [21 CFR §812.100]
2. Ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations.
3. Protecting the rights, safety, and welfare of participants under the investigator's care.

4. The control of devices under investigation.
5. An investigator may determine whether potential participants would be interested in participating in an investigation, but shall not request the written informed consent of any participant to participate, and shall not allow any participant to participate before obtaining IRB and FDA approval. [21 CFR §812.110]
6. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. [21 CFR §812.110]
7. An investigator shall permit an investigational device to be used only with participants under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it. [21 CFR §812.110]
8. A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. [21 CFR §812.110]
9. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs. [21 CFR §812.110]
10. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: [21 CFR §812.140(a)]
11. All correspondence with another investigator, an IRB, the sponsor, a monitor or FDA, including required reports.
12. Records of receipt, storage use or disposition of a device that relate to:
13. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
14. The names of all persons who received, used, or disposed of each device.
15. Why and how many units of the device have been returned to the sponsor, repaired or otherwise disposed of.
16. Records of each participant's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
17. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

18. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
19. A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.
20. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
21. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
22. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. [21 CFR §812.140(d)]
23. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in 21 CFR §812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under 21 CFR §812.140, including the requirements of 21 CFR §812.145. [21 CFR §812.140(e)]
24. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.
25. §812.145 Inspections.
26. An investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept). [21 CFR §812.145(a)]
27. An investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. [21 CFR §812.145(b)]
28. An investigator shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [21 CFR §812.145(c)]
29. An investigator shall prepare and submit the following complete, accurate, and timely reports: [21 CFR §812.150(a)]
30. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as

- soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
31. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
  32. An investigator shall submit progress reports on the investigation to the sponsor, the monitor and the reviewing IRB at regular intervals, but in no event less often than yearly.
  33. An investigator shall notify the sponsor and the reviewing IRB (see 21 CFR §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with §812.35(a) also is required.
  34. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
  35. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
  36. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete and current information about any aspect of the investigation.
  37. An Investigational Device Exemption is an FDA-approval of the application for an exemption that permits an un-marketed device to be shipped for the purpose of doing research on the device. [VHA Handbook 1200.5 3.i]
  38. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR §812, other applicable FDA regulations, and applicable VHA regulations. [VHA Handbook 1200.5 15]
  39. The principal investigator is responsible for compliance with all applicable FDA regulations. [VHA Handbook 1200.5 15.i]

### **C. ADDITIONAL RESPONSIBILITIES FOR A&B (as applicable):**

1. A qualified physician provides the medical care given to, and medical decisions made on behalf of, subjects.
2. The investigator provides evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority.
3. The investigator is familiar with the appropriate use of the investigational product(s), as describe in the protocol, in the current investigator's

- brochure, in the product information and in other information sources provided by the sponsor.
4. The investigator is aware of and follows GCP and the applicable regulatory requirements.
  5. The investigator permits monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority.
  6. A qualified physician (or dentist, when appropriate), who is an investigator or a co-investigator for the clinical trial, is responsible for all trial-related medical (or dental) decisions.
  7. Responsibility for accountability of the investigational product at the clinical trial site rests with the investigator.
  8. The investigator ensures the accuracy, completeness, legibility, and timeliness of the data reports to the sponsor.
  9. The investigator maintains the clinical trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements.
  10. If the investigator terminates or suspends a clinical trial without prior agreement of the sponsor, the investigator informs the IRB and the sponsor.
  11. If the sponsor terminates or suspends a clinical trial, the investigator informs the IRB.
  12. If the IRB terminates or suspends its approval of the clinical trial, the investigator should promptly notify the sponsor.
  13. Upon completion of the trial, the investigator informs the sponsor; the IRB with a summary of the trial's outcome, and the regulatory authority with any reports required.

## **SPONSOR MONITOR VISITS**

1. The Principal Investigator PI (or other study staff as appropriate) must notify the ACOS/Designee\* via E-mail of all monitoring visits by any external entity, e.g.; pharmaceutical companies or Contract Research Organizations (CRO); for any clinical research trials. If the monitoring visit is unscheduled, the ACOS/Designee\* is to be notified as soon as the study personnel are aware of the visit.
2. The study monitor (s) must be under the supervision of the PI or coordinator during their visit. The PI or coordinator must ensure the study monitor reports to the Research Office (D637) prior to beginning the study site visit and sign in on the "Study Site Monitor Visit" sheet.
3. During each visit by the monitor the PI should review the role of the monitor including the new requirement that any potential or actual serious findings be conveyed to the investigator and the ACOS/Designee\* during the exit interview.
4. If the study monitor requires access to the Electronic Medical Record (EMR) to conduct their monitoring visit, a request via E-mail should be submitted to the Administrative Assistant – Research (AA) to obtain such access. Please make this request at least 2-weeks prior to the monitoring visit, if possible, to assure that

access is available at the time of the visit. A list of study participants to be reviewed must accompany the request, as the monitor will only have access to these particular files.

5. The ACOS/Designee\* will fill out a "Study Site Monitor Visit" report describing the outcome of the visit. This report will be filed in the Research Office, a copy sent to the Research Compliance Officer (RCO), and a copy entered into the research office study file.
6. Any follow-up correspondence received by the investigator from the sponsor or duty site monitor (s) must be forwarded to the ACOS/Designee\* to append to the exit-interview report.

\* In the absence of the ACOS, the PI should contact the Designee in the following order, the Administrative Officer Research (AO), x65621, the Human Research Protection Program (HRPP) Coordinator, x65624 or the facility Research Compliance Officer (RCO) x65787.

## **OTHER RESPONSIBILITIES**

1. PI's are responsible for assuring that their research and research team complies with all IRB decisions, conditions, and requirements. The PI must apprise the study staff of their responsibility to report non-compliance to the Research Compliance Officer (RCO) or the ACOS R&D in the absence of the RCO. (Non-Compliance refers to failure to follow medical center policies and procedures, regulatory requirements, ethical treatment of subjects, the requirements of VHA Handbook 1200.5, or the requirements or determinations of the IRB.)
2. PI's must notify the Research Service office when anyone is added to the research staff and when anyone departs from their research staff. PI's are responsible to assure that all research staff, as applicable, are properly appointed and undergo processing by Human Resources Services and Employee Health.
3. Concerns, complaints, questions and suggestions can be brought to the attention of the Research Compliance Officer or the ACOS/R&D or someone outside of the IRB such as the Hospital Director or Chief of Staff.
4. For research in which the local PI is the lead investigator, as in cooperative or multi-center studies, the investigator is responsible for notifying the IRB of the status of research at other sites through submission of: approval letters from all other sites; reports of protocol deviations and violations, serious adverse events and unanticipated problems involving risks to subjects; progress and other reports.
5. Research records and raw data shall be retained by the PI or the research office in accordance with the VA record retention schedule. For FDA regulated research, investigators will permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

6. If the PI leaves the VA facility the original research records must be retained at the institution.
7. PIs receiving support from other Federal agencies, such as the National Institutes of Health (NIH), must meet requirements for the protection of human participants of the funding source in addition to those of VA. [VHA Handbook 1200.5 4.c]
8. PIs conducting clinical trials should consult with the study sponsor to determine if the clinical trial is or needs to be entered in a national registry.  
The VA Office of Research and Development (ORD) currently has established processes for registering the trials it sponsors. The studies that have been identified as clinical trials and some observational studies are registered in the National Library of Medicine's [clinicaltrials.gov](http://www.clinicaltrials.gov) (<http://www.clinicaltrials.gov>) registry. It should be noted that in addition to efforts by the U.S. Congress and World Health Organization to increase clinical trials registration, the International Committee of Medical Journal Editors (ICMJE) has issued a statement that it will consider a clinical trial for publication only if it has been registered in a registry that meet certain criteria ([http://www.icmje.org/clin\\_trialup.htm](http://www.icmje.org/clin_trialup.htm)).
9. External Audits By Regulatory And Granting Agencies (such as: ORO, FDA, OHRP, NIH, NCI, DOD and VA Cooperative Studies Program). This does not include routine monitoring visits from pharmaceutical clinical trial monitors conducted by Clinical Research Associates (CRA's). Before the audit takes place, investigators are to notify the ACOS R&D when external audits by regulatory and granting agencies are scheduled. Reports of audit findings are to be provided to the IRB in a timely manner, but no later than 30 days after the investigator receives the report.
10. When a human subject becomes a prisoner after the research has commenced, the Principal Investigator shall notify the IRB and local institutional officials to determine the appropriate course of action. Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB will promptly re-review the protocol in accordance with the requirements of 45 CFR §46, subpart C if the principal investigator wishes to have the prisoner subject continue to participate in the research. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of 45 CFR §46, subpart C have been satisfied with respect to the relevant protocol. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of 45 CFR §46, subpart C are satisfied. In order to permit continuation of medications when discontinuing a research medication might be harmful to a subject who is imprisoned, the investigator should bring the issues to the Chair of the IRB in order to do what is in the best interest of the subject."

