Purpose:
The purpose of this policy is to provide guidance for research involving human subjects conducted at the James A. Haley Veterans Hospital (JAHVH) or by JAHVH employees or agents or otherwise conducted under the auspices of the JAHVH Administration.

Policy:
This policy is to ensure that the University of South Florida (USF) Human Research Protection Program (HRPP) applies the additional requirements for the review and approval of VHA-regulated human subjects research as set forth in 38 CFR Parts 16 and 17, as well as relevant portions of the VHA Handbooks 1200.01, 1200.05, 1108.04 and 1058.01. The USF IRB serves as a subcommittee to the JAHVH Research & Development (R&D) Committee. The VA R&D Committee must acknowledge the application in eIRB prior to the review and approval of research by the USF IRB. The R&D Committee may not approve human subjects research until it has been approved by the USF IRB. After the USF IRB has approved a study, it cannot be initiated until the investigator has been notified in writing by the Associate Chief of Staff/Research (ACOS) for R&D that all applicable approvals have been obtained and the study may be initiated.

This policy is limited to VHA regulated research reviewed and approved by the USF IRB and does not apply to non-VHA regulated research. Investigators should refer to applicable USF HRPP policies for issues not specifically addressed by this policy.

Definitions:

**JAHVH:** A Veterans Hospital that relies upon the USF IRB to provide review and oversight of its human subjects research activities.

**JAHVH R&D Committee:** Is duly constituted to oversee all research activities at JAHVH. This includes establishing policy to ensure that all research in which JAHVH is engaged has been reviewed and approved for the ethical use of human subjects.

**VHA Handbook 1058.01:** Current VHA policy which sets forth the requirements for VHA research compliance reporting.

**VHA Handbook 1200.05:** Current VHA policy which establishes procedures for the protection of human subjects involved in VA research.

**VHA Handbook 1200.01:** Current VHA policy which establishes the responsibilities for the R&D Committee.

**VHA Handbook 1108.04:** Current VHA policy which provides specific direction and procedures related to the appropriate handling of investigational drugs and supplies.
**Human Subject:** a living individual about whom an investigator who is conducting research either obtains data through intervention or interaction with the individual or obtains identifiable private information. An intervention includes all physical procedures by which data are gathered and all manipulations (physical, psychological or environmental) of the subject or the subject’s environment that are performed. Interaction includes communication or interpersonal contact between the researchers and the subject.

**VHA-Regulated Research:** VHA regulated research is research that is approved by the R&D Committee and is conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, Without Compensation (WOC), or Intergovernmental Personnel Act (IPA) appointments), utilizing VA resources (e.g., equipment), or on VA property including space leased to, and used by the VA. The research may be funded by the VA, by other sponsors, or may be unfunded. Research conducted by non-VA investigators that does not utilize VA resources and that occurs on space, or with equipment, leased from the VA or covered under a use agreement between the VA and a non-VA entity is not considered VA research.

**Administrative Hold:** An administrative hold is a voluntary interruption of research enrollments and ongoing research activities by an appropriate facility official, research investigator, or sponsor including the VHA Office of Research and Development (ORD) when ORD is the sponsor. The term does not apply to interruptions of VA research related to concerns regarding the safety, rights, or welfare of human research subjects, research investigators, research staff, or others.

**Legally Authorized Representative (LAR):** An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research 38 CFR 16.102(c), 45 CFR 46.102(c) and 21 CFR 50.3(l). An individual who is qualified as an LAR to provide informed consent on behalf of a prospective research subject may not always qualify as a personal representative for purposes of consent to use or disclose a subject’s Protected Health Information (PHI) (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a human subject’s PHI, the investigator must ensure the LAR meets the requirements of a personal representative in HIPAA and the Privacy Act of 1974 (legal guardian power of attorney) prior to the LAR signing a HIPAA authorization (see VHA Handbook 1605.1).

**Surrogate:** An individual authorized under VHA policy to make decisions on behalf of a subject who lacks decision-making capacity.

**Office of Research Oversight (ORO):** ORO serves as the primary VHA office in advising the Under Secretary for Health on all matters of compliance and assurance regarding human subjects protections, animal welfare, research safety and security, research information protection and research misconduct.

**VA Investigator:** A VA investigator is any individual who conducts research approved by the VA R&D Committee while acting under a VA appointment on VA time, including full and part-time employees, WOC employees, and individuals appointed or detailed to VA under the Intergovernmental Personnel Act (IPA) of 1970. In addition, a VA investigator must comply with all applicable VA and VHA requirements, and comply with applicable local VA facility policies and procedures.

**Principal Investigator (PI):** The PI is a qualified person or persons designated by an applicant institution to direct a research project or program and who usually writes the grant application. The PI oversees scientific, technical, and day-to-day management of the research. In the event of an investigation
conducted by a team of individuals, the PI is the responsible leader of the team. The USF IRB does not recognize the term Co-PI. Students/trainees cannot serve as principal investigator for VA studies.

**Site Investigator or Local Site Investigator (LSI):** An investigator at a site participating in a multi-site research project who oversees scientific, technical, and day-to-day management of the research at the local site.

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

**Unanticipated Adverse Event (UAE):** An UAE is an Adverse Event (AE) that is new or greater than previously known, in terms of nature, severity, or frequency of occurrence, as documented in the protocol or other materials approved by the IRB. Such materials may include, but are not limited to the informed consent document, clinical investigator’s brochure, and product labeling (see VHA Handbook 1058.01).

**USF IRB Review of VA-regulated Research**

**USF IRB Composition**

The VA Facility Director is responsible for appointing two or more VA-compensated employees who hold a minimum of 1/8 VA-compensated appointments as representatives to serve as voting members of each USF IRB when that IRB serves as the IRB of record. These representatives may not include WOC employees or individuals appointed or detailed to VA under the IPA of 1970, and at least one must have scientific expertise. The representatives must serve as full voting members, and at least one must be present during the review of the VA facility’s research at a convened IRB meeting. VA representatives also serve at the pleasure of the Senior Vice President for Research at USF, and are appointed for a period of up to 3 years. They may be re-appointed to new terms of up to 3 years without a lapse in service at the end of each term.

The VA has no formal provisions to guarantee liability protection for IRB members acting in performance of their duties. However, such protection may be provided on a case-by-case basis at the discretion of the VA and the Department of Justice. VA employees serving as IRB members will be considered agents of USF and will receive liability coverage.

VA facility research office staff including, but not limited to the ACOS for R&D, and the Administrative Officer (AO) for R&D, may not serve as voting members of IRB. They may serve as ex officio, non-voting members, but they and the IRB must be sensitive to and appropriately manage potential, actual, or perceived conflicts of interest. Research Compliance Officers (RCOs) may act as consultants to the IRB, but may not serve as a member (voting or nonvoting) of the IRB. VA Privacy and Information Security Officers may serve as consultants to the IRB.

**Ethical and Regulatory Mandate to Protect Human Subjects**

In January of 1991, the VHA joined 15 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VHA at 38 CFR Part 16. The Common Rule incorporates Subpart A of the DHHS regulations, but does not include the additional DHHS Subparts. Additional VHA regulations that are relevant to the protection of human subjects address patient rights (38 CFR 17.33), treatment of research related injuries to human subjects (38 CFR 17.85) and outpatient care for research purposes (38 CFR 17.86).
The USF IRB will meet the additional requirements for all applicable VA-regulated human subjects research as set forth in 38 CFR Parts 16 and 17, as well as relevant portions of the VHA Handbooks.

**Institutional Responsibilities for IRB Administration**

45 CFR 46.103(b)(2) and VHA regulations 38 CFR 16.103(b)(2) require that USF provide its IRBs with sufficient meeting space, support staff, and budgetary resources to support its substantial review and record keeping responsibilities.

**Initial Review of VHA Regulated Human Subjects Research**

The IRB must conduct review by a convened or expedited (i.e., review by the IRB Chair or a qualified IRB voting member designated by the IRB Chair) review procedure of all proposed human subjects research in accordance with local, VHA, and other Federal criteria including, but not limited to 38 CFR 16.111. This review includes a review of the IRB application, the research protocol, and all other relevant documents such as informed consent forms, surveys and advertising materials that are submitted to the IRB. The IRB must determine that the protocol, the informed consent form, and the HIPAA authorization are consistent with each other.

The JAHVH requires the patient health record to be flagged to indicate the subject’s participation in the study. The only exception to this requirement is for research projects that hold a Certificate of Confidentiality and do not involve medical interventions.

Studies cannot be initiated until the IRB has determined that the study does not constitute human subjects research, is exempt from IRB approval requirements, or has satisfied all requirements for approval (38 CFR 16.101). All research that is determined to be exempt or not to involve human subjects must be reviewed, approved and remain active with the R&D Committee and receive approval from the ACOS.

The IRB is not required to perform a comprehensive scientific review of the study, but is responsible for being sufficiently familiar with the science to perform its review, including a sufficient understanding of the science to carry out its responsibilities including, but not limited to, weighing the potential risks and benefits to the subjects.

**Frequency of IRB Review**

At the time of initial review, continuing review, review of amendments, or review of reportable events, the USF IRB may consider a frequency of review more often than once every year due to the degree of risk involved or the vulnerability of the participants. Factors that may influence frequency of review include but are not limited to:

- The nature of the study. Human subjects research which involves infectious agents, regulated toxins, recombinant DNA, gene transfer, or recombinant DNA vaccine which require concurrent review and approval of the Institutional Biosafety Committee (IBC).
- The degree of the risk involved. If the research has a high probability of risks which may result in serious harm such as death or disability, more frequent reviews may be required.
- The vulnerability of the participant population.
- Any other factors that the IRB deems relevant for the protection of research participants.

**Continuing and Final Review of Human Subjects Research**

The IRB approves human subjects research for a specific time interval not to exceed one year from the date of the convened meeting when the study was approved or approved with contingencies, or one year from the date the Chairperson or Chair designee issued approval for expedited applications.
Studies expire at the end of the business day on the last day of approval of the research unless a continuing review submission has been approved. The federal regulations make no provisions for a grace period to extend the approval of the research beyond the expiration date. The USF IRB utilizes effective dates (anniversary dates) which is the date of annual renewal for research proposals and is consistent from year to year. Due to the use of effective dates, the USF IRB reviews applications for continuing review within 30 days of the study expiration date. If the PI fails to submit an application for continuing review in sufficient time to allow for proper review by the IRB, the IRB may issue a new effective date for that study or may require a new application to be submitted.

If the principal investigator does not submit a continuing review or a final review or if approval has not been granted prior to the expiration of the current IRB approval, the approval will expire. The IRB will report the expiration to the PI and local research office which is responsible for promptly notifying the PI of the expiration. If applicable, the IRB Chairperson will consult with the PI and VA Chief of Staff to determine if subjects may continue participating in the research interventions or interactions.

Approval and Disapproval
The USF IRB must review and has authority to approve, require modifications of (to secure approval), or disapprove all research activities covered by the VHA Handbook 1200.05, regardless of whether the research is funded by the VA, funded from other sources, or unfunded (see 38 CFR 16.109(a) and 38 CFR 16.102(h)). Any VA research reviewed by the IRB must have at least one VA investigator who serves as PI or LSI. An IRB-approved research activity may be disapproved by the VA facility Director, the R&D Committee, or ORD. If a research activity is disapproved by IRB, the disapproval cannot be overruled by any other authority (e.g., the facility Director or R&D Committee).

Classified research involving human subjects (human subject research in which knowledge of the procedures and results is restricted to individuals with United States government security clearances) and planned emergency research cannot be conducted by the VA and therefore, cannot be approved by the USF IRB or R&DC (VHA Handbook 1200.05).

Documentation of Convened IRB Meetings
For VA-regulated research, quorum must include at least one VA voting member. IRB staff is responsible for monitoring quorum and expertise throughout the meeting and for informing the IRB Chairperson when quorum is not met and expertise is not present for each agenda item. IRB minutes clearly document which members were present by conference call or video conference. Members receive all relevant materials prior to the meeting and are able to participate actively and equally in all discussions.

Once approved by the voting members at a subsequent IRB meeting, the minutes are signed by the IRB Chair, or a qualified voting member of the IRB designated by the Chair. The final minutes cannot be altered by anyone, including other authorities or committees (e.g., the VA facility Director, RCO, Privacy Officer or ISO, or the R&DC).

Records Retention and Accessibility
The USF IRB maintains all VHA regulated research records in accordance with the VA Records Control Schedule. These records include correspondence between the IRB and VA investigators, including the IRB’s requirements for modifications to the protocol or informed consent documents, the IRB’s approval, and any other relevant correspondence about the study.

Investigator Responsibilities
The PI, LSI, and investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including the local VA facility’s SOPs and USF HRPP policies regarding the conduct of research and the protection of human subjects. The PI’s and LSI’s USF HRPP Policy 501: Veterans Health Administration Regulated Human Subjects Research
Responsibilities include, but are not limited to (see VHA Handbook 1200.05 Investigator Responsibilities):

- Disclosing conflicts of interest;
- Ensuring there are adequate resources to carry out the research safely;
- Ensuring research staff are qualified to perform the procedures assigned to them during the study;
- Promptly reporting changes in study staff to the IRB;
- Overseeing research staff and ensuring proper implementation of the approved protocol;
- Ensuring the protocol is complete;
- Ensuring all written approvals are obtained prior to initiating research activities;
- Maintaining research records;
- Ensuring no human being is involved as a subject in research until legally effective informed consent of the subject or the subject’s LAR has been obtained (38 CFR 16.116);
- Ensuring the most current version of VA Form 10-1086, VA Research Consent Form, is used as the informed consent document for each study;
- Ensuring HIPAA Authorization is obtained;
- Obtaining IRB approval for all changes to the research prior to implementing the changes unless the changes are necessary to eliminate apparent immediate hazards. In that case, the investigator must promptly report these changes to the IRB;
- Submitting IRB application for continuing review in a timely manner to prevent study expiration;
- Reporting deviations and subject complaints to the IRB;
- Reporting all unanticipated problems involving risks to human subjects or others, and all unanticipated internal SAEs, whether related or unrelated to the research, in accordance with VHA Handbook 1058.01;
- Completing all required documentation at the completion of the research including submission of an application for final review to the USF IRB;
- Transferring records by the VA upon departure of investigator. If the investigator leaves the VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the investigator leaves one VA facility to go to another, the investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility’s research office;
- Maintaining an “Enrolled Subject Log” in accordance with VA standard operating procedures. Ensuring research laboratories not report lab results that are used for diagnosis, treatment, and prevention of disease in patients, unless the research laboratories are properly accredited and meet all requirements of 42 CFR 493 (see VHA Handbook 1106.01).

Use Preparatory to Research

Data repositories including VA medical records may be used by VA investigators for activities that are preparatory to VA research without the requirement to obtain either a HIPAA authorization from the subject or a waiver of HIPAA authorization by an IRB or Privacy Board. This includes use of PHI for the preparation of a research protocol prior to submission to the IRB. Preparatory to research activity is the only instance of access for research purposes allowed in VHA without a written HIPAA authorization signed by the individual, a waiver of HIPAA authorization by an IRB or Privacy Board, or approval by the IRB. This access is granted only to VHA researchers. Non-VHA researchers may not access VHA data for reviews preparatory to research.

Informed Consent Process and Procedures

The most current IRB-approved version of VA Form 10-1086, VA Research Consent Form, must be used for each study. Each informed consent form must include:

- All elements required by 38 CFR Part 16;
• Any additional elements when appropriate (38 CFR 16.116(b));
• Name of the study;
• Name of the PI;
• Name of the sponsor; and
• Designated block for each required signature and for the date of each signature.

When appropriate, VA requires one or more of the following elements of information be provided to each subject. Also, when any of these additional elements are appropriate, VA requires them to be documented in the IRB-approved informed consent form, unless documentation of informed consent is waived:

• Payment for Treatment: Informed consent must include a statement that veteran-participants shall not be required to pay for treatment received as a participant in a VA research program. Investigators should note, however, that veterans in the “discretionary work load” category are subject to co-payments in accordance with VA guidelines.

• Authorization for Use of Bodily Fluids, Substances, or Tissues: If the investigator believes that bodily fluids, substances, or tissues could be part of or lead to the development of a commercially viable product, the informed consent information should include the following verbatim statement: “I authorize the use of my bodily fluids, substances or tissues in this research. It is possible that commercially profitable products may someday be developed from these bodily fluids, substances, or tissues. There are no plans to share any profits from such products with the participants who were the source of these bodily fluids, substances, or tissues.”

• Future Use of Specimens: If the specimens are to be retained after the end of the study for future research, where the specimens will be retained, who will have access to them, and how long they will be retained must be included in the consent document. Current applicable institutional, VA, and other Federal requirements must be met for handling, use, and storage of biologic specimens and data (see VHA Handbook 1200.12).

• Future Use of Data: If any of the data will be retained after the study for future research, where the data will be stored, and who will have access to the data must be included (see VHA Handbook 1200.12). Current applicable institutional, VA and other Federal requirements must be met for use and storage of data (see VHA Handbook 1200.12).

• Re-contact: Include a statement in the consent if the subject will be re-contacted for future research whether within VA or outside VA.

• Payment for Participating in the Study: If appropriate, a statement regarding any payment the subject is to receive for participating in the study and how the payment is to be made. Since VA regulations at 38 CFR 16.116(a)(8), the Common Rule, and FDA regulations all state that participants may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. For this reason there should be a description of how payment will be prorated and calculated for participants who withdraw early.

• IRB approval of the wording of the consent document must be documented through the use of a stamp on each page of Form 10-1086 that indicates the date of the most recent IRB approval of the document.

• If the consent document is amended during the protocol approval period, the IRB stamps the informed consent form with the approval date of the amendment rather than the date of the approved protocol.

• Disclosure of Results: If the subject will receive a report of the aggregate results or any results specific to the subject, this information must be included in the consent.

A copy of the signed and dated informed consent form must be provided to the subject or the subject’s LAR (38 CFR 16.117(a)). Where applicable, a copy of the signed and dated informed consent form must be placed in the medical record in accordance with VHA Handbook 1907.01.
The IRB has the authority to observe, or have a third party observe, the consent process and the research (38 CFR 16.109(e)).

**HIPAA Authorization**
A written HIPAA authorization signed by the individual to whom the information or record pertains is required when VA health care facilities need to utilize individually-identifiable health information for a purpose other than treatment, payment, or health care operations (e.g., research) (VHA Handbook 1605.1). In accordance with 45 CFR 164.508(b)(3)(ii), an authorization for a use or disclosure of psychotherapy notes may not be combined with any other authorization for a use or disclosure unless the other authorization is also for a use or disclosure of psychotherapy notes.

The HIPAA authorization for the use or disclosure of individually-identifiable health information for a VA research study must be a standalone document (i.e., not combined with any other type of written permission for the same research study, including the research informed consent form). Since VHA Handbook 1200.05 requires the HIPAA authorization and the informed consent form to be separate documents, the IRB cannot approve a HIPAA authorization for a VA research study. However, the IRB may waive the requirement for a HIPAA authorization if certain criteria are met. The IRB must ensure the protocol and informed consent form are consistent with the HIPAA authorization. A copy of the signed HIPAA Authorization must be provided to the subject or the subject’s LAR.

**Vulnerable Populations**
The IRB must also be cognizant of the vulnerable nature of many VA patient-participants. To the extent that such participants are economically dependent upon the VA for medical treatment, suffer from cognitive, affective, or other psychological afflictions, or have substance abuse problems, VA patient-participants may be particularly vulnerable to unintended coercive influences relative to participation in research (VA Handbook, 1200.05). Likewise, persons who primarily look to the VA for treatment of their medical problems may not fully understand the implications of research participation, especially when it is offered by someone they consider a provider of clinical care.

Individuals or populations that may be temporarily or permanently vulnerable include, but are not limited to those who:

- Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).
- Lack comprehension of the research and its potential risks (e.g., educationally disadvantaged, dementia, schizophrenia, depression).
- Have increased susceptibility to harm from the procedures of the specific study under review (e.g., individuals who would have to answer study survey questions about their sexual assault).
- Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status).

While all protocols need to be assessed for vulnerability of subjects within the context of the specific protocol, the populations named below must always have the additional protections specified in this paragraph applied. VA considers the following populations to be categorically vulnerable:

- **Fetuses**- Research in which the focus is either a fetus, or human fetal tissue, in-utero or ex-utero (or uses human fetal tissue), must not be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities.
- **Neonates**- Observational or retrospective research related to neonates can be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities.
- **Pregnant Women**- Additional considerations exist for research involving women who are...
pregnant at the time they are entered into a study. The regulations do not preclude entering women of child bearing potential into studies including studies whose interventions include FDA’s Categories for Drug Use in Pregnancy’s Category C drugs.

- **Women of child bearing potential** may not be entered into studies involving the use of FDA Categories for Drug Use in Pregnancy’s Category D or X drugs unless a waiver is obtained from the Chief Research and Development Officer (CRADO). Pregnant women may be the focus of the research if all of the following conditions specified in 45 CFR 46.204 are met.

- **Prisoners** - Prisoners are considered a vulnerable population and may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research (45 CFR 46.302). Research involving prisoners cannot be conducted by VA investigators while on official VA duty, using VA resources, completely or partially in a VA facility or at a VA-approved off-site facility unless a waiver has been granted by the CRADO. If such a waiver is granted by the CRADO, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR 46, Subpart C 46.301–46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects).

- **Children** - Research involving children cannot be conducted by VA investigators while on official VA duty, using VA resources, completely or partially in a VA facility or at a VA-approved off-site facility unless approval has been granted by the Facility Director. Research involving biological specimens or data obtained from children is considered to be research involving children.

- **Subjects who lack decision-making capacity** – No individual who lacks decision-making capacity may participate in VA Research until the IRB has reviewed and approved that individual’s, or that class of individuals’, participation in a given study. The IRB may approve inclusion of individuals who lack decision-making capacity in research when the criteria in VHA Handbook 1200.05 are met and when informed consent from LARs will be obtained.

**Compensation to Human Research Subjects**

The VA facility research office must ensure IRB-approved payment to subjects is made from a VA-approved source for funding research activities.

**Compensation for Human Subjects Research Injury**

The VA will provide necessary medical treatment to any research participant injured as a result of participation in a research project approved by the JAHVHR&D and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries due to noncompliance by the participant with study procedures or research conducted for the VA under a contract with an individual or non-VA institution.

**Investigational Drugs in Research with Human Subjects**

For proposed human subjects research involving an investigational drug or biological product, investigators are responsible for complying with all applicable FDA, DHHS, and VA regulations and USF HRPP policies. Investigators who hold the Investigational New Drug (IND) or Biologics License Application (BLA) for the proposed research must comply with applicable regulations pertaining to both the sponsor and the investigator. Investigators must ensure compliance with the VA human subject regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents. FDA regulations supersede VA requirements for human subjects research under FDA jurisdiction unless VA requirements are more restrictive than applicable FDA regulations.
To receive an investigational drug as defined by VHA Handbook 1108.04, in addition to FDA regulations for the conduct of research under an IND and investigator responsibilities identified in Handbook 1200.05, the investigator must:

- Provide the Pharmacy Service or Research Investigational Pharmacy information on each subject receiving an investigational drug through the electronic medical record or other locally approved means. Documentation is to include allergies, toxicities, or adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements, i.e., herbals, nutriceuticals (see VHA Handbook 1108.04).
- Ensure the local Pharmacy Service or Research Service Investigational Pharmacy receives:
  - Documentation of IRB and any other relevant approvals;
  - A copy of VA Form 10-9012, Investigational Drug Information Record, when applicable;
  - A copy of the current approved protocol;
  - A copy of the informed consent form for each participating subject with all appropriate signatures;
  - Documentation of the IRB continuing review approval;
  - Copies of sponsor-related correspondence specific to the drug(s) as appropriate; and
  - Copies of all correspondence addressed to the investigator from the FDA (and other involved authorities) specific to the investigational drug(s) as appropriate.
- Inform the Chief of the Pharmacy Service, the research pharmacy when applicable, and the IRB in writing when a study involving investigational drugs has been suspended, terminated, or closed.
- Comply with all dispensing requirements.
- Comply with all documentation requirements and make relevant records accessible to the investigational drug pharmacist when requested (VHA Handbook 1108.04).
- Comply with all VHA pharmacy requirements regarding receiving, dispensing, storing, and record-keeping for investigational drugs.

**Investigational Devices in Research with Human Subjects**

IRB review and approval and investigator conduct of all investigational device studies must be in accordance with all applicable VA and other requirements including the VHA Handbook 1200.05 and FDA regulations (e.g., 21 CFR Parts 50 and 56, and Investigational Device Exemptions (IDE) (21 CFR 812)). If the research involves FDA-regulated devices, both VA requirements and FDA regulations apply. FDA regulations supersede VA requirements for human subjects research under FDA jurisdiction unless VA requirements are more restrictive than applicable FDA regulations.

No research involving an investigational device can be approved by the IRB if it is unclear whether the device requires an IDE, or if the IDE status for an investigational device is unknown.

**Emergency Medical Care**

The VHA Handbook or the Common Rule are not intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable local, state, VA, and other Federal requirements (38 CFR 16.116(f)). Emergency medical care is not research and does not need to be approved by an IRB.

**Human Subjects Protection Education**

All individuals subject to the VHA Handbook 1200.05 are required to complete training in ethical principles on which human research is to be conducted before conducting human subjects research. Training must be updated every three years. All other applicable VA and VHA training requirements at the local and national level must also be met and may be required on a more frequent basis (e.g., privacy training).
Apparent Serious or Continuing Noncompliance

In accordance with VHA Handbook 1058.01, members of the VA research community must report any apparent serious or continuing noncompliance with applicable human research protection requirements (e.g., 38 CFR 16, VHA Handbook 1200.05, FDA regulations) in writing to the IRB within five business days. The determination that noncompliance is serious or continuing rests with the IRB. Decision charts related to such reporting are provided on the ORO Web site at [http://www.va.gov/ORO/oropubs.asp](http://www.va.gov/ORO/oropubs.asp).

Examples of **apparent serious noncompliance** that must be reported to the IRB within five business days include, but is not limited to:

- Any finding of noncompliance with human research requirements by any VA office (other than ORO), any other Federal or State entity (e.g., FDA), or any external monitor. Reports to ORO based on findings made by entities external to the facility must include a copy of the official findings;
- Initiation of VA human subject research, regardless of level of risk or number of subjects, without written notification from the ACOS for Research that the project may begin;
- Initiation of VA human subject research, regardless of level of risk or number of subjects, without approval by the IRB;
- Initiation of research interactions or interventions with one or more subjects prior to obtaining required informed consent;
- Lack of a required, signed informed consent document;
- Use of an informed consent document, for one or more subjects, where content was not approved by the IRB;
- Failure to report one or more unanticipated SAEs or unanticipated serious problems involving risks to subjects or others as required by the Handbook;
- Participation by one or more members of the research team in the conduct of an active protocol without the required credentialing, privileging, or scope of practice, or engaging in activities outside the approved scope of practice;
- Continuation of interactions or interventions with human subjects beyond the specified IRB approval period;
- Implementation of substantive protocol changes without IRB approval, except where necessary to prevent immediate hazard to a subject;
- Involvement of prisoners in VA research, or involvement of children without approval of the VA Facility Director;
- Conduct of international VA research without the required approval of the VA Facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO.
- Any noncompliance involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
- Any noncompliance that substantively compromises the effectiveness of the facility’s human research protection or human research oversight programs.

Examples of **apparent continuing noncompliance** that must be reported to the IRB within five business days include, but are not limited to:

- Failure to implement IRB-required changes to an on-going protocol within the time period specified by the IRB;
- Deficiencies in informed consent or HIPAA authorization procedures or documentation for ten or more subjects (e.g., outdated informed consent or HIPAA content; lack of required informed consent elements; lack of information required by VA; lack of signature of individual obtaining consent);
• Failure to maintain documentation required by the IRB or by the IRB-approved protocol for ten or more subjects (e.g., inadequate medical record documentation where required; inadequate case report forms where required); or
• Failure to implement remedial actions within the periods specified within subparagraph 5d(1) or 5d(2) in the absence of the justification described within subparagraph 5d(3) of VHA Handbook 1058.01.

Research Compliance Officer (RCO) Reports of Apparent Serious or Continuing Noncompliance
Within five business days of identifying apparent serious or continuing noncompliance based on an informed consent audit, regulatory audit, or other systematic audit of VA research, an RCO must report the apparent noncompliance directly, without intermediaries, to the facility Director. The report must be made in writing, with a simultaneous copy to the ACOS for Research, the R&D Committee, the IRB, and any other relevant research review committee.

The facility Director must report the apparent serious or continuing noncompliance to the appropriate ORO Regional Office (RO), with a simultaneous copy to the Veterans Integrated Service Network (VISN) Director and the Office of Research & Development (ORD), within five business days after receiving such notification.

An initial report of apparent serious or continuing noncompliance based on an RCO informed consent audit, regulatory audit, or other systematic audit is required regardless of whether disposition of the matter has been resolved at the time of the report.

IRB Review of Apparent Serious or Continuing Noncompliance
The IRB must review any report of apparent serious or continuing non-compliance at the next available convened meeting. Should the IRB determine that the reported incident constitutes serious or continuing noncompliance, the IRB Chairperson, or designee, must report the determination directly, without intermediaries, to the medical center director within five business days after the determination. The report must be made in writing, with a simultaneous copy to the ACOS for research, the R&DC, and any other relevant research review committee.

An initial report of an IRB determination that serious or continuing noncompliance occurred is required, even where the determination is preliminary or disposition of the matter has not been resolved at the time of the report. The IRBs must reach a determination that serious or continuing noncompliance did or did not occur within 30-45 days after receiving a report of apparent non-compliance. Remedial actions involving a specific study or research team must be completed within 90-120 days after the IRBs’ determination. Remedial actions involving programmatic non-compliance must be completed within 120-180 days after the IRB’s determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, or legal negotiations.

Local Unanticipated SAEs
Within five business days of becoming aware of any local (i.e., occurring under the auspices of JAHVH approved research) unanticipated SAE in VA research, members of the VA research community are required to ensure that the SAE has been reported in writing to the IRB.

Serious Unanticipated Problems Involving Risks to Subjects or Others
Members of the VA research community are required to report any serious unanticipated problems involving risks to human subjects or others to the IRB in writing within five business days of becoming aware of the event. Examples include but are not limited to:
• Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others;
• Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death;
• Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility’s research projects. Any Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or Data Safety Monitoring Committee (DSMC) report describing a safety problem;
• Any sponsor analysis describing a safety problem for which action at the facility level is warranted;
• Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
• Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility’s human research protection or human research oversight programs.

IRB Review of Serious Unanticipated Problems and Unanticipated SAEs
Within five business days after a report of a serious unanticipated problem involving risks to subjects or others, or of a local unanticipated SAE, the convened IRB or a qualified IRB member-reviewer must determine and document whether or not the reported incident was serious, unanticipated, and related to the research. Related means the event or problem may reasonably be regarded as caused by, or probably caused by, the research. If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related to the research, the IRB Chair or designee must notify the Office of Research Oversight (ORO) via telephone or e-mail within 48 hours and report the problem or event directly, without intermediaries, to the facility Director within five business days after the determination. The report must be made in writing, with a simultaneous copy to the ACOS for Research and the R&DC. The facility Director must report the problem or event to the appropriate ORO within five business days after receiving such notification.

If the convened IRB or the qualified IRB member-reviewer determines that the problem or event was serious, unanticipated, and related to the research, a simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations in 38 CFR 16.103(b)(4)(iii). All determinations of the qualified IRB member-reviewer, regardless of outcome, must be reported to the IRB at its next convened meeting. If it is determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether or not a protocol or informed consent modification is warranted. If an informed consent modification is warranted, the IRB must also determine and document whether or not previously enrolled subjects must be notified, and if so, when such notification must take place and how it must be documented.

Terminations or Suspensions of Research
The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements, or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval must include a statement of the reasons for IRB’s action and must be reported promptly to the investigator, appropriate Institutional Officials (IO), and the department or agency head, according to applicable local, VA, and other Federal requirements (see 38 CFR 16.113, VHA Handbook 1058.01).

Any termination or suspension of research by the IRB or other research review committee, or by the
ACOS for Research or other facility official related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others must be reported directly, without intermediaries, to the facility Director within five business days after the termination or suspension occurs. The report must be made in writing with simultaneous copies, as applicable, to the ACOS for Research, the R&DC, the IRB, and any other relevant research review committee. The facility Director must report the termination or suspension to the appropriate ORO RO within five business days after receiving such notification.

**Privacy and Confidentiality**
PIs must comply with VA handbooks for all VA regulated research and adhere to the recommendations for securing electronic research data. The IRB is responsible for reviewing the information that will be collected during the course of the research and determining the degree of privacy of the information and adequacy of the measures to be taken to protect the confidentiality of the data. The IRB will consider the nature, probability, and magnitude of harms that likely would result from a disclosure of collected information outside the research as it ensures the protection of privacy of subjects and confidentiality of data of all research proposals in accordance with 45 CFR 46.111(a)(7), 38 CFR 16.111(a)(7) and 21 CFR 56.111(a)(7), and VA Handbooks.

**International Research**
VA international research is defined as any VA-approved research conducted at international sites (not within the U.S., its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research that entails sending such specimens or data out of the U.S. Research conducted at U.S. military bases, ships, or embassies is not considered international research.

Multi-site trials are covered under this definition of VA international research if the VA is a sponsor, functions as the coordinating center, subcontracts to a foreign site, and if the PI for the total study is a VA investigator or the VA investigator is specifically collaborating with an international investigator and the VA investigator sends data or human biological specimens outside the U.S. or receives them from outside the U.S.

Permission must be obtained from the Facility Director prior to initiating any VA-approved international research except for cooperative studies that require CRADO approval. This applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including agreements, MOU, Cooperative Research and Development Agreements (CRADA), grants, or contracts. Please see ORD guidance on international research for additional information.

All international sites must hold an international FWA, and the research must be approved by the IRB or Research Ethics Board of the participating site(s) listed on the international FWA.

Researchers must conduct research in compliance with all applicable VA and other Federal requirements including those for protecting human subjects, tissue banking, use of databases, Federal criminal laws, and the Standards of Ethical Conduct for Employees of the Executive Branch.

**Radiology Devices and Radioactive Materials:** Oversight of use of radiologic and radioactive materials conducted by the VA Radiation Safety Committee (RSC). RSC advises the VA R&DC and other applicable subcommittees to ensure safe use and proper disclosure to potential subjects in those studies where these agents are utilized. Consultation to the IRB for reviews of human subjects research involving these agents will be sought from the VA Radiation Safety Officer, for initial studies and amendments, as applicable.
Safety Subcommittees: Oversight at the JAHVH is handled by the VA Subcommittee on Research Safety and the USF Institutional Biosafety Committee (IBC) which is a subcommittee of the VA R&DC. Consultation to the IRB for reviews of human subjects research activities will be sought from the VA Safety subcommittee or the USF IBC, for initial studies and amendments, as applicable.

Participation of Non-Veterans as Research Subjects: The investigator must justify including non-Veterans in a VA research protocol, and the IRB must review the justification for inclusion of non-Veterans and specifically approve entering non-Veterans into the study before non-Veterans can be recruited. The IRB must appropriately document in the IRB minutes or IRB regulatory file its determinations regarding participation of non-Veterans in the study.

References:
21 CFR Parts 50 and 56
21 CFR 812
38 CFR Parts 16
38 CFR Parts 17
42 CFR 493
45 CFR 46.102(c)
45 CFR 46.103(b)(2)
45 CFR 46.204
45 CFR 46, Subpart C 46.301–46.306
45 CFR 46.111(a)(7)
VA form 10-1086
VA Form 10-9012
VA Handbook 1605.1
VA Handbook 1200.01
VA Handbook 1200.05
VA Handbook 1058.01
VA Handbook 1108.04
VA Handbook 1907.01
VA Handbook 1106.01
VA Handbook 1200.12