



VA Western New York Healthcare System

Institutional Review Board Standard Operating Procedures

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I. INTRODUCTION

The VA Western New York Healthcare System (VAWNYHS) Institutional Review Board (IRB) Standard Operating Procedures (SOP) is a reference for investigators and IRB members. This manual was developed to serve two purposes:

- A. To describe the functions and procedures followed by the IRB of the Research and Development (R&D) committee at the VAWNYHS that ensure the protections of human participants as outlined by Federal regulations and Veterans Healthcare Administration (VHA) policy, and
- B. To outline for investigators the requirements for review of human research proposals by the IRB and for the subsequent conduct of that research.

This SOP is part of the systematic and comprehensive Human Research Protection Program (HRPP) at the VAWNYHS with dedicated resources to insure the rights, safety, and welfare of human research participants participating in research activities.

An HRPP is a comprehensive system to ensure the protection of human participants in research. The HRPP consists of a variety of individuals and committees such as: the Medical Center Director (MCD), Associate Chief of Staff for Research and Development (ACOS/R&D), Administrative Officer for Research and Development (AO/R&D), Research Compliance Officer (RCO), the R&D committee, the IRB, other committees addressing human subjects protection (e.g. Radiation Safety), investigators, IRB staff, research staff, health and safety staff (e.g. Facility Safety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human participants in research.

The HRPP is required to maintain a full accreditation by an accrediting organization under contract with the VA.

The HRPP also includes a performance improvement plan and an assessment of the resource plan. The R&D committee will review annually the budgeting process and the organizational structure for human research (resource plan of the HRPP) to ensure adequate resources are available to properly carry out its functions. The IRB and the research administration office will provide information (feedback) on these issues. The annual review will encompass an evaluation of the volume of research, staffing, computer resources, meeting area, filing space, reproduction equipment, databases, supplies, space, capital equipment, training and education, and any other items as needed. The annual evaluation is submitted to the responsible institutional official.

This SOP will be reviewed as needed to incorporate any change in process, or changes necessary in response to VA and/or Federal regulations regarding the protection of human participants in research.

II. REGULATORY AUTHORITY

The IRB enforces the Federal policies and procedures as dictated by VHA, the Office for Human Research Protection (OHRP), and the Food and Drug Administration (FDA). VHA is one of 17 departments and agencies which follow the Federal Policy for the protection of human participants, known as the Common Rule, which is incorporated in Title 38 Code of Federal Regulation (CFR) Part 16. The procedures for implementing 38 CFR Part 16 are defined in VHA Handbook 1200.05 Requirements for the Protection of Human Subjects in Research. In addition, the VA follows applicable regulations in 38 CFR Part 17 such as patient rights (38 CFR 17.33), treatment of research-related injuries (38 CFR 17.85), hospital care for research purposes (38 CFR 17.45), and outpatient care for research purposes (38 CFR 17.92).

When an activity meets the FDA definition of research and involves human participants as defined by FDA, FDA regulations apply (21 CFR 50 and 56). The following additional regulations are used for specific test articles:

- Investigational New Drug Applications (IND) (21 CFR 312)
- Radioactive Drugs (21 CFR 361)
- Biological Products (21 CFR 600)
- Investigational Device Exemptions (IDE) (21 CFR 812)

Research in the VA supported by the Department of Health and Human Services (DHHS) must also follow regulations at 45 CFR 46. VA has not adopted regulations similar to 45 CFR 46 subparts B through D that include additional protections for fetuses, pregnant women, and human in vitro fertilization (subpart B), prisoners (subpart C), and children (subpart D). Research in which the participant is a fetus, in-utero, or ex-utero (including human fetal tissue) must not be conducted in the VA. Research in prisoners and children can be conducted with a waiver from the Office of Research and Development , in accordance with the appropriate subpart protections.

The VAWNYHS has its own Federal-Wide Assurance (FWA00002279) and the IRB is registered (IRB00002296) under this assurance number. The VA Central IRB is also registered (IRB00006332) under this FWA as an IRB of record. Any VA facility within an FWA must also maintain full accreditation of its HRPP in order to maintain compliance with VHA Handbook 1200.05. An annual report will be provided to ORD and the accrediting organization. Any changes in accreditation status will be reported in accordance with VHA Handbook 1058.01.

III. RESPONSIBILITIES

a. Medical Center Director

The Medical Center Director (MCD) is responsible for:

1. Acting as the Institutional Official (IO) for all assurances and must fulfill all education requirements mandated by VA ORD, the facility's assurance, funding institutions, and OHRP. He/she serves as an ex-officio, non-voting member of the R&D committee and is the point of contact for correspondence addressing human subject's research with OHRP, FDA, and VHA Central Office.
2. Ensuring that VAWNYHS has a systematic and comprehensive approach to ensure the protection of human participants involved in VA approved research. He/she must ensure effective coordination and communication by and among the various individuals, offices and committees that comprise the HRPP to ensure that all research personnel obtain the appropriate credentialing and privileging and required education and training.
3. Ensuring that VAWNYHS maintains an Assurance of Compliance with DHHS through OHRP and submits updated information in a timely fashion.
4. Ensuring that the IRB has the resources to sustain a Research Subject Outreach Program with routine evaluation and implementation of improvements.
5. Ensuring that VAWNYHS has an established and well-functioning IRB which is a subcommittee of the R&D committee.
6. Providing adequate administrative support, including personnel and space sufficient to provide privacy for conducting sensitive duties and storage of records is provided for IRB activities.
7. Ensuring that VAWNYHS provides appropriate educational opportunities for IRB members, staff, and researchers.

8. Ensuring that the local research office maintains accurate, up-to-date records regarding the mandatory training and credentialing of investigators and other appropriate research staff in the protection of human research participants.
9. Ensuring that the IRB of record functions independently, and that its Chair, or Co-Chairs, and members have direct access to the IO for appeal if they experience undue influence or if they have concerns about the IRB.
 - a. Note: Research that has been approved by the IRB is subject to further appropriate review and approval or disapproval by officials (e.g., the MCD) and other subcommittees (e.g., R&D committee). However, officials or committees cannot approve the research if it has been disapproved by the facility's IRB (e.g., the MCD cannot approve a study that has been disapproved by the IRB).
10. Ensuring that the facility's HRPP is accredited by an organization approved by ORD to perform this function.
11. Ensuring that an evaluation of the HRPP is completed annually through the executive summary and resource plan.
12. Developing and monitoring procedures to ensure the safety of participants in research either directly or by delegating the responsibility to other qualified VA staff.
13. Oversight of both the IRB and all VA investigators (compensated, WOC, or IPA).
14. Assurance that IRB members and investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and all applicable regulations.
15. Development and implementation of an educational plan for IRB members, staff, and investigators.
16. Suspending or terminating the IRB membership of any individuals who are not fulfilling their membership responsibilities or obligations.
17. Ensuring a properly executed MOU with the Central IRB that stipulates the respective authorities, roles and responsibilities if utilizing the Central IRB as an IRB of record for any active protocols.
18. Ensuring any international research is conducted with permission from the CRADO, with a facility that maintains an FWA.
19. For research involving investigational drugs and supplies, the facility director is responsible for ensuring:
 - a. There is a HRPP, in order to conduct research involving humans.
 - b. Clinical investigations using investigational drugs and/or supplies are being carried out, and there are written policies and procedures that provide adequate safeguards are in place to protect the subject, staff, and facility.
 - c. The quality of the study.
 - d. All clinical investigations using investigational drugs and/or supplies are compliant with all applicable laws, regulations, and VA and VHA policies.
 - e. That before research is initiated, the clinical investigation:
 - i. Is conducted by properly qualified investigators;
 - ii. Has approval of the IRB of Record and the R&D Committee of the medical facility where the study is conducted; and
 - iii. Meets all requirements of VHA Handbook 1200.01.
 - f. The subject or the subject's LAR is given all required information regarding the research study during the informed consent process. Informed consent must be obtained from the subject, or the subject's LAR in accordance with VHA Handbook 1200.05 and FDA regulations found in 21 CFR Part 50.

- g. Consideration is given to include a representative from the investigational pharmacy or Pharmacy Service as either an ex-officio non-voting member or voting member of the IRB or R&D Committee.
- h. All investigational drugs and supplies required by a clinical trial protocol, being used under an IND, are provided by the study sponsor.
- i. Concurrent, comparator, or rescue medications that are required and supplied by the study sponsor and used for study-related purposes are recorded by the dispensing investigational pharmacy as part of the study treatment.
- j. These medications are stored in accordance with VHA Handbook 1108.04. If the study sponsor does not provide these medications and medical care appropriations are utilized for their purchase, the cost of the medication must be reimbursed from the research funds; unless the study drugs are determined to be "usual care,".
- k. Medications supplied or procured for an investigational study are identified in the drug file as a study medication.
- l. That Pharmacy Service has a specific policy or standard operating procedure in place that specifically addresses investigational drug control and management.
- m. All investigational drug and supply management remain under the direction of the facility Chief of Pharmacy.

b. Chief of Staff

The Chief of Staff (COS) is responsible for:

1. Oversight of the R&D program, including the IRB, along with the MCD.
2. Advising the MCD and the research committees on issues with clinical impact on the program and the medical center.
3. He/she serves as an ex-officio, non-voting member of the R&D committee.
4. Reviewing and approving the minutes of the R&D committee, which also include the minutes of the IRB.
5. He/she advises the IRB and the Principal Investigator when it is appropriate to maintain an individual on an investigational product during the time of protocol lapse, suspension or termination.

c. Associate Chief of Staff for R&D (ACOS)

The ACOS for R&D is responsible for:

1. The overall management of the research program, including the HRPP program and the operations of the IRB committee.
2. The ACOS for R&D recommends appointment of members to the IRB committee.
3. He/she serves as an ex-officio, non-voting member of the R&D committee and its subcommittees, including the IRB.
4. He/she is responsible for providing guidance to the members of the IRB committee on the regulations governing human participant research.
5. Ensuring that human research conducted at the VAWNYHS is conducted in compliance with all applicable regulations.
6. The ACOS for R&D has been appointed as the Research Integrity Officer (RIO) for VAWNYHS and is responsible for investigating any allegations of research misconduct (defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting results). He/she reports the findings of such an investigation to the COS and MCD.
7. Ensuring that accurate up-to-date records regarding mandatory training and certification of committee members, investigators, and research staff are maintained in the Research Office.

8. Submission of documentation necessary to obtain and/or maintain a properly executed institutional assurance in accordance with OHRP procedures and VA regulations.
9. Ensuring that all studies have received approvals by appropriate bodies (R&D, IRB/Central IRB, IACUC, Safety, etc.) before signing a final approval letter for any new study or continuing review. No study may begin prior to receiving such approval.
10. Receiving and Evaluating all participants concerns or questions. The Patient Advocate may be expected to review or respond to participant concerns. These concerns and/or questions will be presented to the IRB at the next convened meeting by the ACOS for R&D. An emergency meeting of the IRB will be called as applicable for significant safety or regulatory concerns based on the information obtained by the ACOS for R&D.
11. Facilitating the dissemination of all research information to the investigators and the research staff. In addition, questions, concerns or suggestions will be directed to the ACOS for R&D through an annual survey, or as needed by phone call, email or appointment.

d. Administrative Officer for R&D (AO)

The Administrative Officer for R&D is responsible for:

1. Providing staff support to the IRB committee by assuring that meetings are held as scheduled, minutes are recorded accurately and promptly, correspondence relating to committee actions is processed, required records and reports are maintained, and actions mandated by the committees are executed.
2. The AO for R&D serves as an ex-officio, non-voting member of the R&D committee and its subcommittees, including the IRB.

e. Compliance and Business Integrity Officer

The Compliance and Business Integrity Officer is appointed by the MCD to serve as the Conflict of Interest Administrator.

f. Principal Investigator (PI)

The PI, Local Site Investigator (LSI), and investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including the VAWNYHS SOP's regarding the conduct of research and the protection of human subjects. The responsibilities of the investigator may be defined in the protocol or IRB application. Specifically, the PI's and LSI's responsibilities include, but are not limited to: *(Some of the following responsibilities may be assumed by an investigator working under a PI or LSI)*

1. **Disclosing Conflicts of Interest.** This means disclosing to the IRB any potential, actual, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research, and complying with all applicable VA and other Federal requirements regarding conflict of interest.
2. **Ensuring Adequate Resources.** This means ensuring there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
3. **Ensuring Qualified Research Staff.** This means ensuring research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study. This includes compliance with all mandatory trainings, applicable and appropriate appointment status and current credentialing, privileging, licensure and scope or work/functional statement. In a protocol, study team members are generally identified by name or by title. (1) IRB may require a specific individual(s) by name to be part of the study team as a condition for IRB approval of the research. In that case, a proposed change in that specific individual would require IRB approval. Non compliance with the expectations listed above will lead to an administrative hold on personnel or protocol.

4. **Promptly Reporting Changes in PI or LSI.** This means promptly reporting any changes in the PI or LSI to the IRB. Changes in other key research staff, if any, must be reported to the IRB prior to implementation. These changes include, but are not limited to, additions to or loss of staff. Changes in the PI, LSI, Co-PI, or Co-LSI of an IRB-approved project must be evaluated and approved by IRB to ensure the new individual meets the criteria described in 38 CFR 16.111.
5. **Overseeing the Research Staff.** This means overseeing and being responsible for ensuring the research staff under the investigator's direction comply with all applicable requirements including, but not limited to, implementing the research study in accordance with the approved protocol.
6. **Obtaining Written Approvals.** This means obtaining written approval(s) before initiating research. Before initiating the research study at a given site, IRB approval must be obtained in writing from the Chair or other voting member of the IRB, and all other committees (e.g., R&D Committee), subcommittees, and other approvals according to applicable local, VA, and other Federal requirements.
 - a. For a VA multi-site study, not only the PI, but also all LSIs, must obtain such approvals from the relevant local VA facilities' IRBs of record and all other local committees, subcommittees, and other approvals according to the respective applicable local, VA and other Federal requirements.
 - b. Research cannot be initiated at any given site until the local investigator has obtained written notification that the research can be initiated from the local ACOS for R&D (see VHA Handbook 1200.01).
7. **Implementing the Study as Approved.** This means ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable, those for research involving investigational drugs or investigational devices.
8. **Maintaining Investigator's Research Records.** This means maintaining written documentation on file that the protocol is being implemented as approved by IRB and in accordance with other required approvals.
 - a. Research records include the following when relevant to the study:
 - i. Copies of all IRB approved versions of the protocol and amendments.
 - ii. Case report forms and supporting data, including, but not limited to, signed and dated informed consent forms and HIPAA authorizations.
 - iii. Documentation on each subject including, but not limited to:
 1. Informed consent,
 2. Interactions with subjects by telephone or in person,
 3. Observations,
 4. Interventions, and
 5. Other data relevant to the research study, including, but not limited to:
 - a. Progress notes,
 - b. Research study forms,
 - c. Surveys, and
 - d. Questionnaires.
 - iv. Reports of adverse events.
 - v. Data analyses.
 - vi. Reports including, but not limited to, abstracts and other publications.
 - vii. All correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D committee, ORO, and FDA.
 - viii. A master list of all subjects for whom informed consent has been obtained in the study.

- b. Documents must be maintained so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements, and
 - c. An Accounting of Disclosure must be maintained for each and every disclosure of information from this study to a non-VA entity. (*The Privacy Officer can assist in providing a mechanism to account for this disclosure*).
9. **Obtaining Informed Consent.** This means ensuring that no human being is involved as a subject in research covered by this Handbook unless legally effective informed consent of the subject or the subject's LAR has been obtained (38 CFR 16.116). The informed consent must be obtained and documented prospectively (i.e., no screening or other interaction or intervention involving a human subject can occur until after the IRB-approved informed consent requirements have been met). The only exceptions are if the IRB determines the research is exempt (38 CFR 16.101(b)), or approves a waiver of informed consent (38 CFR 16.116(c) and (d)), or approves a waiver of the signed informed consent form (38 CFR.117(c)).
- a. **Designating Responsibility for Obtaining Informed Consent.** If the PI or LSI does not personally obtain informed consent, the investigator must formally and prospectively designate to another research team member in writing the protocol or the application for IRB approval the responsibility for obtaining informed consent, whether or not a waiver of documentation of informed consent has been approved by the IRB. This designee must be a member of the research team.
 - i. Any person designated to obtain informed consent must receive appropriate training and be knowledgeable enough about the protocol to answer the questions of prospective subjects.
 - ii. The PI or LSI does not have to designate the individual by name, but can designate the position(s) title in the protocol or the application for IRB approval.
 - b. **Version of Informed Consent Form.** The most current IRB-approved version of VA Form 10-1086, Research Consent Form, for each study (or the most current IRB-approved electronic version of VA Form 10-1086) must be used as the informed consent form.
 - c. **Circumstances Under Which Informed Consent is Obtained.** The investigator, or designee, must seek informed consent only under circumstances that:
 - i. Provide the prospective subject or LAR sufficient opportunity to consider whether or not to participate, and
 - ii. Minimize the possibility of coercion or undue influence.
 - d. **Usual Care.** The investigator, or designee, must ensure the Informed Consent process clearly defines for the subject which potential risks are related to the research (38 CFR 16.116(a)(2)) and, therefore, must be discussed with the research team, versus those associated solely with usual care provided by the subject's health care provider. The informed consent process must include language advising subjects to review the risks of the latter with their health care providers.
 - e. **Documentation of Informed Consent**
 - i. When documentation of informed consent is not waived by IRB, the investigator or designee must ensure the documentation is in accordance with paragraph 33 of VHA Handbook 1200.05 and includes:
 - 1. The signature and date of the subject or the subject's LAR, and
 - 2. The signature and date of the person obtaining the informed consent, and

- a. **Initial Contact.** During the recruitment process, ensuring the research team makes initial contact with the potential subject in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research (e.g., if the potential subject has diabetes, the subject may indicate a desire to be notified of any diabetes-related research studies). The initial contact must provide a telephone number or other means that the potential subject can use to verify the study constitutes VA research.
 - b. **Later Contact.** Ensuring the research team begins telephone calls to the subject by referring to previous contacts and, when applicable, the information provided in the informed consent form, and ensuring that the scope of telephone contacts with the subject is limited to topics outlined in IRB-approved protocols and informed consent forms.
14. **Obtaining IRB Approval for All Changes.** This means obtaining IRB approval for all changes to the research protocol (e.g., amendments or modifications), including changes to the IRB informed consent form (the IRB informed consent form is unique to each research study), prior to implementing the changes. The only exception is when it is necessary to change the protocol to eliminate apparent immediate hazards to the subject. The investigator must report these changes to the IRB within 3 business days.
15. **Submitting Continuing Review Materials.** This means ensuring continuing review materials are complete and submitted in a timely manner to provide the IRB sufficient time for reviewing and approving the study before IRB approval expires. IRB approval automatically expires if the continuing review and approval does not occur by the expiration date of the current approval.
16. **Reporting Deviations and Complaints.** This means reporting deviations from the protocol and subject complaints to IRB within 5 business days.
17. **Reporting Problems and SAEs.** This means reporting all unanticipated problems involving risks to subjects or others, and all internal (i.e., local) SAEs, whether related or unrelated to the research, in accordance with this SOP and VHA Handbook 1058.01.
18. **Completing Appropriate Actions at Research Project Completion.** This means at completion of the research study, completing the study closure report form with all required documentation and storing research records according to all applicable VA and Federal records retention requirements. If appropriate, the investigator communicates the results to subjects or the community from which subjects were recruited.
19. **Transferring of Records.** This means transferring of records by VA upon departure of the investigator. If the investigator leaves 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 VA facility, the investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility's research office. The approval must be obtained from the first VA facility's research office, any other relevant individuals or offices according to VA and local requirements (e.g., Compliance, Privacy or Information Security Officers and the sponsor). *Note: The investigator is not the grantee, nor does the investigator own the data.*
20. **Maintaining a Master List of All Subjects.** This means the investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not the IRB granted a waiver of documentation of informed consent (38 CFR16.117(c)).
 - a. Investigators must not add a subject's name to the master list of all subjects until after:
 - i. Informed consent has been obtained from that subject, and

- ii. When appropriate, informed consent has been documented using an IRB-approved informed consent form.
 - b. The IRB may waive the requirement for the investigator to maintain a master list for a given study if both of the following conditions are met:
 - i. There is a waiver of documentation of informed consent, and
 - ii. The IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.
 - c. If the IRB waives the requirement to maintain such a master list, the IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.
 - d. The investigator must secure the master list appropriately in compliance with all VA confidentiality and information security requirements in the investigator's file for each study.
21. **Ensuring Appropriate Research Laboratory Test Reporting.** This means ensuring research laboratories not report laboratory 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 (VHA Handbook 1106.01).
 22. **Documenting in the Medical Record.** The PI is also responsible for documenting in the medical record all research interactions, adverse events or any other applicable progress notes.
 23. **Minimization of Risks.** Each investigator must personally ensure that every reasonable precaution has been taken to reduce or to minimize any potential or actual risk to the participant.

g. Research and Development Committee (R&D)

While the MCD is responsible for the HRPP, the IRB, and R&D committee ensure that the HRPP is operational. The R&D committee reports to the MCD who is the IO accountable for all research activities conducted under the VAWNYHS auspices.

The R&D committee assists the MDC in fulfilling responsibilities for the facility's research program. The R&D committee is responsible for ensuring the effective operation of the research program through oversight of the R&D's subcommittees, including the IRB, and making appropriate recommendations, including space and resource needs, to the MCD based on the committee's oversight and evaluation of the research program. The R&D Committee assesses the impact of potential research proposals on the VAWNYHS and its Care Lines, and advises the ACOS for R&D and the Medical Center Director on professional and administrative aspects of proposals.

All research activities within the facility, whether funded or unfunded, are within its purview.

The R&D cannot alter an adverse report or recommendations (e.g., disapproval for ethical or legal reasons) made by the IRB.

All human subjects' research must be reviewed and approved by the R&D committee prior to initiation at VAWNYHS. All subsequent protocol approvals (e.g., amendments, continuing reviews, etc) are communicated to the R&D committee through the minutes of the IRB.

h. Institutional Review Board (IRB)

The IRB is a formally established subcommittee of the R&D committee (VHA Handbooks 1200.01 and 1200.05). The IRB is an appropriately constitute group that the VA has designated to review and monitor research involving human participants to protect the rights and welfare of the participants. The IRB also provides oversight and monitoring of such protections. In accordance with the Common Rule, VA and FDA regulations, the IRB has responsibility for approving, requiring modifications (to secure approval), or disapproving human subject research.

The VA Central IRB will serve as the IRB of record for multi-site VA studies that are requested by ORD to be reviewed and overseen by the VA Central IRB.

The VAWNYHS recognizes the IRB as the reviewing body for ethical issues involving research protocols, and the FDA recognizes the IRB as its reviewing body at the local level, established to protect the rights and welfare of human research participants recruited to participate in research activities conducted under the auspices of the VAWNYHS. All research involving human participants conducted completely or partially in VAWNYHS, conducted in approved off-site locations, facilities, and/or conducted by VA researchers while on official VA duty time, including research funded from extra-VHA sources and research conducted without direct funding, must be reviewed and approved by the VAWNYHS IRB prior to the initiation of any research activities (VHA Handbook 1200.05).

The IRB with the support of the research administration office will disseminate all new policies, forms and guidance as applicable. The VAWNYHS research website will provide all current policies and procedures, including any changes that may occur. In addition, list serve emails and quarterly newsletters are also utilized. An annual summary of IRB committee performance will be submitted to the R&D Committee. Each committee member will conduct annual a self evaluation which will be reviewed by the IRB Chair. The IRB Chair will address areas of concern or provide adequate guidance and resources.

The R&D committee assesses the qualifications and experience of the IRB chair and vice-chair(s) prior to making its recommendations to the MCD. The MCD appoints the members, the chair and the vice-chair(s) of the IRB individually in writing. It is the responsibility of the IRB to ensure that due care is taken to protect human research participants. Additionally, the IRB will protect the confidentiality of participants, protocols, and the data generated during the research.

i. IRB Chair

The VAWNYHS IRB will have a chair, and one or two vice-chair(s). The role of the chair is to provide oversight and guidance for the HRPP. His/her duties include but are not limited to:

1. Conducting all convened meetings.
2. Reviewing requests for exempt and expedited reviews.
3. Reviewing the entire project submission packet for each study.
4. Participating in any investigation of non-compliance.
5. Submitting required reports to appropriate agencies.

The vice-chair(s) will act in the chair's role if the chair cannot be present at a meeting or is recused from a particular discussion or vote.

j. Privacy Officer (PO) and Information Security Officer (ISO)

The Privacy Officer and Information Security Officer are responsible for:

1. Ensuring the proposed research complies with all applicable local, VA and other Federal requirements for privacy and confidentiality, and for information security, respectively, by identifying, addressing, and mitigating potential concerns about proposed research studies, and by serving in an advisory capacity to the IRB or R&D Committee as a non-voting member.
2. Reviewing the proposed study protocol and any other relevant materials submitted with the IRB application.
 - a. It is not sufficient for the PO or ISO to review a checklist completed by the investigator, and not the study protocol and related materials themselves. To facilitate the review of the proposal by the PO and ISO, the investigator must either dedicate specific sections of the protocol to privacy and information security, respectively, or the investigator must develop an additional document

that specifically addresses all privacy and information security issues in the proposal, and that additional document will become part of the IRB protocol file.

3. Completing their respective reviews of the proposed research and informing the IRB of all their findings related to privacy and confidentiality, and to information security, respectively.
 - a. The PO and ISO are not responsible for approving or disapproving a study, nor do they have the authority to prevent or delay IRB approval of a study. The IRB is responsible for approving all non-exempt human research studies. Exempt studies should be approved in accordance with VHA Handbook 1200.01.
4. Identifying deficiencies in their respective reviews of the proposed research, and making recommendations to the investigator of options available to correct the deficiencies.
5. Following up with the investigator, in a timely manner, to ensure the proposed research is in compliance with relevant privacy and confidentiality, and information security requirements, respectively, before the investigator initiates the study.
6. Providing summary reports of their review and assessment of each study according to the requirements of this section. The summary report must clearly:
 - a. Indicate either that all applicable local, VA and other Federal requirements for privacy and confidentiality, and for information security, respectively, have been met, or
 - b. Identify specific deficiencies and suggest available options for correcting those deficiencies.
7. Providing their summary reports on each study to the IRB staff within a time frame that does not prolong the study approval process. They must provide their summary reports prior to, or at, the convened IRB meeting at which the study is to be reviewed or, in the case of expedited review, prior to, the IRB approval determination of the IRB Chair, or designee. For exempt studies, they must submit their summary reports to the ACOS for R&D, and ensure the study is in compliance before the study is initiated.
8. Providing their final reports on each study to the IRB staff in a timely manner.

IV. IRB COMPOSITION

- a. **Member Background.** The IRB must have at least five members with varied backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB members must be sufficiently qualified to review the research through their experience, expertise, and diversity, including consideration of race, gender, cultural backgrounds, impaired decision making capacity, including mental disabilities, and sensitivity to community issues and/or attitudes. The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human participants and possess the professional competence necessary to review specific research activities (38 CFR 16.107(a)).
- b. **Understanding of Institutional Commitments and Requirements.** In addition to possessing the professional competence necessary to review specific research activities, the IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and applicable local, VA and other Federal requirements, and standards of Government ethics and professional conduct and practice. The IRB must therefore include persons knowledgeable in these areas (38 CFR 16.107(a)).
- c. **Knowledge about Vulnerable Subjects.** If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration must be given to the inclusion of one or more individuals who are knowledgeable about and are experienced in working with these subjects (38 CFR 16.107(a)).
- d. **Gender.** In the appointment of IRB members, equal consideration must be given to qualified persons of both genders. No appointment to the IRB will be made solely on the basis of gender. Every non-discriminatory effort

will be made to ensure that the IRB membership does not consist entirely of men or entirely of women (38 CFR 16.107(b)).

- e. Profession.** The IRB may not consist entirely of members of one profession (38 CFR 16.107(b)).
- f. Scientific and Non-Scientific Expertise.** The IRB must include at least one member whose primary expertise is in scientific areas and at least one member whose primary expertise is in non-scientific areas (38 CFR 16.107(c)). These members are to be selected primarily to reflect the values of the research community and the community from which the research participants are drawn with respect to the rights and welfare of human research participants.
- g. Non-Affiliated Members.** The IRB must include at least one member who is not otherwise affiliated with VAWNYHS and who is not part of the immediate family of a person who is affiliated with the medical center (38 CFR 16.107(d)). Members of the community such as clergy persons, teachers, attorneys, veterans, or representatives of legally recognized veterans' organizations, and practicing physicians need to be considered for appointments to the IRB. The non-affiliated voting member must be given a VA WOC appointment for the length of term on the committee.
 - 1. The requirement for non-affiliated members to obtain a VA WOC appointment does not apply to members of the affiliate IRBs.
 - 2. Veterans whose only relationship with the VA is receiving care at a VA facility or receiving benefits from the Veterans Benefits Administration are not considered to be affiliated for the purpose of being an IRB member. Individuals who perform occasional volunteer activities without a WOC appointment are not considered to be affiliated. However, those who hold a WOC appointment for volunteer activities other than IRB service are considered to be affiliated.
 - 3. Individuals who have retired from VA and who are receiving VA retirement benefits are considered affiliated.
 - 4. Employees of institutions that have formal academic affiliation agreements with the VA, and employees of VA nonprofit research and education foundations are considered to be affiliated with the VA.
 - 5. Non-affiliated members who feel they are being subjected to undue influence should report to the following: ACOS for R&D, COS and the MCD. The ACOS for R&D will investigate the allegation and report to the convened IRB. The IRB will make recommendations to the COD for appropriate action through the ACOS for R&D. The COS will implement the action and communicate such actions to the MCD and the ACOS for R&D. The ACOS for R&D will report to the IRB with the results of actions taken.
- h. Conflict of Interest.** The IRB may not have a member participate in the review of any project in which the member has a conflict of interest, except to provide information requested by the IRB (38 CFR 107(e)).
 - 1. The member with a conflict of interest of a financial, professional, or personal nature must not be present during the vote or during any related IRB discussion except to answer questions; this member cannot be counted toward the quorum.
 - 2. "Not Present" means that the IRB member must leave the room or, if the participant is in the meeting via conference call or videoconference, the connection must have been terminated, not just placed on "hold".

Please see Center Memorandums 151-5 and 151-6 for additional information regarding Conflict of Interest.
- i. Consultants or Ad Hoc Advisors.** The ACOS for R&D or any member of the IRB may request individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB as consultants. Documentation of this consultation will be kept in the protocol file. These individuals may not vote with the IRB (38 CFR 16.107(f)). The IRB will evaluate and identify any potential

conflict of interest with each consultant. For a consultant with a conflict of interest, the IRB may allow the consultant to provide information requested, but may be required to leave the room for discussion and vote. The conflict of interest will be disclosed to all IRB members, and documented in the meeting minutes.

- j. Ex-Officio, Non-Voting Members.** Include the ACOS for R&D, the AO for R&D, and either or both the ISO and PO. All ex-officio, non-voting members must be sensitive to the occurrence or appearance of conflict of interest.
- k. Research Compliance Officer (RCO).** The RCO will serve as a non-voting consultant to the IRB and may attend meetings at the request of the IRB committee.
- l. Appointment of Members.** The ACOS for R&D and current IRB members recommend appointment of members to the IRB. The names are forwarded through the R&D committee to the MCD who appoints the members individually in writing.
- m. Term of Appointment for Voting Members.** Voting members will be appointed to a three-year term with membership staggered so that 1/3 of the membership is replaced annually. No time lapse between appointments is required.
- n. Term of Appointments for Alternate Members.** Alternate members will be formally appointed to the IRB by the MCD following the same procedures as for appointments of primary members. Alternate members will be appointed to replace specific primary members when such primary members cannot be present at a meeting. The alternate members must have similar areas of expertise and experience as the member(s) they are appointed to replace. The IRB roster will identify the primary member(s) for whom each alternate member may substitute. When an alternate member replaces the primary member, the alternate member must receive and review the same material that the primary member received. In addition, the IRB minutes must document instances in which an alternate member replaces a primary member.
- o. Term of Appointment for Chair and Vice-Chair(s).** The IRB chair and vice-chair are selected annually by the membership of the IRB and are appointed by the MCD for a term of one (1) year. Either or both may be re-appointed indefinitely.
- p. Performance of Chair and Vice-Chair(s).** Will be evaluated annually by the R&D committee chair with input from the ACOS for R&D. Their record of attendance at meetings and adherence to applicable regulations and local policies and procedures will be considered, along with any other issues deemed appropriate by the R&D committee chair and the ACOS for R&D. The evaluations will be shared with the chair and the vice-chair(s).
- q. Performance of IRB Members and Staff.** The performance of the IRB members and IRB staff will be evaluated annually by the IRB chair with input from the ACOS for R&D. Their record of attendance at meetings and adherence to applicable regulations and local policies and procedures will be considered, along with any other issues deemed appropriate by the IRB chair and the ACOS for R&D. Committee members are also asked to complete an annual self evaluation for their performance. The IRB chair reviews the self evaluations and provides feedback to the convened IRB.

V. EDUCATION AND TRAINING FOR MEMBERS

All members will initially receive a copy of the publication "Protecting Study Volunteers in Research". They are required to successfully complete training on the ethical principles on which human research is conducted and accepted good clinical practice (GCP) initially and every two years after. Routine education will be provided to the members on the meeting agendas. Members are also encouraged to participate in other continuing educational offerings. Training for non-scientists and community members will be appropriate for level of

responsibility and access to identifiable data and will include definitions, acronyms, meeting format and HRPP principles.

VI. IRB RESPONSIBILITIES AND AUTHORITY

VA Regulations at 38 CFR 16.111, FDA regulations, and the Common Rule delineate specific criteria for the approval of research. The IRB shall determine that all of the following requirements are satisfied before approving proposed human subject research.

- a. Determination of Human Subject Research.** The IRB will first review research proposals based on guidance from 38 CFR 16.102(f) to determine if the research constitutes human subject research. (*Note: See OHRP Guidance on Engagement of Institutions in Human Subject Research, October 16, 2008, for examples and additional guidance.*)

1. Engagement in Human Subject Research.

- a. In general, a VA facility is considered “engaged” in a particular non-exempt human subjects research study when an individual with a VA appointment (including full and part-time employees, WOC employees, and employees under IPA) at that facility obtains for the purposes of the research study:
 - i. Data about the subjects of the research through intervention or interaction with them;
 - ii. Identifiable private information about the subjects of the research; or
 - iii. The informed consent of human subjects for the research.
- b. When a VA facility is engaged in human subject research, it must:
 - i. Hold an FWA;
 - ii. Have a PI or LSI for that study; and
 - iii. Have the facility’s IRB of records approve the study.

2. Not Engaged in Human Subject Research:

- a. If a VA facility is not engaged in any human research then the VA facility does not need to have an FWA.
- b. IF a VA facility is not engaged in research for the purposes of an individual study, then its IRB of record does not need to approve that study.
- c. If a VA facility is not engaged in research for the purposes of a given study, it has no jurisdiction over that study, except the MCD may determine that the study cannot be conducted on its premises.

- b. IRB Review.** If the proposal meets the criteria for human subject research, the IRB will review and provide written documentation of human research proposal approval. Activities such as quality improvement, case reports, program evaluation, and surveillance activities may or may not meet the criteria for human research. The IRB will refer to ORD guidance and VHA Handbook 1058.05 to assist in making the determinations. 3 In the review of human subject research, the IRB considers the following criteria:

1. **Levels of Risk.** The IRB must consider the overall level of risk to participants in evaluating proposed research. The IRB distinguishes among research projects that appear to carry minimal risk, or greater than minimal risk, and also takes into consideration whether vulnerable populations are being studied. The IRB also assesses the risk relative to potential benefit for all research proposals and the importance of knowledge that may reasonably be expected to result from such research. Under specific circumstances, research that is minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of informed consent. Waiver of informed consent is not generally appropriate for FDA regulated test articles. Under VA regulations at 38 CFR 16.102(i), the Common Rule, and FDA regulations, “minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves

than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Determination of the frequency of continuing review of each research project is, in part, based on degree of risk as determined by the IRB. Degree of risk will be assessed as:

- a. Minimal Risk
- b. Greater than Minimal Risk

2. **Risks Minimized (38 CFR 16.111(a)(1)).** Before approving a research project, the IRB must determine that risks are minimized by:
 - a. Using procedures that are consistent with sound research design and do not expose participants to unnecessary risks, and
 - b. Whenever appropriate, utilize procedures that are already being performed on the participants for diagnostic or treatment purposes.

The IRB is expected to examine the research plan, including research design and methodology, to determine that there are no obvious flaws that would place participants at unnecessary risk. This includes the risk that the research is so poorly designed or is so lacking in statistical power that meaningful results cannot be obtained. The IRB will consult experts when aspects of research design seem to pose a significant problem. The IRB shall also consider the professional qualifications and resources of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges.

3. **Risks Reasonable Relative to Anticipated Benefits (38 CFR 16.111(a)(2)).** Before approving a research project, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to participants, and the importance of the knowledge that may reasonably be expected to result. The IRB considers only those risks and benefits, which may result from the research (as distinguished from those risks and benefits of therapy that the participants would receive even if not participating in the research). For biomedical research, the IRB is required to determine and differentiate between the risks associated with the research and the risks associated with standard diagnostic or therapeutic interventions or therapies participants would undergo regardless of participation in research. Since the IRB does not establish or determine what constitutes standard of care, it is important for investigators to clearly distinguish procedures that are standard of care from those which are conducted solely for research purposes in the protocol and informed consent form.

The IRB considers that the risks to participants may include the following:

- a. **Physical Risk.** Some biomedical research presents risk of physical injury to participants. Although most of these risks are transient, some adverse effects of study participation may result in permanent injury to participants. For all research with the potential to cause physical harm, investigators need to think through all risk possibilities so that they can be resolved quickly and minimize the harm to participants. Investigators need to address procedures to minimize physical risk to the greatest extent possible.
- b. **Psychological Risk.** Some research has the potential to cause undesired changes in thought processes and emotion including episodes of depression, confusion, and hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem. As is the case with physical risks, these effects are usually transient. For all research with the potential to cause psychological harm, investigators need to think through all risk possibilities so that they can be resolved quickly and minimize the harm to participants. Investigators need to address procedures to minimize psychological risk to the greatest extent possible.

- c. **Social and Economic Risk.** Some research involves the handling of sensitive information, which may result in injury to participants through a breach in confidentiality. These breaches may result in embarrassment within a participant's business or social group, loss of employment, or criminal prosecution. The IRB is especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior and illegal activities. For these situations, investigators should detail strong safety precautions to ensure that the research does not cause social or economic risks to the participant. Research may also pose direct economic risk to study participants (e.g., billed procedures, transportation cost, and loss of wages). Investigators should minimize economic costs to participants. If the research may involve additional actual cost to individuals, the anticipated costs should be described to participants during the consent process.

The IRB distinguishes among research projects that appear to have the following prospects of benefit:

1. Prospect for direct benefit to participant
2. Little prospect for benefit to the participant but likely to yield generalizable knowledge
3. No prospect for benefit to the participant but likely to yield generalizable knowledge
4. No prospect for direct benefit to the participants and unlikely to yield generalizable knowledge

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research. The IRB should consider only those risks that result from the research, and should not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research.

The IRB must ensure protocols with treatment or services that constitute "usual care" include a narrative section that clearly differentiates the research interventions from usual care, whether usual care is delivered to only some or to all the research subjects.

In addition, the IRB must ensure the informed consent process clearly defines for the subject which potential risks are related to the research, and therefore, need to be discussed with the research team, versus those associated solely with usual care provided by the subject's health care provider. The informed consent process is to include language advising subjects to review the risks of the latter with their health care providers.

If the IRB is questioning the protocol's characterization of "usual care," its associated risks, or the person or entity responsible for specific aspects of "usual care," the IRB will seek clarification from the investigator and, if warranted, from qualified experts. The IRB will document its determination accordingly.

4. **Equitable Selection of Participants (38 CFR 16.111(a)(3)).** Before approving a research project, the IRB must determine that the selection of participants is equitable. This is the concept of "Justice" detailed in *The Belmont Report*. In making this determination, the IRB evaluates the purposes of the research, the research setting, and the inclusion/exclusion criteria.

The IRB is especially cognizant of the problems of research involving vulnerable participant populations. Generally, a population that stands no chance of benefiting from the research should not be selected to assume the risk.

The IRB is mindful of the importance of including members of minority groups in research, particularly when the research holds out the prospect of benefit to individual participants or the groups to which they belong. Non-English speaking participants should not be systematically excluded because of inconvenience in translating informed consent documents. The IRB considers the scientific and ethical reasons if classes of persons who might benefit from the research are excluded.

The IRB is mindful of the desirability of including both women and men as research participants and should not arbitrarily exclude the participation of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

With regard to children (defined as under the age of 18), it is VA policy that children cannot be included in VA-approved research unless a waiver has been granted by the Chief Research and Development Officer. See VHA Handbook 1200.05.

The IRB prohibits non-veterans from being entered into VA-approved research studies unless there are insufficient veterans available to complete the study.

c. Initiation of Research Projects. All proposed research involving human participants must be reviewed and approved by the IRB and the R&D Committee prior to initiation of the research project. The date of continuing review will be based on the date of IRB approval. *Note: The R&D committee shall not give final approval to the research project until all appropriate subcommittees (e.g., Biosafety, Radiation Safety, etc) have reviewed and approved the research.*

1. If the IRB approves research contingent upon substantive modifications or clarifications to the protocol and/or the informed consent, IRB approval of the proposed research must not occur until subsequent review by the convened IRB of the material the PI submitted.
2. If the convened IRB approves research contingent on specific minor conditions, the IRB chair, or another IRB member designated by the chair, may approve the revised research protocol on behalf of the IRB. The date of approval is the date the fully convened IRB approved the protocol with minor conditions or contingencies rather than the date that the minor changes were approved by the IRB chair, or designee. The research may not begin until the IRB chair, or designee has approved the changes and the R&D committee has approved the research. The approval by the IRB chair, or designee, must be documented in the minutes of the first IRB meeting that takes place after the date of the approval.

d. Review of Compliance Audits. The IRB is responsible for reviewing RCO audit findings and determining required remedial actions. The IRB committee will set a deadline for completion of remedial actions and is responsible for following up to ensure completion. Any instance of a missed deadline will be reviewed by the convened committee to determine what actions should be taken, including possible suspension or termination of research. Documentation of audit findings, remedial actions and completion of remedial actions will be maintained in the protocol file.

1. The IRB accepts RCO audits to fulfill the requirement set forth in VHA Handbook 1200.05 of the IRB responsibility to ensure the performance of periodic and random audits of human subject research studies and requiring investigators to take appropriate and timely corrective actions when deficiencies are identified. Refer to the RCO SOP.
2. The IRB may require more frequent audits by the RCO, or require the RCO to conduct more focused audits of one or more aspects of a study. The requirement to increase the frequency of audits or to audit specific aspects of a study may be based on considerations including, but not limited to:
 - a. Involvement of vulnerable populations;
 - b. Level of risk;
 - c. Phase I or Phase II studies;
 - d. Involvement of FDA approved drugs for which there have been a new safety warning issued, or change in the labeling that indicates increased risks;
 - e. Issues of non-compliance; or
 - f. Data confidentiality or security concerns.

VII. REVIEW OF RESEARCH PROTOCOLS

a. IRB Review

The IRB must conduct a review by a convened committee or expedited review procedure of all proposed human subject research in accordance with local, VA, and other Federal criteria. This review includes a review of the application to the IRB, the research protocol, and all other relevant documents submitted to the IRB. No such study can be initiated until the IRB has determined that the study does not constitute human subject research, is exempt from IRB approval requirements, or has satisfied all requirements for approval. All research that is determined to be exempt or to not involve human subjects must be reviewed and approved by the R&D committee. The IRB may consider the following questions in making these determinations:

1. **Is the project research?** The IRB's first responsibility is to determine whether or not the proposed project constitutes a research study. If the project does not constitute research, the IRB has no responsibilities for review or approval beyond the determination that the project does not constitute research (38 CFR 16.102(d)).
2. **Does the research involve human subjects?** If the project does constitute a research study, the IRB must determine whether or not it involves human subjects as defined in VHA Handbook 1200.05 and 38 CFR 16.102(f).
3. **Is the human research project exempt from IRB review?** If the study constitutes research involving human subjects, then the IRB chair or another IRB voting member designated by the IRB chair must determine whether or not the study is exempt from IRB review. If the study is exempt from IRB review, the IRB does not have to approve it and it will be reviewed and approved by the R&D committee.
4. **Non-Exempt Research.** If a proposed human research study does not meet the criteria for exemption from IRB review, the study is considered "non-exempt," and the IRB must:
 - a. Conduct initial review using a convened or expedited review procedure,
 - b. Determine whether the research has satisfied all relevant criteria for approval, and
 - c. Perform subsequent continuing review as appropriate.

b. Initial Review

VAWNYHS utilizes a Proposal Review Committee for the scientific review of new research studies. Refer to the Proposal Review Committee SOP for the detailed processes.

1. Once the scientific review of the study is completed, an IRB primary reviewer is selected by the ACOS for R&D along with the IRB chair. Attention will be paid to the field of expertise of the reviewer when the selection is made.
 - a. The IRB coordinator will then forward the proposal submission packet to the IRB primary reviewer. The primary reviewer receives the entire proposal submission packet which includes:
 - i. Full protocol
 - ii. Informed consent form, request for waiver or alteration of informed consent, or request for waiver of documentation of informed consent
 - iii. HIPAA Authorization and/or request for waiver of HIPAA authorization
 - iv. Any relevant grant application
 - v. Investigator's brochure (if applicable) or equivalent material
 - vi. Final copies of printed advertisements or participant information (if applicable)
 - vii. Final copies of audio/visual taped advertisements (if applicable)
 - viii. Participant surveys or questionnaires (if applicable)
 - ix. Investigational drug information records (VA Form 10-9012)

- x. Abstract and/or executive summary
 - xi. Budget information
 - xii. Conflict of interest forms for PI and study staff
 - xiii. PO and ISO checklist/review
 - xiv. CV of investigators
 - xv. Scientific review of the proposal
2. The full protocol and any supplementary material are available in the research office for review by all members of the IRB prior to the convened meeting, as well as during the meeting.
 3. The scientific reviewer may attend the IRB meeting as a guest, in a non-voting capacity, if not a member.
 4. The IRB will review advertisements and recruitment incentives associated with the research that they oversee; this includes the initial documents and all final versions. These documents include, but are not limited to, flyers, letters, newspaper ads, audio/video tapes, TV announcements, bulletin boards, and posters. When direct advertising is to be used, the IRB should review the information contained in the advertisement and the mode of its communication, to determine that the advertising is limited to the information prospective participants needed to determine their eligibility and interest, such as:
 - a. The name and address of the investigator or research facility.
 - b. The purpose of the research or the condition under study.
 - c. In summary form, the criteria that would be used to determine eligibility for the study.
 - d. A brief list of participation benefits, if any.
 - e. The time or other commitment required of the participants.
 - f. The location of the research and the person or office to contact for further information.

The advertisements will also be reviewed to ensure that they do not use terms such as “new treatment”, “new medication”, or “new drug”, without explaining that the test article is investigational. Recruiting documents, flyers and advertisements for non-VA research are not to be posted within or on the premises of a VA facility.

The IRB will determine that the procedure for recruiting participants is not coercive, that it does not include exculpatory language, and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. For participation in FDA–regulated research, advertisements should not include compensation that will include a coupon good for a discount on the purchase price of the product once it has been approved for marketing. Advertisements should not promise “free medical treatment,” when the intent is only to say participants will not be charged for taking part in the investigation. Advertisements may state that participants will be paid but should not emphasize the payment or the amount to be paid by such means as larger or bold type.

5. Payments to participants must be reviewed by the IRB to determine that such payments meet the VA regulations as stated in VHA Handbook 1200.05, which include but are not limited to:
 - a. Payments to participants may not be made when the research is integrated into their regular medical care and places no special demands on them;
 - b. that credit for payment accrued as the study progressed and was not contingent on the participant completing the entire study and if a bonus was paid for completion, that the bonus was not so large as to unduly induce participants to stay in the study when they would have otherwise withdrawn.

- c. When transportation expenses are incurred, by the participants that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.
 - d. The research is not directly intended to enhance the diagnosis or treatment of the medical condition for which the participant is being treated, and when the standard of practice in affiliated non-VA institutions is to pay participants in this situation.
 - e. The research is a multi-institutional study and participants at collaborating non-VA institutions are paid for the same participation in the same study at the same rate proposed.
 - f. In the opinion of the IRB, payment of participants is appropriate in other comparable situations.
6. Payments (finder's fees) may not be made to professionals in exchange for referrals. Investigator may not accept payments from sponsors designed to accelerate recruitment that are tied to the rate or timing of enrollment.
7. The IRB allows non Veterans to be entered into VA-approved research studies only when there are insufficient Veterans available to complete the study.
8. The IRB will review the protocol to ensure that the investigator provides for clinical expertise. If the investigator is not a clinician, when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not limited to:
 - a. Reviewing the data, adverse events, and new study findings; and
 - b. Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject).
9. All members receive and review a protocol abstract, proposed informed consent form or request for waiver of consent, HIPAA Authorization or request for Waiver of Authorization, IRB primary reviewer form, scientific reviewer form, written review by scientific reviewer, budget information, Conflict of Interest forms for PI and staff, data security forms and any advertising material intended to be seen or heard by potential participants. Other pertinent documents may also be included.
10. When the IRB reviews research that involves participants likely to be vulnerable to coercion or undue influence, the ACOS for R&D or IRB chair evaluates each protocol to ensure that at least one IRB member knowledgeable about or experienced in working with such participants will be present at the meeting.
11. The convened IRB will determine that the regulatory criteria for approval are met.
12. The IRB will determine the approval period for the project. All projects must be reviewed within a period not greater than one year. The IRB may determine that a project requires review more often than annually for reasons which include, but are not limited to:
 - a. Risk level
 - b. Investigator history of non-compliance
 - c. Investigator experience
13. The PI will be notified in writing of the IRB's determinations.

c. Continuing Review

1. **Continuing Review Period.** The IRB conducts a substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, within one year. Thus, the IRB approval period must be within one calendar year from the convened IRB meeting at which the research was last reviewed and approved, or approved with minor changes not requiring additional full IRB review.

- a. When expedited review is used for an initial or continuing review as permitted in the regulations, continuing review must take place within one (1) year from the date the IRB chair, or experienced IRB voting member(s) designated by the IRB chair, gives approval to the research study.
 - b. No other dates for continuing review should be used (for example, the date of R&D committee approval, or project start date).
 - c. If minor changes were approved by expedited review as permitted by 38 CFR 16.110(b), continuing review must still be performed within the original “less than one year period”.
2. **Continuing Review Submission.** To assist the PI, the research office will forward the continuing review submission form to the PI approximately two months in advance of the identified required review date.
- a. The PI must complete all necessary paperwork for continuing review in a timely manner to ensure adequate time for subcommittee action before the IRB approval period expiration date is reached.
 - b. A progress report must be submitted with the continuing review packet and must include:
 - i. Original abstract update with any changes
 - ii. A brief summary of the methodology and procedures used in the study (if not explained in the abstract)
 - iii. Summary of any new research findings and whether they may change the ratio of risks to benefits
 - iv. Summary of unanticipated problems involving risks to subjects or others
 - v. Complaints about the research
 - vi. Any significant new findings that arose from the research
 - vii. Any significant new findings that might have determined subjects willingness to continue participation
 - viii. Any adverse events, protocol deviations, or unanticipated problems that required corrective measures
 - ix. Progress to date that will lead to completion of the study
 - x. List of publications or presentations on the research
 - xi. Specification of plans for work to be accomplished in the upcoming year
3. **Review Type.** Continuing reviews are conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited review.
4. **Review Process.** Once the submission is received by the IRB coordinator, a reviewer from the IRB membership is appointed by the IRB chair or his/her designee to review the continuing review submission for each project.
- a. The IRB coordinator provides the primary reviewer with the complete continuing review submission packet, including the progress report, and updated consent form, along with the complete protocol file including all protocol modifications previously approved by the IRB, and any unanticipated events or problems which occurred during the review period. The primary reviewer is expected to conduct an in-depth review of these materials in advance of the meeting and to lead the discussion at the convened IRB meeting.
 - i. The primary reviewer will complete the Continuing Review – IRB Reviewer Worksheet to ensure an adequate review.
 - b. The primary IRB reviewer will present his/her findings and recommendations on each project reviewed at a convened IRB meeting.

- c. The IRB members will review the investigator's completed continuing review form, progress report, literature review, and the updated version of the informed consent form, or newly proposed consent form, if applicable.
 - i. The IRB must ensure that the master list of subjects submitted by the investigator at the time of continuing review contains only those subjects who have signed informed consent, unless the IRB has granted a waiver of informed consent, or a waiver of documentation of informed consent.
 - 1. The IRB may rely on assurances from the PI and audits conducted by the RCO.
 - ii. The IRB has the authority to obtain verification from sources other than the investigator that no substantive modifications have occurred since the previous IRB review.
 - d. The convened IRB will determine whether the criteria for approval of the continuing review are met.
 - i. The IRB will determine whether:
 - 1. Regulatory criteria for approval were met
 - 2. Any material changes to the protocol were appropriately addressed
 - 3. The current informed consent form is accurate and complete
 - 4. Any new findings that may related to participants willingness to continue are being provided to participants
 - 5. Frequency of continuing review is adequate to ensure continued protection of the rights and welfare of research participants.
 - e. A positive vote by a majority of the members present is required for approval.
 - i. IRB approval to continue the study will not be granted if the required documents (continuing review submission form, progress or status report, literature review, and informed consent document, if applicable) have not been submitted for review.
 - f. The IRB will determine the interval for the next continuing review. All projects must be reviewed within a period not greater than one year. The factors in considering the frequency of review will include:
 - i. Nature of the study
 - ii. Degree of risk
 - iii. Vulnerability of the study population
 - iv. Investigatory experience
 - v. Investigator history of non-compliance
 - g. Minutes of the IRB meetings will document separate determinations, actions, and votes for each protocol undergoing continuing review by the convened IRB. The findings and decision of the IRB will be communicated in writing to the PI. If the investigator disagrees with the IRB decision, he/she may appeal following the procedures outlined in section 14 of the IRB SOP.
5. Following continuing review approval, the IRB will identify the new approval and expiration date of the informed consent form, if applicable, and the consent will be stamped with those dates and returned to the PI for use with new participants.
- a. When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur. There is no provision for any grace period to extend the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur on or before the date when IRB expires.

6. The IRB will report its findings and action in writing to the investigator and through the IRB minutes to the R&D Committee.

d. Approval Period. The approval period and expiration date are determined as follows:

1. When the convened IRB approves research with no changes for less than one year on 04/23/08 then the dates of approval interval are 04/23/08 to 04/22/09. The expiration date is 04/22/09 at 11:59pm.
2. If the convened IRB approves research pending minor changes for one year on 04/23/08; when the IRB Chair or designee determines that the investigator has submitted the required changes on 05/06/08, the dates of the approval interval are 04/23/08 to 04/22/09. The expiration date is 04/22/09 at 11:59pm.
3. When the convened IRB approves research with no changes for X months (where $X < 12$) on 04/23/08 the dates of the approval interval are 04/23/08 to one day less than X months. The expiration date is one day less than X months of the date of approval of the convened IRB on 04/23/08. For example, the six month expiration date would be 10/22/08 at 11:59pm.
4. If the convened IRB approves research pending minor changes (as defined in Appendix C) for X months (where $X < 12$) on 04/23/08; when the IRB Chair or designee determines that the investigator has submitted the required changes on 04/23/08, so the dates of the approval interval are 04/23/08 to one day less than X months from convened IRB approval date. The expiration date is one day less than X months of the date of approval of the convened IRB on 04/23/08. For example, the six month expiration date would be 10/22/08.

e. Lapse in Approval. If the continuing review does not occur on or before the expiration date, the research proposal is automatically placed in a lapsed status. The VAWNYHS IRB considers such lapsed approval as an automatic action. However, it will be reported to the sponsoring agency, private sponsor, ORD (if funding the research), and funding agencies as appropriate. The IRB office will promptly notify the investigator of the expiration via e-mail followed by a signed letter that the expiration of IRB approval has occurred and all study activities must stop immediately, including the enrollment of subjects and data analysis. The investigator must immediately submit a list of subject names to the IRB chair for whom cessation of study interventions would cause harm. Continuation of research interventions or interactions in previously enrolled subject(s) will only continue when the IRB chair, in consultation with the COS, finds that it is in the best interest of individual subjects to do so (VHA Handbook 1200.05, section 7g). If the study is FDA regulated, the COS and IRB must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision. The IRB must review and re-approve the study prior to allowing any study activities to occur on research that has expired IRB approval. The PI will have 30 days, post lapse of the study, to resubmit the protocol for IRB approval to avoid administrative closure. All protocol lapses are reported on the monthly IRB and R&D committee agendas.

f. Review and Approval of the Informed Consent Form. The IRB is responsible for the review and approval of the informed consent form prepared by the PI.

1. **VA Form 10-1086, Research Consent Form.** VA Form 10-1086 must be used as the research informed consent form.
 - a. The wording on VA Form 10-1086 must contain all of the required elements and meet all other requirements outlined in section 8 of this SOP.
 - b. IRB approval of the wording of the consent must be documented through the use of a stamp on each page of the VA Form 10-1086 that indicates the date of the most recent IRB approval of the document and the expiration date of that approval.
 - i. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment rather than the date of the approved protocol.
 - c. A version date must appear on each date.

- d. The IRB needs to ensure the language in the informed consent form is consistent with that in the protocol and, when applicable, the HIPAA authorization.
2. **Long Form Consent.** For the long form of consent, the IRB should make the following determinations as a condition of approving the research:
 - a. The consent document embodies the basic and appropriate additional elements of informed consent.
 - b. The participant or the participant's legally authorized representative will sign and date the consent document.
 - c. A copy of the signed and dated consent document will be given to the person signing the consent document.
 - d. The investigator will give either the participant or the representative adequate opportunity to read the consent document before it is signed.
 - e. When required by the IRB and/or sponsor, a witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
 - f. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person needs to serve both capacities, a note to that effect was placed under the witness's signature line.
3. **Short Form Consent.** For the short form of consent, the IRB should make the following determinations as a condition of approving the research:
 - a. The consent document (short form) states that the elements of disclosure required by regulations had been presented orally to the participant or the participant's LAR.
 - b. A written summary (equivalent to the information in the long form of consent documentation) embodies the basic and appropriate additional elements of disclosure.
 - c. There will be a witness to the oral presentation. (This must be a witness to the entire presentation, not just the signature.)
 - d. For participants who do not speak English, the witness is conversant in both English and the language of the participant.
 - e. The participant or the participant's LAR will sign and date the short form.
 - f. The witness will sign and date both the short form and a copy of the summary.
 - g. The person actually obtaining consent will sign and date a copy of the summary.
 - h. A copy of the signed and dated short form will be given to the participant or the representative.
 - i. A copy of the summary will be given to the participant or the representative.

g. HIPAA Authorization

1. All research protocols involving human subjects or the use of identifiable information must obtain HIPAA Authorization and/or a Waiver of HIPAA Authorization. The IRB does not have the authority to approve a HIPAA Authorization form. Approval must be obtained by the Privacy Officer. HIPAA Authorization must clearly define what information will be obtained and used for research purposes, as well as whom the information will be disclosed to during the course of the research.
2. The IRB has the authority to waive the requirement for HIPAA authorization. This decision must be justified, and fully documented in the minutes of the IRB meeting where the action was taken or approved.

h. Expedited Initial and Continuing Categories. The IRB may utilize expedited review procedures for the initial or continuing review of specific categories of research as defined in the Federal Register: Volume 63, Number 216, Pages 60364-60367; November 9, 1998. Studies on marked drugs that significantly increase the risks or decrease the acceptability of the risks associated with the used of the drugs are not eligible for

expedited review. The categories of research activities eligible for expedited review must be found by the IRB reviewer(s) to involve no more than minimal risk and fall into one of the 9 categories below:

1. **Drugs and Devices.** Clinical studies of drugs and medical devices only when condition (a) or (b) is met:
 - a. The research is on drugs for which an IND application is not required.
 - b. The research is on medical devices for which:
 - i. An investigational device exemption (IDE) application is not required; or
 - ii. The medical device is cleared or approved for marketing, and the medical device is being used in accordance with its cleared or approved labeling.
2. **Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:**
 - a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 milliliters (ml) in an 8-week period, and collection may not occur more frequently than two times per week; or
 - b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kilogram (kg) in an 8-week period, and collection may not occur more frequently than two times per week.
3. **Non-invasive Collection of Biological Specimens.** Biological specimens for research purposes are to be collected prospectively by non-invasive means. Examples are as follows:
 - a. Hair and nail clippings in a non-disfiguring manner.
 - b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
 - c. Permanent teeth if routine patient care indicates a need for extraction.
 - d. Excreta and external secretions (including sweat).
 - e. Un-cannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gumbase or wax, or by applying a dilute citric solution to the tongue.
 - f. Placenta removed at delivery.
 - g. Amniotic fluid obtained at the time of rupture of the membrane prior to, or during, labor.
 - h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
 - i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
 - j. Sputum collected after saline mist nebulization.
4. **Non-invasive Collection of Data.** Data must be collected through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared or approved for marketing.

NOTE: *Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.* Examples of noninvasive collection of data are:

 - a. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.
 - b. Weighing the subject.
 - c. Testing sensory acuity.
 - d. Magnetic resonance imaging (MRI).

- e. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.
- f. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing, where appropriate, given the age, weight, and health of the individual.

5. **Collected Materials.** Research involves:

- a. Materials (data, documents, records, or specimens) that have been collected for any purpose, including previous research; or
- b. Materials (data documents, records, or specimens) that will be collected solely for non-research purposes (such as medical treatment or diagnosis).

Note: Some research in this category may be exempt from the regulations for the protection of human subjects.

6. **Collection of Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes.**

7. **Group Characteristics, Surveys, Interviews, and Quality Assurance.** Research must be on individual or group characteristics or behavior (including, but not limited to: research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior), or will employ survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. *Note: Some research in this category may be exempt from the regulations for the protection of human subjects.*

8. **Continuing Review of Research Previously Approved by the Convened IRB as Follows:**

- a. Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
- b. No subjects have been enrolled and no additional risks have been identified; or
- c. Where the remaining research activities are limited to data analysis.

9. **Continuing review of research, not conducted under an IND or IDE where categories two (2) through eight (8) do not apply but the IRB as determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.**

i. **Expedited Initial and Continuing Review Procedures.** Requests for expedited review of research must meet the applicability criteria above. The review will be conducted by the IRB chair or his/her designee. Any proposal for which the chair identifies a real or perceived conflict of interest will be reviewed by a designee. Such designations will be recorded in the IRB minutes. This will apply to initial review, continuing review, or amendments.

1. **Initial Review or Continuing Review:**

- a. The IRB chair, or his/her designee, will review the study documents to determine whether an expedited review is warranted.
- b. The IRB chair, or his/her designee, considers all pertinent documents and all information that the convened IRB would have reviewed. In reviewing the research, he/she may exercise all of the authorities of the IRB except that he/she may not disapprove the research. A research activity may be disapproved only by a convened IRB. The review of new research or continuing review through expedited procedures will be documented in writing, the decision and expedited review eligibility category reported to the convened IRB at the next convened IRB meeting, and recorded in the IRB minutes. 38CFR 16.110(b)(2)

- c. The submission of a protocol for expedited review follows the same procedures as full review protocols.
- d. The appropriate Initial, or Continuing Review, reviewer worksheets are used to determine that all criteria for approval are met.
- e. The IRB's decision, including the expedited review eligibility category, is conveyed in a letter to the investigator.

j. Dual Enrollment. The VAWNYHS IRB is mandated with ensuring research studies are conducted in such a manner that the potential for benefit is maximized and risks are minimized. Therefore, before a subject can be enrolled in more than one trial, the IRB must acknowledge the request. The IRB reserves the right to request additional information or deny the request.

The IRB requires consensus among the Principal Investigators of each study that dual enrollment is appropriate, given the possibility of increased variables and the possibility of increased risks to subjects.

All investigators are required to place either a Research Study Initiation Note or Research Study Minimal Risk Note into the CPRS record of all research subjects, thereby increasing awareness of subject participation and decreasing chance of inadvertent dual enrollment.

VAWNYHS IRB will not approve concurrent enrollment in two interventional studies or participant's involvement with studies outside VA.

1. Procedures:

- a. Approval for dual enrollment must be received prior to the potential subject being enrolled into the second study. To request dual enrollment the investigator must:
 - i. Complete an IRB Miscellaneous Submission Form if the study is an active study. If dual enrollment is requested during submission of the initial review, it can be included as part of the initial application.
 - ii. The PI requesting dual enrollment must provide the IRB with a memo stating that there are no conflicting regimens of drugs or devices and there is no undue stress or use of subject population including the signature of all applicable PI's.
 - 1. If the investigator is the same for both (or all) studies, a written assurance that there is no conflicting regimens of drugs or devices and there is no undue stress or use of subject population must be provided to both the R&D committee and the IRB.
- b. The memo is required to state specifically what protocols may utilize the dual enrollment process.
- c. In the case of a subject being inadvertently dually enrolled into a trial:
 - i. The PI of the second trial must notify the PI of the first trial. Ensuring the subject's safety is priority.
 - ii. Notify the IRB of the dual enrollment via the Miscellaneous Submission Form as a protocol deviation. Include the title of both studies and a summary of protocol related activities that were conducted prior to knowledge of dual enrollment and a plan to prevent recurrence in the future.
 - iii. If both PI's agree dual enrollment does not increase risk and foresee potential future dual enrollments, the PIs may request IRB approval for future dual enrollment.
- d. VAWNYHS IRB recommends and encourages investigators to notify all involved study sponsors of the dual enrollment approval.

k. Amendments. Changes to previously approved research are cannot be initiated without IRB approval, except when necessary to eliminate apparent immediate hazards to participants. The PI is required to submit a completed amendment request form, including justification for the change and any supporting documentation

for consideration of changes to a previously approved research protocol and/or informed consent form. The criteria for approval of an amendment/modification to previously approved research are the same as those for an initial review.

1. **Minor Changes in Previously Approved Research.** Minor changes proposed for previously approved research may be reviewed in an expedited manner. A minor change is defined as one that:
 - a. Does not substantially alter any of the following:
 - i. Level of risk or the risk/benefit ratio
 - ii. Research design or method
 - iii. Number of subjects
 - iv. Qualifications of the research team
 - v. Any other factor that would warrant review by the convened IRB
 - b. Does not involve the addition of procedures that involve more than minimal risk to participants.
 - c. Does not involve the addition of procedures that do not fall into categories 1-7 of research that can be reviewed using the expedited procedure.
2. **Expedited Review of Minor Changes in Previously Approved Research.**
 - a. Changes meeting the applicable criteria for expedited review may be reviewed by the chair or designee, reported to the IRB, and documented in the IRB minutes.
 - b. Changes to the study are reviewed by the IRB chair or designee, and include a review of all modified documents submitted by the investigator. The chair or designee conducts an in-depth review of all changes. The chair or designee will serve as the IRB reviewer and will determine if the change is eligible for expedited review, or requires full committee review.
 - c. The IRB chair or designee will complete the Expedited Review Worksheet, as well as the Amendment Review Worksheet in order to ensure a complete review of the changes.
 - d. The IRB chair or designee can approve, or require modifications for approval, but the amendment can only be disapproved by the full committee.
 - e. All amendments approved under expedited procedures will be reported to the next convened IRB meeting.
 - f. The findings and decision of the IRB will be communicated to the PI in writing and responses will be considered. If the investigator disagrees with the IRB decision, he/she may follow the Investigators Appeals process.
3. **Amendments Requiring Full Committee Review.** When a proposed change in research study is not minor, then the entire IRB must review and approve the change at a convened meeting before the change can be implemented.
 - a. An IRB reviewer will be assigned to the amendment, and will be required to complete an in-depth review of the requested changes. The reviewer will complete the Amendment Review Worksheet, and present the revisions to the convened IRB for discussion.
 - b. The convened IRB will receive a copy of the amendment request, all modified documents, which may include a summary of the proposed changes or a complete copy of the revised protocol, and revised consent document, if applicable, and will determine whether the modified research continues to fulfill the criteria for approval.
 - c. The findings and decision of the IRB will be communicated to the PI in writing and responses will be considered. If the investigator disagrees with the IRB decision, he/she may follow the Investigators Appeals process.

4. **Changes Necessary to Eliminate Immediate Hazard(s) to Subject(s).** The only exception to above is the rare circumstance in which a change is necessary to eliminate apparent immediate hazards to the research participants.
 - a. In this case, the IRB should be informed of the change(s) within 3 days following implementation and should review the change(s) to determine that it is consistent with the protection of human participants.
 - i. The reporting of such changes should be submitted using the “Adverse or Unanticipated Event Submission Form” which will be reviewed by the IRB chair and reported at the next convened IRB meeting.
 - b. The IRB chair will determine whether the immediate action appears warranted, but may also confer with the R&D chair if scientific issues are involved, and/or request the COS, RCO, or the Research Pharmacist to perform an in depth review of the entire protocol.
 - c. The IRB chair will determine whether the report involves any non-compliance. If so, the policy regarding non-compliance will be followed.
 - d. The IRB chair will determine whether the report involves an unanticipated problem involving risks to participants or others. If so, the policy on unanticipated problems involving risks to participants or others will be followed.
 - e. The IRB will vote whether the changes made to the protocol eliminate the hazard to participants, and will determine whether the change was consistent with ensuring the participants’ continued welfare. Unanticipated risks to participants or new information that may affect the risk/benefit assessment must be reported to and reviewed by the IRB to ensure adequate protection of human participants.

I. Research Exempt from IRB Review. Selected types of research are exempt from IRB review because they are considered to pose no risk to participants. Research activities in which the only involvement of human participants will be in one or more of the no risk categories listed below are exempt from review by the IRB. The exempt status must be approved by the IRB chair or designee. The PI will submit a Request for Exempt Review, which will reviewed and completed by the IRB chair or designee. When research is determined to be exempt by the IRB, the R&D committee will be notified and is responsible for acting as the parent committee for the review of the study. The exempt categories may be found in 38 CFR 16.101(b).

1. Research conducted in established or **commonly accepted educational settings**, involving normal educational practices, such as:
 - a. Research on regular and special education instructional strategies, or
 - b. Research on the effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods.
2. Research involving the use of **educational tests** (cognitive, diagnostic, aptitude, achievement), **survey procedures, interview procedures, or observation of public behavior**, unless:
 - a. Information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants, or
 - b. Any disclosure of the human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability or reputation, or loss of insurability.
3. Research involving the **use of educational tests** (cognitive, diagnostic aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is **not exempt under item 2**, if:
 - a. The human participants are elected or appointed public officials or candidates for public office, or

- b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- 4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants. (Such materials **must already exist** at the time the research is proposed and not involve prospective collection of such material.)
- 5. **Research and demonstration projects:** The project has been determined to be exempt by the Under Secretary of Health on behalf of the Secretary of Veterans Affairs, after consultation with Office of Research of Development, the Office of Research Oversight, the Office of General Counsel, and other experts, as appropriate. The IRB chair cannot make this exemption determination.
- 6. **Taste and food quality evaluation and consumer acceptance studies:**
 - a. If wholesome foods without chemical additives are consumed, or
 - b. If a food is consumed that contains a food ingredient at or below the level of safety and for a use found to be safe, or agricultural chemical or environmental contaminant at or below a level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

VIII. INFORMED CONSENT

- a. **General Requirements for Informed Consent.** No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's LAR. An individual who is qualified to be an LAR for research purposes may not always qualify as a personal representative for purposes of completing a HIPAA authorization. Therefore, in circumstances involving authorization for use of disclosure of a subject's PHI, the investigator must ensure the LAR meets the requirements of a personal representative in HIPAA and the Privacy Act of 1974 prior to the LAR's signing a HIPAA authorization.
 - 1. **Circumstances Under Which Informed Consent May Be Sought.**

The Common Rule requires:

 - a. The investigator seek such consent only under circumstances that:
 - i. Provide the prospective participant or the participant's LAR sufficient opportunity to consider whether or not to participate, and
 - ii. Minimize the possibility of coercion or undue influence.
 - b. The information that is given to the subject or the subject's LAR must be in language understandable to the subject or the subject's LAR.
 - c. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's LAR:
 - i. Is made to waive, or appear to waive, any of the subject's legal rights; or
 - ii. Releases, or appears to release, the investigator, the sponsor, the institution, or its agents from liability for negligence.
 - 2. **Person Obtaining Informed Consent.** The person obtaining informed consent must be approved to do so by the VAWNYHS IRB. All new research personnel who will be obtaining informed consent must undergo training on the informed consent process, and requirements with the RCO prior to approval to consent research subjects.

3. **Informed Consent Process.** Obtaining informed consent is an ongoing process that begins with the initial presentation of the research to the prospective participant by the investigator or his/her authorized designee. The prospective research participant or surrogate should be provided the informational brochure “Volunteering in Research – Here are some things you need to know” when approached to take part in a project. The project must be presented to the participant or his/her legally authorized representative, in a language that is understandable to the participant or surrogate. The research participant must give consent without coercion or undue influence. Adequate time should be given for the participant to ask questions and give his/her participation careful consideration. It is recommended that the participant be given the informed consent document to take home to review before giving his/her written consent. Informed consent must be obtained prior to entering a participant into a study and/or conducting any procedures, including screening procedures that are done solely for research purposes required by the protocol.
4. **Consent with Participants who have Impaired Decision Making Capacity.** Prior IRB approval is required to obtain consent from a participant’s LAR. The investigator or designated clinician must evaluate the patient’s capacity to make decisions concerning health care, in order to obtain informed consent. Decision making capacity is defined as being able to understand and comprehend the nature of the proposed research and its associated risks and benefits, alternative options, and the likely outcomes. The patients must understand that they do have a choice whether or not to participate.
 - a. An individual is presumed to have decision making capacity unless any one or more of the following apply:
 - i. It has been documented by a qualified practitioner in the individual’s medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study. *NOTE: The qualified practitioner may be a member of the research team.*
 - ii. The individual has been ruled incompetent by a court of law.
 - b. If it is determined that the patient lacks decision-making capacity the investigator may obtain surrogate consent with prior IRB approval. The investigator must provide the IRB with a description of the procedures to ensure that subjects’ LARs are well informed regarding their roles and obligations to protect persons who lack decision-making capacity.
 - c. For any potential participant whose capacity to make decisions regarding treatment is in question, the investigator must ensure an appropriate clinical evaluation is conducted and documented for any participant whose capacity to make decisions regarding treatment is in question. The IRB may request that a PI document this clinical evaluation using the IRB-approved screening tool (Protecting Research Participants with Impaired Decision Making Capacity (IDMC)). To further protect these participants, the IRB staff will ensure that at least one member with expertise in the area of research with decisionally-impaired participants is present at all meetings where studies involving decisionally-impaired participants will be discussed. In reviewing protocols that will enroll participants with IDMC, the IRB presenter will use the “Enrolling Participants Who May Be Incompetent or Have Impaired Decision Making Capacity (IDMC)” Form, to ensure all safeguards and protection of their rights and welfare are addressed as referenced in VHA Handbook 1200.05.
 - d. A space on the approved consent form will be provided for the signature and date of a surrogate as well as the signature and date of the witness and the research staff obtaining the consent, if applicable. Documentation in the medical record will specifically include the use of the surrogate.

- e. VAWNYHS will utilize the more stringent rules of the law, state or federal, as applicable when utilizing a legal authorized representative. NYS specifies the following for LARs in order of preference:
 - i. A guardian authorized to decide about health care pursuant to article eighty-one of the mental hygiene law;
 - ii. The spouse, if not legally separated from the patient, or the domestic partner;
 - iii. A son or daughter eighteen years of age or older;
 - iv. A parent;
 - v. A brother or sister eighteen years or older;
 - vi. A close friend.
 - f. LAR's are acting on behalf of the potential subjects, therefore:
 - i. LAR's must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision.
 - ii. If the potential subject's wishes cannot be determined, the LAR's must be told they are responsible for determining what is in the subjects' best interests.
 - iii. LAR's generally assume the same rights and responsibilities as the individuals who lack decision making capacity in the informed consent process.
 - g. If feasible, the investigator must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent.
 - h. Investigators, IRB members and LAR's must be aware that decision-making capacity may fluctuate in some subjects. 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.
5. **Observing the Process.** The IRB has the authority to designate an observer to any part of the consent process and verify records to insure that only approved research activities are being conducted [21 CFR 56.108(a)(2)]. The need for verification may be prompted by an investigator or research staff that has no experience, complaints, observations that indicate non-compliance, unanticipated problems, adverse events and quality improvement efforts.
6. **Consent for Use of Picture and/or Voice.** Informed consent for research must be obtained from each research subject before taking photographs or making voice or video recordings that will be used for research purposes.
- a. Unless the IRB grants a waiver of documentation of informed consent for research, the informed consent form for research (VA Form 10-1086) must include a discussion of why photographs, or voice or video recordings are being taken for the research, who will have access to them, and what their disposition will be after the research is completed.
 - b. VA Form 10-3203 documents permission for pictures, video and voice recordings to be made or taken. When the research subject is a patient, the subject must sign VA Form 10-3203 to permit photographs or video and voice recordings that will be used for research purposes even if the IRB has waived the requirement for documentation of informed consent for research.
 - c. When the research subject is a patient, the subject's signed and dated VA Form 10-3203 must be placed into the medical record along with, if applicable, the signed and dated research informed consent form. The signed VA Form 10-3203 must be obtained and placed in the subject's medical record, even if the IRB has waived documentation of informed consent for research.

7. **Obtaining Consent from Non-English Speakers.** VA regulations at 38 CFR 16.116, the Common Rule, and FDA regulations require that informed consent be obtained in language that is understandable to the participant (or the participant's LAR). In accordance with these regulations, the IRB may require that the informed consent process include a reliable translator when the prospective participant does not understand the language of the person who is obtaining consent. The VAWNYHS maintains a list of staff members who are qualified to act as interpreters.
8. **Waiver of Informed Consent.** The IRB may waive or alter the consent process by determining that the criteria for waivers or alternatives are met. The IRB may waive the requirement for written documentation of the consent process by determining that the criteria for waivers are met.
 - a. Determinations of the IRB justifying the waiver or alteration will be documented in the protocol file.
 - b. Waivers or alterations of the consent process are not allowed if the research is regulated by the FDA.
 - c. When a waiver of documentation of informed consent is granted, the IRB will consider requiring the researcher to provide participants with a written statement regarding the research. If this is required, the IRB will review the written description of the information that will be provided to the participants.

b. Required Elements of Informed Consent

1. **Elements of Informed Consent Required by the Common Rule.**
 - a. **A statement that the study involves research.**
 - b. **An explanation of the purposes of the research.**
 - c. **The expected duration of the subject's participation.** A description of the expected length of the subject's commitment to active participation in the interventions or interactions of the study, including long-term follow-up. This does not include the time after all interventions and interactions with the subject have ended and the study activities include only analysis of specimens and/or data, and/or preparations for publication of results.
 - d. **A description of the procedures to be followed.**
 - e. **Experimental procedures.** Identification of any procedures that are experimental.
 - f. **Risks or discomforts.** A description of any reasonably foreseeable risks or discomforts to the subjects.
 - i. This description is to include, but not be limited to, physical, social, legal, economic, and psychological risks.
 - ii. Risks that do not result from the research, but that result solely from treatments or services that have been designated in the IRB-approved protocol to be the responsibility of the health care provider should not be described in the consent form. The informed consent process is to include language advising subjects to review the risks of such clinical treatments or services with their health care provider(s).
 - g. **Benefits.** A description of any benefits to the subject or to others that may reasonably be expected from the research.
 - h. **Alternatives.** A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
 - i. **Confidentiality.** A statement describing the extent to which confidentiality of records identifying the subject will be maintained. If appropriate, a statement that Federal agencies including, but not limited to, the FDA, OHRP, ORO, and the VA Office of the Inspector General (OIG) may have access

to the records. If an FDA-regulated test article is involved, FDA requires a statement that the FDA may choose to inspect research records that include the subject's individual medical records.

- j. **Research-Related Injury.** For research involving more than minimal risk, a statement that includes:
 - i. An explanation as to whether any compensation is available if injury occurs, and
 - ii. An explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.Although the Common Rule at 38 CFR 16.116(a)(6) only requires that the informed consent contain information on research-related injury if the study is more than minimal risk, VA regulations (38 CFR 17.85) require VA to provide care for all research-related injuries including those studies that are considered minimal risk.
 - k. **Contact Information.** An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and who to contact in the event of research-related injury to the subject is to be provided. There must be at least one contact other than the investigator or study personnel
 - l. **Participation is Voluntary.** A statement that participation is voluntary, refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
2. **Other Elements of Informed Consent Required by VA.** In addition to the elements for informed consent required by the 38 CFR Part 16, VA requires the following elements of informed consent:
- a. **The name of the study.**
 - b. **The name of the PI.** The name of the PI and, in multi-site studies, the name of the LSI.
 - c. **The sponsor of the study.**
3. **Additional Elements of Informed Consent.** When appropriate, the Common Rule requires one or more of the following elements of information be provided to each subject (38 CFR 16.116(b)). 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.
- a. **Unforeseeable risks.** A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or becomes pregnant) which are currently unforeseeable.
 - b. **Termination of subject's participation.** Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
 - c. **Additional Costs.** Any additional costs to the subject that may result from participation in the research.
 - i. Pursuant to 38 CFR 17.102, subjects in VA-approved research cannot be charged, nor can their insurance be billed, for research-related interventions or procedures (e.g., tests, drugs, clinic visits, hospital admissions, transportation) that are required by the protocol. If medical services are furnished to a person who is not eligible for medical services as a Veteran, the medical care appropriation will be reimbursed from the research appropriation.
 - ii. When appropriate for the informed consent for VA-approved research to include information on additional costs to the subject that may result from participation in the research, the informed consent must contain a statement that a Veteran subject or a non-Veteran subject will not be required to pay for medical services received as a subject in an approved VA research study. The only exception is that certain Veterans are required to pay applicable co-

payments for medical care and services provided by VA that are not rendered as part of the VA-approved research study (see 38 U.S.C. 1710(f) and 1710(g)). An example of language that may be appropriate for the informed consent form is “Some Veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to VA-provided medical care and services that are not part of this study.”

- d. **Consequences of withdrawal from the study.** The consequences of a subject’s decision to withdraw from the research and procedures for orderly and safe termination of participation by the subject.
- e. **New findings.** A statement that any significant new findings which may relate to the subject’s willingness to continue participation, developed during the course of the research, will be provided to the subject.
- f. **Number of subjects.** The approximate number of subjects involved in the study.

4. **Additional Elements of Informed Consent Required by VA.** 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.

- a. **Commercial product.** If applicable, that the investigator believes that the human biologic specimens obtained could be part of, or lead to the development of, a commercially valuable product.
- b. **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. Current applicable institutional, VA, and other Federal requirements must be met for handling, use, and storage of biologic specimens and data (VHA Handbook 1200.12).
- c. **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 (VHA Handbook 1200.12). Current applicable institutional, VA and other Federal requirements must be met for use and storage of data (VHA Handbook 1200.12).
- d. **Re-contact.** If the subject will be re-contacted for future research whether within VA or outside VA.
- e. **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.
- f. **Disclosure of results.** If the subject will receive a report of the aggregate results or any results specific to the subject.

c. **Documentation of Informed Consent.** Informed consent must be documented by the use of a written consent form VA Form 10-1086. It must be signed and dated by the participant or the participant’s legally authorized representative, unless the consent requirement has been waived by the IRB. If applicable, the form must be dated and signed by a witness who is not a part of the research team. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the participant’s signature and if the same person serves in both capacities, a note to that effect will be placed under the witness signature. “Observer of Consenting Process”, will be written in under the witness signature by the witness.

1. **Documentation in the Medical Record.** Documentation of the informed consent process must be entered into the medical record within 24 hours of obtaining the consent. The progress note containing the consenting process is included in the research templates in CPRS. A Research Study Initiation Note or a Research Minimal Risk Note provides a template for all the required documentation required. Research Study Initiation Note is a template found under “new notes” titles. It contains information about the study, the possible adverse events, whom to contact for further information about the study, and information related to the informed consent process. The Research Initiation Note is automatically posted under the

“clinical warnings” heading in the participant’s electronic medical record, flagging this record as a research participant.

- a. A Research Study Initiation Note is required for all studies, except when the following criteria are met. If the subject’s participation in the study involves only the below criteria, a Research Study Minimal Risk Note may be entered.
 - i. Only one encounter
 - ii. Only the use of a questionnaire

The Research Study Minimal Risk Note template includes the required documentation elements, and should include a statement on how the participant tolerated the study and that their participation ended with this one visit. This note is not placed in the “Clinical Warning” of CPRS.

A Research Progress Note must be created for all additional visits when Veterans are admitted to VA facilities as in-patients, treated as outpatients at VA facilities, or when research procedures or interventions are used at the VA or contracted through the VA. Following VHA 1907.01 a health record is required if utilizing clinical resources or if the intervention may lead to physical or psychological AEs.

2. The original signed and dated consent form must remain in the investigator’s files. Copies of the signed and dated consent form must be given to the participant or their representative, sent to the research office where it will be scanned into the participant’s electronic medical record, to the research pharmacy, if appropriate, and to the IRB which will review them for completeness and file them under conditions of confidentiality.

IX. PRIVACY AND CONFIDENTIALITY OF PARTICIPANTS

The privacy and confidentiality of the research participant must be protected. Privacy and confidentiality are not the same. For the purposes of human participant research, privacy related to the *person*, confidentiality relates to the *data*. Privacy and confidentiality regulations and statutes are referenced in VHA Handbook 1200.05.

Adequate provisions must be taken to protect the privacy of participants and to maintain the confidentiality of individually-identifiable data. Such provisions must consider the requirements of Standards for Privacy of Individually-Identifiable Health Information (HIPAA Privacy Rule), 45 CFR Parts 160 and 164, and other laws regarding protection and use of veterans’ information, including Privacy Act of 1974, 5 U.S.C. 552a; VA Claims Confidentiality Statute, 38 U.S.C. 5701; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Infection with Human Immunodeficiency Virus (HIV), and Sickle Cell Anemia Medical Records, 38 USC 7332; and Confidentiality of Healthcare Quality Assurance Review Records, 38 USC 5705.

Please see Center Memorandum 00-166 Sensitive Information Protection for additional information.

a. Privacy

1. The IRB must assure there are adequate provisions to protect the privacy of the participant. This is evaluated on a continuing basis.
2. Privacy refers to the person’s desire to limit the access of others to themselves, such as being seen at a certain clinic (for example, HIV or counseling center), or being seen talking to someone, that may cause them embarrassment or feeling uncomfortable, or being seen.
3. The IRB will evaluate the Investigator’s plan for recruitment and obtaining consent, and how information is obtained about the participant.

4. The IRB may require that the PI apply for a Certificate of Confidentiality (CoC) if the research protocol contains highly sensitive information about individuals. This could include studies related to alcohol or drug use or HIV status. The research office staff will assist the investigator with this application.

b. Confidentiality

1. The IRB must assure there are adequate provisions to protect the confidentiality of identifiable data. This is evaluated on a continuing basis.
2. The IRB will evaluate the Investigator's plan for handling, managing, storage, and sharing of identifiable information, this also includes recruitment and obtaining consent, and how information is obtained or about the participant.
3. The VA Privacy Act and VA Privacy Handbook 1605.1 provide more complete explanation of the regulations covering veteran's data.

c. Certificate of Confidentiality

The IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual participants for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to VA, DHHS or FDA for audit purposes. Consequently, the IRB requires that these conditions for release be stated clearly and explicitly in the informed consent document.

d. Loss of a Participant's Research Records Containing Identifiable Private Information

Whether or not confidentiality is actually breached, the loss of any participant's private health information or personally identifiable information - whether located on paper, computerized storage media or laptops - must be immediately reported (within 1 hr) to the VAWNYHS Privacy Officer and Information Security Officer.

X. TISSUE BANKING

The VA tissue banking program prohibits biological samples obtained during VA-approved research, (defined as any material derived from human participants, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or fluids, whether collected for research purposed or as residual specimens) from being forwarded to a sponsor or non-VA approved tissue bank for future research purposes unless there is specific approval from the Chief Research and Development Officer (CRADO).

If the investigator is using a VA approved tissue bank, the consent form must clearly state:

1. If the specimen will be used for future research, and allow the participant the choice of how the specimen will be used (i.e., any research, research by specific PI, genetic analysis, research related to a specific area).
2. If the research results of reuse of the specimen will be conveyed to the participant.
3. If the participant will be re-contacted after the original study is completed.
4. If the participant requests, the specimen and all links to the clinical data will be destroyed.

The informed consent template contains suggested language and directions to assist the investigator in meeting these requirements.

If an investigator wishes to establish a tissue bank at VAWNYHS, the request must be submitted to the R&D and IRB Committees and include at least the following information:

1. Investigator

2. Address (location of tissue bank)
3. Person responsible for maintaining the bank
4. Are samples from one specific study or more?
5. Title of study/studies
6. Is this bank associated with an approved protocol?
7. Study start date
8. Study end date
9. For what purpose(s) have the samples been agreed to? (Specific to one study, open ended, genetic?) Attach approved consent form
10. What information is on the samples (i.e. Study ID, SSN, initials, etc)
11. Are the samples linked to the participant's identity? If yes, describe and what precautions are in place to protect confidentiality.
12. How are the samples secured? (i.e. locked room, locked freezer, etc)
13. Who has access to the samples?
14. What will happen to the samples if the PI leaves the facility, or has an unexpected, extended leave of absence?
15. Are the samples infectious?
16. What samples be analyzed off VA facility? If so, describe procedure, personnel, plan for return of remaining specimen, etc. *(Note, there should be an agreement in place specifying analysis/use as defined in protocol)*
17. Do you plan on sharing samples with other investigators? If yes, how do you determine appropriateness of sharing, obtain IRB approval, etc?

Please refer to the ORD – VA Tissue Banking Program for more information regarding off-site tissue banking and storage. http://vaww.research.va.gov/programs/tissue_banking/default.cfm

XI. REPORTING PROTOCOL DEVIATIONS/VIOLATIONS, ON-SITE ADVERSE EVENTS, AND UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

See the Definitions section for definitions of Adverse Events (AE), Deviations, Violations, and Unanticipated Problems (UPR) involving risks.

- a. **Protocol Deviations or Violations that May Increase Risk.** Protocol deviations or violations can be deliberate or accidental, and can be caused by a variety of factors, including study staff, participants, weather-related issues, etc. If a deviation in the protocol has occurred because of imminent danger to participants, it must be reported within **five (5) business days** to the chair of the IRB. The PI should report such protocol violations/deviations on the Adverse or Unanticipated Event Submission Form. Any departure from the defined procedures described in the IRB-approved protocol must be reported to the IRB **within 5 business days** if the event is likely to adversely affect: (i) the rights and welfare of the research participant; (ii) the safety of the research participant; (iii) the integrity of the research data; and/or (iv) the participant's willingness to continue study participation. Protocols deviations and violations include accidental or unintentional changes to the IRB-approved protocol. The IRB chair will determine whether the immediate action appears warranted, but may also confer with the R&D chair if scientific issues are involved, and/or request the RCO or the Research Pharmacist to perform an in depth review of the entire protocol.

The IRB chair will review the report and determine whether it involves any non-compliance. If so, the policy on non-compliance will be followed.

The IRB chair will also review the report and determine whether it involves an unanticipated problem involving risks to participants or others. If so, the policy on unanticipated problems involving risks to participants or others will be followed.

Even if a sponsor "approves" a deviation in a protocol, the investigator does not have the authority to proceed without approval by the VAWNYHS IRB.

b. Serious Adverse Events that Involve Risks to Participants or Others. Investigators are to report all local, unanticipated, Serious Adverse Events (SAE) to the ACOS for R&D and the IRB as soon as possible, but no later than 5 business days after the event has become known to the investigator. Anticipated SAEs are to be reported to the IRB at the time of continuing review.

The unfounded classification of an SAE as "anticipated" constitutes serious non-compliance.

The IRB does not require submission of offsite SAE reports. An acknowledgment of the submission will be provided if a sponsor requires.

c. Unanticipated Problems and Related Problems (UPRs). The term "unanticipated" refers to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

A "related" problem in VA research is a problem that may reasonably be regarded as caused by, or probably caused by, the research.

Within 5 business days of becoming aware of any serious unanticipated problem involving risks to subjects or others in VA research, members of the VA research community are required to ensure that the problem has been reported in writing to the IRB. Serious unanticipated problems involving risks to subjects or others include:

1. 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.
2. 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.
3. 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. **NOTE:** *PBM generally forwards such communications directly to the ACOS for R&D, who is responsible for determining if any of the facility's research projects are affected and, if so, reporting the alert to the IRB and the relevant investigators.*
4. Any DMC, DSMB, or DSMC report describing a safety problem.
5. Any sponsor analysis describing a safety problem for which action at the facility level may be warranted.
6. 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;
7. Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs.

d. Procedures.

1. The Adverse Event / Unanticipated Problem Form must be submitted to the IRB within 5 business days of the event. Within 5 business days after a report of a problem involving risks to subjects or others or a local SAE, a qualified IRB member-reviewer without an identified real or perceived conflict of interest, (or alternatively, the convened IRB) must determine and document whether or not the problem is serious, whether or not it is anticipated or unanticipated, and whether it is Related, Probably Related, or Unrelated to the research.
2. The qualified IRB member-reviewer (or the convened IRB) must also document whether or not one of the following applies:
 - a. Immediate action (e.g., suspension of activities; notification of subjects) is necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii), and review by the convened IRB is needed; or
 - b. Review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted.
3. If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related or probably related to the research, the IRB chair or designee must notify ORO via telephone or e-mail within 48 hours and report the problem or event directly (without intermediaries) to the facility Director within 5 business days after the determination.
4. The report must be made in writing, with a simultaneous copy to the ACOS for Research and the R&D Committee.
5. The facility Director must report the problem or event to the appropriate ORO Regional Office within 5 business days after receiving such notification.
6. The facility Director will also report to the following:
 - a. OHRP, in all cases
 - b. FDA, when the research is FDA regulated
 - c. Other federal agencies when the research is overseen by those agencies, and they require reporting separate to that from OHRP
 - d. The Office of Research and Development, if VA-funded
 - e. The VA Central Office, if the unanticipated problem involving risks to participants or others is an adverse event
 - f. Privacy Office, when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information
 - g. Information Security Officer when the report involves violations of information security requirements
7. If it is determined that an informed consent modification is warranted, the convened IRB must determine and document in its records whether or not previously enrolled subjects must be notified of the modification and, if so, when such notification must take place and how such notification must be documented.
8. All determinations of the qualified IRB member-reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting.
9. The IRB will take an action on each unanticipated problem involving risks to participants or others. The range of actions considered includes items listed below, but the list does not preclude the IRB from taking additional actions as determined on a case-by-case basis.
 - a. Modification of the protocol
 - b. Modification of the information disclosed during the consent process

- c. Providing additional information to current participants (This must be done whenever the information may relate to the participant's willingness to continue participation)
 - d. Making arrangements for clinical care outside the research or additional follow-up for participants
 - e. Providing additional information to past participants
 - f. Requiring current participants to re-consent to participation
 - g. Alteration of the frequency of continuing review
 - h. Observation of the research or the consent process
 - i. Requiring additional training of the investigator
 - j. Notification of investigators at other sites
 - k. Obtaining additional information
 - l. Termination or suspension of the research
10. When items are reported to the convened IRB, documents provided to the IRB may include:
- a. The report of incident
 - b. Miscellaneous Submission Form, or Adverse Event / Unanticipated Problem Form
 - c. IRB protocol or relevant protocol documents, including the informed consent form
 - d. Investigator correspondence or documentation
 - e. Any other relevant information available

XII. ISSUES OF SERIOUS OR CONTINUING NON-COMPLIANCE

- a. Serious Non-Compliance.** Serious noncompliance is a failure to adhere to the laws, regulations, or policies governing human research that may reasonably be regarded as:
- 1. 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
 - 2. Substantively compromising the effectiveness of a facility's human research protection or human research oversight programs.
- b. Continuing Non-Compliance.** Continuing noncompliance is a persistent failure to adhere to the laws, regulations, or policies governing human research.
- c. Requirements.**
- 1. All investigators conducting research as employees or agents of the VAWNYHS are required to comply with institutional policies regarding research. This includes VA or other Federal requirements related to human research, privacy policy or information security, or local IRB or Central IRB (CIRB) requirements or determinations.
 - 2. Any employee of VAWNYHS, research investigator or member of a research team (including Without Compensation Employees) who becomes aware of an incident(s) of non-compliance of HRPP regulations, requirements, or determinations is required to provide a prompt report to the RCO or to other senior institutional officials (i.e., ACOS for R&D, Chief of Staff, Patient Advocate, Hospital Director). In addition, participants in human research studies, their designated representatives, or members of their community are also encouraged to report any activities or behaviors that they believe may be non-compliant or inappropriate. The RCO will be responsible for providing immediate notification to the ACOS for R&D and the IRB chair.
 - 3. Within 5 business days of becoming aware of any apparent serious or continuing noncompliance with applicable human research protection requirements (e.g., 38 CFR 16, VHA Handbook 1200.05, FDA regulations), members of the VA research community are required to ensure that the apparent noncompliance has been reported in writing to the IRB.

4. The IRB will also take into consideration any complaints as possible noncompliance. The IRB must review any report of apparent serious or continuing noncompliance at its next convened meeting to decide whether each allegation of non-compliance has a basis in fact. The IRB chair will review all complaints and allegations prior to the next convened meeting. A primary review system may be utilized. The documents that will be distributed to the chair and the IRB members may include:
 - a. A summary of the incident
 - b. A copy of the protocol and/or consent form for the relevant study
 - c. Any data or information gathered during the investigation of the incident
5. Any IRB members with a real or perceived conflict of interest must identify this conflict and recuse themselves from evaluation or determination of non-compliance.
6. The IRB chair, or designee, will consult the ORO Regional Office if the significance of a reported event is not clear.
7. Should the IRB determine that the reported incident constitutes serious noncompliance or continuing noncompliance the IRB chair, or designee must report the determination directly (without intermediaries) to the facility Director within 5 business days after the determination.
 - a. The IRB chair's report must be made in writing, with a simultaneous copy to the ACOS for R&D, the R&D committee, and any other relevant research review committee.
8. The facility Director must report the determination to the appropriate ORO Regional Office, with a simultaneous copy to the VISN Director and the ORD, within 5 business days after receiving such notification.
9. The non-compliance will also be reported to:
 - a. OHRP, in all cases
 - b. FDA, when the research is FDA regulated
 - c. The Office of Research and Development, if VA-funded
 - d. The Privacy Office, when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information
 - e. The Information Security Officer when the report involves violations of information security requirements
10. An initial report of an IRB determination that serious non-compliance or continuing non-compliance occurred is required, even where the determination is preliminary or disposition of the matter has not been resolved at the time of the report.
11. The IRB must reach a determination that serious or continuing non-compliance did (or did not) occur within 30-45 days after receiving a report of apparent non-compliance.
12. Remedial actions involving a specific study or research team must be completed within 90-120 days after the IRB's 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, legal negotiations, etc.
13. **RCO identified non-compliance.** An RCO identifying apparent serious or continuing non-compliance during an informed consent or regulatory audit must report the apparent non-compliance, directly (without intermediaries) to the Facility Director within 5 business days.
 - a. The report must be made in writing, with a simultaneous copy to the ACOS for R&D, the R&D committee, the IRB (or VA Central IRB if appropriate), ISO and/or PO if applicable, and any other relevant research review committee.

- b. The facility Director must report the apparent serious or continuing non-compliance to the appropriate ORO Regional Office, with a simultaneous copy to the VISN Director and the ORD, within 5 business days after receiving such notification.
 - c. The IRB must then review the allegation reported by the RCO at the next convened meeting. If the IRB determines that the reported incident constitutes serious or continuing non-compliance, the IRB Chair, or designee must report the determination directly (without intermediaries) to the facility Director within 5 business days after the determination.
 - d. If an allegation of non-compliance is substantiated, but the facts do not support a finding of serious or continuing non-compliance the IRB will take corrective actions as required to remedy the non-compliance. If required, remedial actions for non-compliance with the HRPP will take into consideration the rights and welfare of current research participants. Relatively minor or one-time non-compliance that does not pose an immediate risk to human participants will be promptly addressed through local administrative mechanisms.
14. If more than minor modifications to previously reviewed research are made in response to serious or continuing non-compliance, they will be reviewed by the convened IRB.
15. If the facts support a finding of serious or continuing non-compliance, the IRB will take corrective actions which may include but are not limited to:
- a. Temporary suspension of the protocol
 - b. Termination of the protocol
 - c. Restrictions on privileges to conduct research
 - d. Disciplinary actions against perpetrators of violations
 - e. Modification of the protocol
 - f. Modification of the information disclosed during the consent process
 - g. Providing additional information to past participants
 - h. Notification of current participants when such information may relate to participants' willingness to continue to take part in the research
 - i. Requiring current participants to re-consent to participation
 - j. Modification of the continuing review schedule
 - k. Monitoring of the research
 - l. Monitoring of the consent process
16. IRB decisions to suspend or terminate research, substantiated allegations of serious or continuing non-compliance must be reported to the appropriate authorities per VHA Handbook 1058.01. In addition, if an investigator has a study or studies under the authority of the VA Central IRB, VA Central IRB will be informed when there has been a local finding of serious or continuing non-compliance.

XIII. SUSPENSION OR TERMINATION OF APPROVAL

- a. 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 ORD when ORD is the sponsor). The term "administrative hold" does not apply to interruptions of VA research related to concerns regarding the safety, rights, or welfare of human research participants, research investigators, research staff, or others. An administrative hold must not be used to avoid reporting deficiencies or circumstances otherwise covered by VHA Handbooks or other federal requirements governing research.
- b. Suspension or Termination of VA Research.** Suspension refers to a temporary interruption in the enrollment of new participants, activities involving previously enrolled participants, or other research activities.

Termination refers to a permanent halt in the enrollment of new participants, activities involving previously enrolled participants, or other research activities. The terms “suspension” and “termination” apply to interruptions related to concerns regarding the safety, rights, or welfare of human participants, research investigators, research staff, or others. Suspensions and terminations do not include “Administrative Holds” or other actions initiated voluntarily by an appropriate facility official, research investigator, or sponsor for reasons other than those described in the preceding items.

1. **Suspension** of IRB approval is an action initiated by the IRB chair, IRB vice-chair, or convened IRB to stop temporarily some or all research procedures pending future action by the IRB or by the Investigator or his/her study personnel.
2. **Termination** of IRB approval is a determination by the convened IRB to permanently halt some or all previously approved research activities including, but not limited to, enrollment of new subjects in research.

c. Procedures.

1. The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with IRB’s requirements, or that has been associated with unexpected serious harm to subjects. This may include the following:
 - a. Serious or continuing non-compliance
 - b. Serious harm to participants has occurred and/or been identified; and
 - c. Unanticipated problems involving risks to participants or others
2. The IRB chair or IRB vice-chair can initiate a suspension prior to a convened IRB meeting. The action will be reported at the subsequent convened IRB meeting where it will be determined if further actions are required, such as notifying the participants of the suspension or termination. The convened IRB also has the authority to initiate a suspension or termination of IRB approval. However, only the convened IRB may terminate IRB approval.
3. Any termination or suspension of research (e.g., by the IRB or other research review committee, or by the ACOS for R&D or other facility official) related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others must include a statement of the reasons for IRB’s action and must be reported directly (without intermediaries) to the facility Director within 5 business days after the termination or suspension occurs.
 - a. The report must be made in writing with simultaneous copies, as applicable, to the ACOS for R&D, the R&D committee, the IRB, and any other relevant research review committee.
4. The facility Director must report the termination or suspension to the appropriate ORO Regional Office within 5 business days after receiving such notification.
5. The suspension or termination will also be reported to:
 - a. OHRP, in all cases
 - b. FDA, when the research is FDA regulated
 - c. The Office of Research and Development, if VA-funded
 - d. The Privacy Office, when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information
 - e. The Information Security Officer when the report involves violations of information security requirements
6. Once notified of the suspension, the PI must immediately submit to the IRB chair, a list of research subjects for whom suspension of the research would cause harm. The IRB chair, with appropriate consultation with the COS, determines if the subject(s) may continue in the research.

7. Suspensions and terminations do not include interruptions of research due to expiration of the IRB approval period, known as a lapsed approval.

XIV. INVESTIGATOR APPEAL OF IRB ACTION

A principal investigator may appeal a decision made by the IRB by submitting a formal written request to the Research Office within a month of the adverse decision. If the PI wishes to provide a different interpretation of materials that the IRB previously reviewed or additional information, the IRB will carefully and fully consider it at the next convened meeting of the IRB prior to making its final decision. No other institution or committee can set aside or overrule a determination by a designated IRB to disapprove or require modifications to human research protocols submitted to the VAWNYHS IRB. If an investigator wishes to re-submit a protocol that has been disapproved by the IRB, it must undergo initial review as a new protocol, and all IRB concerns and reasons for disapproval must be addressed in the resubmission.

XV. RESEARCH INVOLVING INVESTIGATIONAL DRUGS OR DEVICES

The FDA regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements and food additives, hereinafter referred to as “FDA regulated test articles.” All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test articles are used in research being done at the VA or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS human participant regulations as well as VA regulations and the Common Rule. Where regulations differ, the IRB should apply the stricter one.

- a. VA Requirements.** VA policy (VHA Handbook 1200.05) requires that all research comply with the VA human participant regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents.
 1. A VA Investigational Drug Information Record (VA Form 10-9012) must be completed by the PI, submitted to Pharmacy Service, and monitored by the R&D committee (VHA Handbook 1200.05).
 2. Clinical research being done on FDA regulated test articles with either an IND or IDE will need initial review at a convened IRB meeting.
- b. Investigator Responsibilities.**
 1. Obtaining IRB approval
 2. Getting informed consent from each participant
 3. Submitting a signed and dated informed consent for each participant to the Chief, Pharmacy Service
 4. Informing the Chief, Pharmacy Service and the R&D committee when a study involving investigational drugs is terminated
 5. Following the investigational plan
 6. Complying fully with the regulations
 7. Protecting the rights, welfare and safety of the participants
 8. Supervising the use and disposition of the test article
 9. Maintaining accurate, current and complete records; and
 10. Disclosing relevant financial information

- c. FDA Form 1572.** When the investigator signs the FDA 1572, called the Investigator Statement, he/she is making a commitment to:
1. Conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of participants
 2. Comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements
 3. Personally conduct or supervise the described investigation(s)
 4. Inform any potential participants that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent [CFR 21 Part 50] and IRB review and approval [21 CFR Part 56] are met
 5. Report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with Sec. 312.64
 6. Read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug; and.
 7. Ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments

In addition, the investigator commits to:

1. Administer the drug only to participants under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it [21 CFR 312.61].
2. 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]. Case histories include the case report forms and supporting data including but not limited to progress notes for visits. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
3. Send study closure documentation to the sponsor shortly after the completion of participation in the study.
4. Inform the Chief, Pharmacy Service, and the R&D committee when a study involving investigational drugs has been terminated.

- d. Sponsor Access to Medical Records.** The IRB is responsible for ensuring that informed consent documents include the extent to which the confidentiality of medical records will be maintained [21 CFR 50.25(a)(5)]. FDA requires sponsors (or research monitors hired by them) to monitor the accuracy of the data submitted to FDA in accordance with regulatory requirements. These data are generally in the possession of the clinical investigator. Each participant must be advised during the informed consent process of the extent to which confidentiality of records identifying the participant will be maintained and of the possibility that the FDA may inspect the records. While FDA access to medical records is a regulatory requirement, FDA does not usually request 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 cases studied or actual results obtained. The consent document should list all other entities (e.g., the sponsor, IRB) that will have access to records identifying the participant. The extent to which confidentiality will be maintained may affect a participant's decision to participate in a clinical investigation.

All sponsor visits will be reported to the research office when scheduled by the study coordinator or PI. Non-compliance detected on monitoring visits and Research Pharmacy evaluations must be reported to the ACOS for R&D immediately. The ACOS for R&D will discuss the report with the IRB chair and investigate accordingly.

e. Local VA Requirement.

1. The use of all Investigational Medical Products will be conducted in accordance with the policy and procedures as set forth in Pharmacy SOP No. 25 – “Investigational Drugs: Policy and Procedures”. The Research Pharmacy has documented processes for handling investigational drugs, follows policies and procedures, and evaluates compliance for handling investigational drugs relative to (1) receipt, (2) storage, (3) security, (4) dispensing, (5) inspection, and (6) disposition of unused stock as found in Pharmacy SOP No.25. This SOP is maintained in the research pharmacy. All medications to be administered within the conduct of a protocol are received and dispensed through VAWNYHS Research Pharmacy Service with the exception of radioactive drugs. Research Pharmacy will provide secure custody, proper storage, and dissemination of pertinent information on all investigational medications. It is the responsibility of the PI to submit VA Form 10-9012, “Investigational Drug Information Record,” as part of the application package for each investigational medication to be used in a protocol. The PI must furnish the Pharmacy Manager of VAWNYHS with a copy of the approved protocol and a completed “Investigational Drug Information Record” (VA Form 10-9012), a signed informed consent form, and HIPAA authorization for each participant in the study. The investigator is responsible to file a copy of the VA Form 10-9012 in each participant’s medical record. The PI arranges to have the investigative drug or biologic delivered from the manufacturer to the Research Pharmacy or arranges to have it obtained through the Research Pharmacy and delivered to the custody of the Research Pharmacist. Special circumstances such as radioactivity may warrant custody by another service.
 - a. Note: The Primary IRB Reviewer will be responsible for determining if an investigational drug requires an IND using the IND Checklist. If an IND has been provided, it will be validated by the Primary Reviewer. Acceptable documentation for validation of the IND will be the written protocol from the sponsor, a letter from the FDA or a letter from the sponsor. The Investigator’s Brochure is not acceptable for validation. The Primary reviewer will report his findings to the convened IRB.
2. The Research Pharmacy maintains investigational drug logs, which include the name of drug, manufacturer, date of receipt of the drug, quantity received, expiration date, control number, date protocol approved, name of practitioner authorized to order drug, name of participant receiving the drug, serial number of the prescription, quantity dispensed and balance remaining after the transaction.
3. Research Pharmacy coordinates QA review of process quarterly. Results of Research Pharmacy evaluations are reported to the IRB, the R&D committee, and Diagnostic and Therapeutic Care Line, which have the responsibility for the oversight of research pharmacy activities. If areas of non-compliance are identified, they will be reported to the ACOS for R&D immediately. The ACOS for R&D will discuss the report with the IRB chair and investigate accordingly.
4. The PI or study coordinator will place a “clinical warning” in CPRS, noting that the patient has been enrolled in a study protocol and listing the telephone number of the study contact person. If the study is a non-interventional study which only requires one visit with the investigator, a “clinical warning” note is not necessary.
5. Authorized prescribers will order investigational medical products from Pharmacy: for inpatients and outpatients the VISTA/CPRS hospital computer system will be utilized to order medications (with the exception of Schedule 2 Narcotics which require a hand written order) only after the following criteria have been met:
 - a. Fully inform the patient concerning the administration of the investigational medical product, all inconveniences and adverse events to be reasonably expected, the existence of alternative

forms of therapy if any, and the effects upon his/her health and person that may possibly come from the administration of the investigational medical product.

- b. Obtain consent and HIPAA authorization of the patient by signature on VA Form 10-1086 (VA Research Informed consent form) and separate HIPAA authorization. If the patient is unconscious, has been adjudged incompetent by a court, is unable to give consent, or is incapable of comprehending the significance of such action, the consent of his/her LAR will be obtained. The original VA Form 10-1086, once signed by the patient or his/her LAR, will be kept in the PI's confidential file. In addition, copies of the signed and dated consent form must be given to the participant or their LAR, sent to the research office to be reviewed and scanned into the participant's electronic medical record, and then maintained to the research pharmacy, if appropriate.
- c. Record in the electronic medical record, a statement that subparagraphs (i) and (ii) above, have been accomplished.

f. IRB Review of Investigational Medical Devices. 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 Part 812 and applicable VHA regulations.

1. The device has to be exempt from the requirements for an IDE (21 CFR 812.2(c)), meet the abbreviated IDE requirements, or have an IDE issued by the FDA. To meet the abbreviated IDE requirements, the device must be characterized as "significant risk" (SR) or "non-significant risk" (NSR) by the IRB. The IRB must determine and document that the device represents SR or NSR.
2. SR device studies that are not exempt from the requirement for an IDE must be conducted in accordance with the full IDE requirements (21 CFR Part 812). Pursuant to these regulations, an investigation may begin 30 days after FDA receives the application (unless FDA provides notification that the investigation may not begin), or after the FDA approves, by order, an IDE for the investigation (21 CFR 812.30). In addition, the investigator must have approvals from the IRB and R&D committee. The FDA considers all SR studies to be greater than minimal risk.
3. The IRB needs to verify the existence of an IDE when an IDE is required. The Primary IRB Reviewer will be responsible for determining if an investigational device requires an IDE using the IDE Checklist. If one has been provided, it will be validated by the Primary Reviewer. The Primary Reviewer will report his findings to the convened IRB.
4. Devices that are not exempt from IDE requirements and meet the abbreviated IDE requirements (21CFR 812.2(b)) do not require submission of an IDE application.
 - a. **NOTE:** NSR devices may represent greater than minimal risk depending upon the research study.
5. Unless otherwise notified by the FDA, a NSR study is considered to have an approved IDE if all abbreviated requirements are fulfilled.
6. The IRB must review the research in accordance with these requirements and needs to use the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).
7. NSR device studies may commence immediately following IRB and R&D committee approval, if no changes are required by either committee.
8. The VA facility must have procedures for receipt, control, custody, and dispensing of the investigational devices.
9. The PI is responsible for compliance with all applicable FDA regulations.
10. Emergency use of unapproved devices must follow FDA guidance.

11. The PI is responsible for reporting to the sponsor, within 5 working days, of the withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
12. The PI is responsible for sending the sponsor study closure documentation within 3 months after termination or completion of the investigator participation in the study.
13. Investigational devices can only be used after appropriate approvals of the protocol and informed consent form, explanation of the study to the research participant, and research participants' signing of the VA consent form and HIPAA authorization.
14. Investigators initiating or participating in research under an IDE must adhere to FDA regulations, federal, and VA regulations. Any PI submitting a human research protocol involving an investigational device must submit a cover letter with their IRB application explaining the plan for receipt, storage, custody, dispensing, security, and disposal of the investigational devices. A copy of any applicable dispensing log must be included with the cover letter. The IRB must evaluate the PI's plan for handling of the investigational device and approve the plan prior to approving the protocol.
15. The PI maintains records and tracking of investigational devices. All investigational medical devices must be stored in a secure location, accessible only to study personnel. The storage area must meet any conditions provided by the manufacturer related to environmental review. Investigational medical devices will be dispersed only to participants in the approved research protocol who have signed a VA Form 10-1086 (VA Research Informed Consent Form).
16. The Research Compliance Officer is responsible for ensuring the PI's compliance with the IRB-approved plan.

g. Radioactive Investigational Drugs. When a protocol involves a radioactive investigational drug, the protocol will require approval from the VAWNYHS Radiation Safety Committee. Once approval is obtained, the Pharmacy Manager will authorize delivery of the radioactive drug directly to the VAWNYHS Nuclear Medicine Department or the Center for Positive Emission Tomography (PET). The Radiation Safety Committee will be responsible for providing oversight on the receipt, administration, termination, and disposal of the radioactive drug.

h. Data Retention. When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study related interventions and continued follow up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information. The investigator must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original consent form). The IRB must approve the consent document. If a participant withdraws from the interventional portion of a study and does not consent to continued follow up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

XVI. EMERGENCY USE OF A TEST ARTICLE

The FDA regulations exempt research from prior IRB review for the use of a test article in a life-threatening situation in which no standard acceptable treatment is available and there is insufficient time to obtain IRB

approval. FDA requirements for emergency use of a test article must be met {21 CFR 56.101(d); 21 CFR 56.102(d); 21 CFR 104(c)}. The IRB requires notification of any emergency use of a test article to evaluate whether the situation met the FDA regulatory requirements that allow exemption from IRB review. FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had time to convene a meeting. However, if subsequent use of the test article is contemplated on the same participant or others, a complete IRB application must be submitted for full board review prior to any additional use of the test article.

Investigators should complete the Emergency Test Article Checklist to guide them through this process.

Prior to Administration of the Emergency Use of the Test Article, investigators are strongly encouraged to call the IRB chair or designee to review whether the conditions for emergency use of a test article are met and/or whether the conditions for an exception from obtaining informed consent are met. Investigators also need to inform the IRB chair on the status of the IND or IDE.

a. Emergency Investigational New Drug (IND). If a responsible practitioner believes there is a need for the emergency use of an unapproved investigational drug or biologic and the intended participant does not meet the criteria for an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND. If the manufacturer elects not to name the PI on the IND, the PI must then contact FDA directly for an IND or obtain evidence of an IND Exemption.

1. The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.36]. The PI should request a copy of the investigational drug monograph or protocol (if available).
2. The responsible practitioner must communicate with the Chair of the Medication Use Committee (MUC), the Research Pharmacist, and the IRB chair concerning emergency use as soon as possible. The discussion will include how to obtain the consent of the participant. The PI must obtain the consent of the participant or the LAR of the participant in accordance with 21 CFR 50.20. The consent must disclose the required and appropriate additional elements of consent disclosure in 21 CFR 50.25. The consent must be documented in accordance with the requirements of 21 CFR 50.27. A progress note must be entered into the participant's Electronic Medical Record documenting the informed consent process as required by VHA Handbook 1200.05. No participant may be given an investigational drug, or biologic without obtaining informed consent (signature and date) from the participant or the participant's LAR unless the PI and Chair of the MUC certify in writing all four of the following specific conditions in a progress note entered into the participant's medical record:
 - a. The participant is confronted by a life-threatening situation, necessitating the use of the test article;
 - b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the participant;
 - c. Time is not sufficient to obtain consent from the participant's legally authorized representative, and
 - d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the participant's life.

If time is not sufficient to obtain consent before use of the investigational drug or biologic, the PI must enter a progress note into the participant's medical record certifying the previous four conditions and rationale for proceeding without the approval of the Chair of the MUC, who is an independent practitioner. The actions of the PI must be reviewed and evaluated in writing by an independent physician following the use of the

test article. The written certification that all requirements have been met must be submitted to the IRB within five working days of the use of the test article.

3. Requests for emergency approval should be submitted to the Chair of the Medication Use Committee by entering a progress note into the participant's medical record documenting that the conditions of emergency use of a test article are met and that includes the following information:
 - a. The participant is in a life-threatening situation and there is no standard acceptable treatment available
 - b. Diagnosis and name of the test article to be used
 - c. Name and VA title of the PI responsible for therapy and contact information
 - d. Literature reference
 - e. Authorized source of investigational drug
 - f. IND number
4. Upon receipt of the electronic emergency request, if the Chair of the MUC agrees, the Chair should indicate the approval by signing an addendum to the request to use an emergency investigational drug. The Chair of the MUC will then instruct the practitioner under whose supervision the investigational drug is to be used to fully inform the patient concerning the following and enter a progress note into the participant's medical record:
 - a. Name, dose and route of the investigational drug or biologic
 - b. Reasons for its use
 - c. Inconveniences and adverse events which can reasonably be expected
 - d. Existence of any alternative forms of therapy, rather than the use of the investigational drug
5. The requesting practitioner will provide Pharmacy with a copy of the investigational drug monograph and/or protocol (if available), consent form (signed and dated) or a copy of the progress note entry if informed consent was not obtained (by meeting the necessary 4 conditions as described above), if an investigational drug or biologic is prescribed, an Investigational Drug Information Record, (VA Form 10-9012), is required containing the product manufacturers' information, PI's signature and date, and a properly completed order for the investigational drug or biologic prior to dispensing by the research pharmacist. No approval signatures will appear on VA Form 10-9012 because the emergency use does not represent IRB or R&D committee approval.
6. The requesting practitioner in conjunction with Pharmacy will prepare, make available, and distribute to the professional nurse responsible for administering the investigational drug, a summary of basic information regarding the investigational drug (e.g., Investigational Drug Information Record, VA Form 10-9012) prior to dispensing the approved investigational drug.
7. The principal investigator must enter a progress note into the participant's medical record documenting that the conditions of emergency use of a test article are met. The progress note will contain, at a minimum, the following information:
 - a. The participant is in a life-threatening situation
 - b. There is no standard acceptable treatment available
 - c. There is not sufficient time to obtain IRB approval
 - d. IRB chair and Chair of MUC notified
 - e. Rationale for the drug or biologic use
 - f. The diagnosis and drug or biologic to be used, and
 - g. Contact information for the principal investigator

8. All supplies of the emergency investigational drug must be delivered to the pharmacy as with any other investigational drugs. A preliminary report will be made to the MUC on results of use of the investigational agent within 90 days after administering the test article. A final summary report will be made upon completion of diagnosis or treatment as applicable.
9. The physician, not otherwise participating in the clinical investigation must certify in writing that the requirements have been met for the emergency use of all investigational drugs or biologics to the IRB chair within 5 days after the administration of an investigational drug or biologic. The report will include the following information:
 - a. Name of investigational drug, or biologic
 - b. Explanation of participant life-threatening situation necessitating the use of the test article, including diagnosis and age
 - c. Date of notifying Chair of the IRB and MUC prior to use
 - d. Participant's name
 - e. Rationale for test article use
 - f. IND number or IDE number (if applicable)
 - g. Supporting documentation of IND or IDE number, FDA correspondence, or sponsor correspondence
 - h. Informed consent document (signed and dated). If no informed consent, statement that informed consent could not be obtained from the participant because of; an inability to communicate with, or obtain legally effective consent from the participant, time is not sufficient to obtain consent from the participant's LAR and there is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant available
 - i. Participant's diagnosis and outcome if known
 - j. Any adverse events or unanticipated problems
 - k. Likelihood of needing to use the test article again, and
 - l. All adverse events and unanticipated problems associated with the emergency use of the test article must be reported to the IRB
10. If subsequent use of the investigational drug is contemplated, the PI must submit a complete IRB application for full board review prior to any additional use of the test article.
11. The IRB chair will review the follow-up report to determine whether FDA regulatory requirements are met. The IRB chair is responsible for making the following evaluations:
 - a. The emergency use of the test article met the FDA criteria allowing the exemption from IRB review
 - b. Written informed consent was obtained and documented; and
 - c. If written informed consent was not obtained by applying the exception from informed consent requirements for emergency use of a test article, the situation met the FDA criteria.
12. If FDA regulations were not met, the matter will be handled according to IRB policies and procedures for non-compliance. The IRB will be notified on the next available IRB meeting agenda.

b. Emergency Use of an Investigational Device Exemption (IDE). Emergency use of an investigational device may be required when there is no standard acceptable treatment available and there is insufficient time to obtain IRB approval. The PI must contact the manufacturer to determine if the product can be made available for use under the company's IDE. If an investigational device is being used, the PI is responsible for assuring that the device sponsor/manufacturer notifies the FDA immediately after an unapproved device is shipped for emergency use.

1. If an IDE does not exist, the FDA expects the principal investigator to determine the following:
 - a. Whether the criteria for emergency use have been met

- b. Assess the potential for benefits from the unapproved use of the device and to have substantial reason to believe that benefits exist; and
 - c. Assure the decision of the principal investigator that an "emergency" exists is not based solely on the expectation that IDE approval procedures may require more time than is available.
2. The PI must enter a progress note into the participant's medical record documenting that the conditions of emergency use of an investigational device are met. The progress note will contain, at a minimum, the following information:
 - a. The participant is in a life-threatening situation
 - b. There is no standard acceptable treatment available
 - c. There is not sufficient time to obtain IRB approval
 - d. Rationale for test article use
 - e. The diagnosis and test article to be used
 - f. Contact information for the principal investigator
3. The PI must obtain the consent (signed and dated) of the participant or the LAR of the participant and enter a progress note into the participant's medical record documenting the informed consent process as required by VHA Handbook 1200.05. No participant may receive an investigational device without obtaining informed consent from the participant or the participant's LAR unless the PI and the COS or designee (independent practitioner) who is not otherwise participating in the emergency use, certify in writing all four of the following specific conditions in a progress note entered into the participant's medical record:
 - a. The participant is confronted by a life-threatening situation, necessitating the use of the investigational device
 - b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the participant
 - c. Time is not sufficient to obtain consent from the participant's LAR, and
 - d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the participant's life.
4. If time is not sufficient to obtain the COS's determination before use of the investigational device, the PI must enter a progress note into the participant's medical record certifying the previous four conditions and rationale for proceeding without an independent physician determination. The actions of the PI must be reviewed and evaluated in writing by the COS within 5 working days following use of the test article.
5. Emergency use of all investigational devices must be reported to the IRB. The PI must submit a written report to the IRB chair within 5 days after the administration of the investigational device. The report must include the following information:
 - a. Name of the investigational device
 - b. Explanation of participant's in a life-threatening situation, including diagnosis and age
 - c. Date of notifying IRB chair prior to use (if applicable)
 - d. Participant's name
 - e. Rationale for test article use
 - f. IDE number (if applicable)
 - g. Supporting documentation IDE number, FDA correspondence, or sponsor correspondence
 - h. Informed consent document. If no informed consent, date of COS or designee confirmation of emergency use request
 - i. Participant's diagnosis and outcome if known
 - j. Any adverse events or unanticipated problems

- k. Likelihood of needing to use the investigational device again
 - l. Copy of the signed informed consent form
 - m. All adverse events and unanticipated problems associated with the emergency use of the investigational device must be reported to the IRB
6. If subsequent use of the investigational device is contemplated, the PI must submit a complete IRB application for full board review prior to any additional use of the test article.
 7. The IRB chair will review the follow-up report to determine whether FDA regulatory requirements are met. The IRB chair is responsible for making the following evaluations:
 - a. The emergency use of the test article met the FDA criteria allowing the exemption from IRB review
 - b. Written informed consent was obtained and documented; and
 - c. If written informed consent was not obtained by applying the exception from informed consent requirements for emergency use of a test article, the situation met the FDA criteria.
 8. If FDA regulations were not met, the matter will be handled as non-compliance. The IRB chair has the authority to require an additional 30-day follow-up report from the PI that includes information of the participant's outcome and any adverse events or unanticipated problems. The IRB will be notified on the next available IRB meeting agenda.

XVII. MULTI-SITE STUDIES, COORDINATING CENTERS, DATA ANALYSIS CENTERS AND INTERNATIONAL RESEARCH

A VA IRB cannot serve as the IRB of record for a non-VA institution. It is the policy of this VA facility to assure that all facilities participating in a human participants study receive adequate documentation about the study in order to protect the interests of study participants. Before a study can begin, it must be approved by the IRB of record for the coordinating facility, the IRBs of record for each participating facility, and all applicable R&D committees at all sites. In the case where the VA Central IRB is the IRB of record, documentation of VA Central IRB approval and R&D approvals from participating sites will not be required by this facility. The Research Office staff collects documentation of all approvals and will file in the project file. The study will not be approved, until all approvals are received.

- a. **Principal Investigator's Responsibilities for Multi-Site Studies.** Investigator responsibilities when this VA facility is the coordinating facility:
 1. A method for ensuring that all engaged participating sites have the most current version of the protocol, the most current version of the informed consent form, and the most current version of the HIPAA authorization.
 2. A method for ensuring that all required approvals have been obtained at each engaged participating site (including approval by the site's IRB of record) before the study is implemented at that site.
 3. A method for notifying the Director of any facility deemed by the PI's IRB of record not to be engaged in the research, but on whose premises research activities will take place, before initiating the study (e.g., the PI conducts a survey of employees at a facility that is not engaged in the research). The facility Director has the authority to disapprove the conduct of these research activities on that facility's premises.
 4. A method for confirming that all amendments and modifications to the protocol, the informed consent form, and the HIPAA authorization have been communicated to engaged participating sites, and that all required local facility approvals (including approval by the local facility's IRB of record) have been obtained before the amendment or modification is implemented.
 5. A method for assuring that all engaged participating sites will safeguard VA data as required by VA information security policies.

6. A method for communicating to engaged participating sites SAEs that have the potential to affect implementation of the study.
7. A method of communicating regularly with engaged participating sites about study events and interim results (if appropriate).
8. Methods for ensuring all LSI's conduct the study appropriately.
9. A method to ensure all non-compliance with the study protocol or applicable requirements is reported in accordance with VHA Handbook 1058.01.
10. A method for notifying local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).
11. When the investigator is a LSI for a multi-site study (whether the LSI is also a PI or solely a Local Site Investigator), the LSI must:
 - a. Conduct the study according to the most recently approved version of the protocol, the most recently approved version of the informed consent form, the most recently approved version of the HIPAA authorization, and all applicable local, VA and other Federal requirements;
 - b. Ensure that all amendments and modifications to the protocol and the informed consent form are submitted to and approved by the local IRB of record prior to initiating any changes;
 - c. Report any unanticipated internal or local SAEs, whether related or unrelated to the research, in accordance with VHA Handbook 1058.01;
 - d. Report study events and interim results (if available) to the local IRB of record as required by local IRB policies; and
 - e. Oversee all aspects of the study at their local site

b. Local VA Facility's IRB of Record's Responsibilities for Multi-Site Research When the VA Facility's Investigator is the Multi-Site Study PI for All Participating Facilities and the VA Central IRB is Not Being Used. In addition to other IRB responsibilities, when the VA facility's investigator is the multi-site study PI or study sponsor for all participating facilities, and VA Central IRB is not being used, the PI's or study sponsor's local VA facility's IRB of record is responsible for:

When a participating site is added to the study, determining:

1. Whether or not that site will be engaged in human subject research
2. If the site will be engaged in research, then reviewing and confirming that it:
 - a. Has an active FWA; and
 - b. Has provided documentation of all relevant approvals, including approval of its IRB of record.
3. Approving the study-wide protocol and sample informed consent document to be provided to each LSI at engaged facilities.
4. Ensuring the study-wide protocol contains a mechanism for ensuring that any differences in the protocol or informed consent at engaged local participating sites are justified by the LSI, and that they are approved by the PI before being implemented.
5. Ensuring there are clear AE reporting requirements, a data monitoring committee if applicable (or other reliable monitoring mechanism) with clear procedures and requirements, and a clearly defined feedback loop to the PI's or study sponsor's IRB.
6. Reviewing the PI's plan for communicating appropriate critical information (e.g., reports of data and safety monitoring) to engaged participating sites.
7. Ensuring, when relevant, confidentiality and information security requirements are met for information storage at and transmission to statistical or coordinating centers.

8. Reviewing reports from applicable DMCs.

c. Research and Development Committee Responsibilities. The R&D committee at both the coordinating facility and at all participating facilities must review and approve their IRB's recommendations for the study. The study cannot be initiated without approval from the R&D committees. When the VA Central IRB is the IRB of record, the R&D committee must review and approve the VA Central IRB's recommendations for the study.

d. ACOS/R&D Responsibilities. The ACOS for R&D provides final approval when all committees have approved the study. This includes the VA Central IRB. In the event that a study has been disapproved by the VA Central IRB, the ACOS for R&D will ensure that the study is not submitted for a local site approval. Likewise, if a study has been disapproved by the local IRB, the ACOS for R&D will ensure that the study will not be submitted to VA Central IRB.

e. Procedures. Investigator procedures when this VA is the coordinating site:

1. During the initial IRB submission of the multi-site study, the investigator indicates in writing on the application form or in an application letter that the VA facility is the coordinating facility of a multi-site study.
2. The investigator submits the following information in their IRB application materials:
 - a. Whether research activities at participating institutions are defined as engagement
 - b. Name of each participating facility
 - c. Confirmation that each participating facility has an FWA (including FWA number)
 - d. Contact name and information for investigator at each participating facility
 - e. Contact name and information for IRB of record at each participating facility
 - f. Method for assuring all participating facilities have the most current version of the protocol
 - g. Method for confirming that all amendments and modifications in the protocol have been communicated to participating sites
 - h. Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to participants or others
 - i. Method of communicating regularly with participating sites about study events
3. The investigator submits approval letters from all the IRBs of record for all participating facilities and all R&D committees.
4. The investigator maintains documentation of all correspondence between participating facilities and their IRBs of record.

f. IRB Review for Coordinating Centers and Data Analysis Centers. The Center is engaged in human subject research if the center is receiving identifiable information and /or links to identifiable information.

1. In most cases, full IRB approval is not required. Review and approval will be done by the IRB chair, and reported to the IRB. If the study involves highly sensitive data, or complex issues, full board review and vote may be requested by the chair.
2. The IRB chair must review the information provided by Coordinating Centers or Lead Investigators of Multi-Site Studies Information Form, and then uses the Coordinating Centers and Statistical Analysis Centers engaged in Research checklist to determine if the facility is to be engaged in research. The IRB chair will determine if the study meets the criteria as being engaged in research as a Statistical Analysis Center or Coordinating Center or determined that this study is not engaged in research based on Criteria specific

criteria. The chair dates and signs the checklist. If approval is given VA 10-1223 Approval Form is signed and dated by the IRB chair.

3. Risk Assessment – is based on the activities performed by the center, and the risk of potential loss of confidentiality/privacy, not on the protocol.
4. Annual Review: If identifiable information is involved, annual review will be required.
5. Interim Amendments and Adverse Event reports will be reviewed by the IRB as they are submitted by the investigator. OHRP Guidance, Engagement of Institutions in Research
<http://www.hhs.gov/ohrp/humanparticipants/assurance/engage.htm>

g. International Research. All individuals who participate as subjects in research in international sites must be provided appropriate protections that are in accord with those given to subjects within the US, as well as appropriate by local authority. Permission must be obtained from the CRADO prior to initiating and all international sites must hold an international FWA.

XVIII. IRB ADMINISTRATION

a. Meetings. The IRB generally will meet the 4th Wednesday of every month at 1:00 PM. A meeting schedule is distributed to members of IRB, and is available in the research office. The IRB chair or his/her designee may call an emergency meeting at any time. A quorum must be present in order to conduct the meeting. Records are kept of any emergency meeting.

b. Quorum Requirements.

1. A majority of the IRB voting members (or their designated alternates), including at least one member whose primary concerns are in non-scientific areas, must be present to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those voting members present at the meeting. If the quorum is not achieved at a meeting due to members with conflict being recused, early departures, or loss of a non-scientist, the meeting is terminated from further votes unless the quorum can be restored. The IRB chair will ensure that quorum is met, and maintained throughout the meeting. This will be documented in the IRB minutes.
2. When studies to be reviewed at a convened meeting involve decisionally-impaired participants, the IRB chair will ensure that at least one IRB member with expertise in the area of research with decisionally-impaired participants is present at the meeting.
3. When studies to be reviewed at a convened meeting involve an FDA-regulated article, an IRB member who is a licensed physician must be present at the meeting.
4. When there is not appropriate scientific or representational expertise, the protocol will be deferred to another meeting, or the IRB will obtain a consultation.
5. Voting members may be present in person or audio (telephone) or audio-visual teleconference. Voting members present via teleconference shall be noted as such in the meeting minutes, which shall also indicate that members attending by telephone received all pertinent information prior to the meeting and were able to actively and equally participate in all discussions.
6. Members who recuse themselves due to conflicts of interest may not be counted toward quorum requirements. Members abstaining from voting will be counted toward quorum.
7. An agenda will be distributed to members one (1) week prior to the meeting and will include minutes of the last meeting, copies of the informed consent, scientific abstract, expert review of new and revised proposals, requests for continuing approval, amendments, reports of adverse events or unanticipated events involving risk or other on site problems, study closures and a list of research approved since the last

meeting utilizing expedited review procedures. Additional materials may be distributed prior to or at the meeting.

c. Voting.

1. An individual who is not listed on the official IRB membership roster may not vote with the IRB.
2. Any ex-officio member of the IRB may not vote with the IRB.
3. Ad Hoc consultants may not vote with the IRB.
4. The non-scientist must always be present for a vote to be taken.
5. When a member and his/her alternate both attend a meeting, only the primary member can vote.
6. All motions require a positive vote by the majority of members in attendance for approval.

d. Actions Taken by the Convened IRB. IRB actions for initial or continuing review of research include the following:

1. Approved with no changes (or no additional changes). The research may proceed.
2. Approved pending minor changes. The IRB chair or designee reviews the responsive materials from the investigator and determines whether the investigator has made the changes requested by the IRB, and if so, grants approval on behalf of the IRB. The revisions requested by the convened IRB need to be specific enough that IRB chair or designee is not making judgments about the regulatory criteria for approval. Such minor changes must be clearly delineated in the minutes, so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified.
3. Tabled pending substantive changes. The IRB determines changes are needed in the plan or protocol that may affect the risks, potential benefits, or rights of the participants or that it lacks sufficient information about the research to proceed with its review. When the IRB requests clarifications or modifications that are directly relevant to the regulatory determinations, the protocol must be returned to the convened IRB for review and approval. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
4. Disapproved. The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility in its present form. Research may not commence. If disapproved, the IRB must include in its written notification a statement of the reasons for the decision and give the investigator an opportunity to respond in person or in writing.
5. Deferred. The IRB has postponed action until a later time due to a lack of quorum or pending receipt of requested information.

e. Minutes. IRB proceedings must be written and available for review within three (3) weeks of the meeting date. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority. The Minutes Checklist is used by Research Office Staff to ensure that minutes include all required information. All Minutes Checklist items are required in the IRB minutes unless stipulated specifically for the R&D Committee minutes. Minutes of all IRB meetings will include the following:

1. Date and time of the meeting.
2. Names of members present. Minutes must clearly document which members were present by conference call or videoconference and that the criteria for a member participating by conference call have been satisfied.
3. Names of absent members.
4. Names of alternates attending in lieu of specified (named) absent members. Alternates may substitute for specific absent members only as designated on the official IRB membership roster.
5. Names of consultants present.
6. Name of investigators present.

7. Names of guests present.
8. Approval of previous minutes, including corrections if necessary.
9. All actions taken by the convened IRB and the votes underlying those actions. Actions will be categorized as:
 - a. Approved with no changes
 - b. Approved pending minor changes
 - c. Deferred
 - d. Disapproved
 - e. Tabled pending substantive changes
10. Votes will be categorized as:
 - a. For
 - b. Against
 - c. Abstained
 - d. Recused
 - e. Excused
11. The approval of research contingent on specific minor conditions by the IRB Chair or designee must be documented in the minutes of the first IRB meeting that took place after the date of the approval.
12. Name of person(s) who leave the meeting or recuse themselves due to a conflict of interest and note that the absence is due to the conflict of interest.
 - a. Note: "Not present" means that an IRB member must leave the room or, if participating in the meeting by conference call or videoconference, must have terminated the connection.
13. The basis for requiring changes in or disapproving research.
14. A written summary of discussion of all controverted issues and their resolution.
15. The level of risk of the research and the rationale for the IRB's determination of the level of risk.
16. The approval period for the research, including identification of research that warrants review more often than (at least) annually. Approvals are valid for less than one (1) calendar year unless the IRB feels that potential risks are such that the review period should be for a shorter period.
17. Justification for waiver or alteration of informed consent, addressing each of the four (4) criteria at 38 CFR 16.116(d). *(Note: This cannot be done if a FDA test article is involved)*
18. Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 38 CFR 16.117(c).
19. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
20. The special protection warranted in specific research projects on groups of participants who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research. For proposals that identify the potential for enrolling participants who could be vulnerable to coercion or undue influence, the IRB documents its consideration of additional safeguards to protect the rights and welfare of vulnerable participants.
21. Summary of the justification for including non-veteran subjects, if applicable.
22. Summary of the discussion when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used in the study. The summary needs to include the security measures that are in place to protect the SSN instances embedded in the study.
 - a. Note: This does not apply if the only use of SSNs is on the informed consent form or the HIPAA authorization as required by VHA Handbook 1907.01.

23. Consideration of the impact of study design on risk.
24. Consideration of provisions for safety monitoring.
25. Determination that risks have been minimized to the extent possible.
26. Determination that all appropriate elements were included in the informed consent form, and are included in the informed consent process.
27. Determination of the risk level of investigational devices.
28. The rationale for significant risk/non-significant risk device determinations.
29. The interval of continuing review is appropriate to the degree of risk.
30. Approval of research on the basis that risks to participants are reasonable in relation to anticipated benefits (if any) to participants, and the importance of the knowledge that may be expected to result from research.
31. Statements of significant new findings provided to participants when reviewed at an IRB meeting, must be documented in the minutes. (VHA Handbook 1200.05)
32. If the IRB decides a proposal is exempt from the Common Rule (and, therefore further IRB review) or approves a proposal for expedited review, the minutes will quote the regulatory basis for the decision from 38CFR16/45CFR.46.
33. Minutes of the IRB, whether draft or final, will be forwarded to the R&D committee for review at their next convened meeting. IRB minutes are included in the R&D minutes which are reviewed and approved by the COS and the facility Director. The final, approved IRB minutes will be signed by the IRB chair. If substantive changes are made to the IRB draft minutes subsequent to review by the R&D committee, the final approved minutes will be forwarded to the R&D committee.

f. Conflict of Interest. Please refer to Center Memorandum 151-05 “Research Conflict of Interest”, and Center Memorandum 151-06 “Institutional Conflict of Interest in Research” which can be found in the Western New York Resources folder.

g. Monitoring for Compliance. IRB monitors the ongoing research project during the period for which the research is authorized with consideration, which may include:

1. Consenting process
2. Changes to the research
3. Serious and unanticipated adverse event reports
4. All safety reports forwarded by sponsors of Investigational New Drugs and Investigational Device Exemptions including MedWatch data
5. Protocol violations or deviations
6. Investigator non-compliance
7. Annual research education certificates
8. A separate in depth review of selected protocols is performed by the RCO
9. Review of inclusion/exclusion criteria and initial study documentation in electronic medical records
10. The IRB has the authority to request the RCO to observe the consenting process for any study. This request may be in response to a concern on the part of the IRB or may be requested randomly. If requested, the RCO will notify the PI for the study chosen for observation. He/she will request notification of the next participant scheduled to be consented and will observe the entire process after explaining the reason for his/her presence and obtaining the verbal permission of the participant. A report of his/her observations will be conveyed to the IRB in writing.

h. Monitoring Process. The monitoring process will include review of any, allegations, or findings of non-compliance with institutional policies, and/or of scientific misconduct. Research participants and research

personnel are instructed to report such incidents to the Research Office, IRB chair, or R&D committee chair. The RCO will conduct routine audits of clinical studies to monitor compliance with regulatory and IRB requirements.

- i. Complaints.** All complaints will be reviewed in accordance with this SOP.
- j. Allegations of Scientific and Ethical Misconduct.** All allegations of Research Misconduct must be reported to the Research Integrity Officer (RIO), who will review and investigate such allegations. The RIO is a permanent position that is appointed by the MCD. At VAWNYHS, the Director has appointed the ACOS for R&D to fulfill this role. The RIO is responsible for reviewing any allegation of research misconduct, and determining whether it falls within the scope of “fabrication, falsification or plagiarism in proposing, performing or reviewing research or in reporting research results”. The RIO will notify the R&D chair, COS, MCD and begin the investigation. Should the RIO find that research misconduct has occurred he/she will follow the process outlined in VHA Handbook 1058.2.

XIX. IRB RECORDS

The Research Office maintains accurate and complete records of all communications to and from the IRB, the R&D committee and other subcommittees. The IRB chair signs IRB correspondence. Copies of all correspondence are filed in the appropriate research protocol file in the VAWNYHS Research Service office. In cases in which a research protocol being performed at the VAWNYHS has multiple investigators, correspondence will be sent to the PI in charge of the study and to a designated Study Coordinator, if applicable. The PI is responsible for communicating to the other investigators and for assuring that, they comply with IRB requirements. In cases where communication is electronic, upon resolution of an issue, a hard copy of all the electronic communications will be generated and placed in the protocol file.

- a. IRB Records.** Generally, IRB records include files contain:
 - 1. Written operating procedures
 - 2. IRB membership rosters
 - 3. Resume or CV for each voting IRB member
 - 4. Training records
 - 5. IRB correspondence (other than protocol related)
 - 6. IRB research protocol files
 - 7. Research (protocol) tracking system
 - 8. Documentation of exempt reviews
 - 9. Documentation of expedited reviews
 - 10. Documentation of convened IRB meetings – minutes
 - 11. Documentation of review by another institution’s IRB, when appropriate
 - 12. Documentation of cooperative review agreements, e.g., Memoranda of Understanding (MOUs)
 - 13. Federal Wide Assurances (FWA)
 - 14. Serious adverse event (SAE) reports
 - 15. Project tracking documents
- b. IRB Membership Rosters.** The IRB coordinator shall ensure that current IRB membership rosters are maintained and that any changes in IRB membership are reported promptly to OHRP with a copy to ORO. All IRB membership rosters shall include the following information required by OHRP:
 - 1. Names of IRB members
 - 2. Names of alternate members and the corresponding regular member(s) for who each alternate may serve
 - 3. Earned degrees of each member and alternate, where applicable

4. Specific scientific qualifications (such as board certifications and licenses) or other relevant experience sufficient to describe each member's chief anticipated contribution to IRB deliberations
5. The representative capacity of each member or alternate
6. Any employment or other relationship (affiliated or non-affiliated) between each member and the institution (e.g., full-time employee, part-time employee)

c. Education and Training Records. VA policy requires a plan for continuing education in human participant protections for research investigators. The terms of the FWA require continuing education for IRB members. All research investigators and all members of the research team who have direct contact with participants and/or identifiable participant information, must complete all VA-mandated education related to human participants research protection and good clinical practice, privacy and data security with their initial research proposal and annually thereafter (bi-annually for required CITI training). They must provide a certificate of completion for each educational module to the Research Office where education compliance will be tracked.

d. IRB Correspondence. The Research Office staff will ensure that accurate records are maintained of all correspondence to or from the IRB.

e. IRB Research Protocol Files. The IRB shall maintain a separate file for each research application (protocol) that it receives for review. Protocols are numbered, when they are activated, by the VA national research database (PROMISE) using a 4-digit number for the number of proposals submitted by each investigator, i.e., John Public 0001. Each IRB protocol file will include but not be limited to the following materials:

1. The Request to Review Research Proposal/Project Form
2. The IRB-approved informed consent document(s), with the approval date and dates of each change on the affected page
3. Scientific evaluations of the proposed research including scientific reviewer comments, if any.
4. For drugs, the Investigator's Brochure; for devices, a report of prior investigations
5. A complete copy of the protocol, research plan, or investigational plan. In addition, the complete DHHS-approved protocol and DHHS-approved sample consent document when one exists.
6. Advertising or recruiting materials, if any
7. Statements of significant new findings provided to participants
8. Requests for protocol amendments or modifications
9. Continuing review progress reports and related information
10. Reports of injuries to participants
11. Reports of unanticipated problems involving risks to participants or others
12. Reports of adverse events occurring within VAWNYHS (or involving employees or agents of the VAWNYHS) and reported to any regulatory agency
13. Unexpected adverse events submitted to the IRB
14. Protocol violations/deviations submitted to the IRB
15. Reports of external adverse events received from sponsors or cooperative groups
16. Data and Safety Monitoring Board (DSMB) reports, if any
17. Results of any internal quality control and monitoring activities
18. Correspondence between the IRB and the R&D committee
19. All other IRB correspondence related to the research
20. Documentation of all IRB review and approval actions, including initial and continuing convened (full) IRB review

21. Documentation of type of IRB review
22. For initial and continuing review of research by the expedited procedure:
 - a. The specific permissible category
 - b. Description of action taken by the reviewer
 - c. Any findings required under the regulations
23. For exemption determinations the specific category of exemption
24. Determinations required by the regulations and protocol-specific findings supporting those determinations for waiver or alteration of the consent process
25. For each protocol's initial and continuing review, the frequency for the next continuing review
26. Documentation of project closeout

f. Documentation. Adequate documentation of all the activities of the IRB must be maintained, including, but not limited to, the following:

1. Copies of all research proposals, all amendments reviewed, and any accompanying materials
2. All continuing and final reports
3. Minutes of the IRB meetings
4. Copies of all written correspondence related to a specific protocol, correspondences related to IRB, and correspondences from other agencies
5. Membership rosters and appointment letters for the IRB

g. Record Retention. All required records, including IRB records and investigator records, must be retained indefinitely after completion of the study and in accordance with VHA's Record Control Schedule (RCS 10-1). Research records have not been assigned a category for destruction therefore, no records may be destroyed. This includes records of projects cancelled without participant enrollment or **never activated**. All retained records must be kept in a secure and locked location. **NOTE:** Any protocols involving human participants in radiation therapy, radioisotopes, or nuclear medicine will be retained indefinitely.

h. Access to Records. All records shall be accessible for inspection and copying by representatives of VA and other Federal regulatory agencies at reasonable times and in a reasonable manner. Access to research records is limited to the ACOS for R&D, AO for R&D, the research committee chairpersons, and research committee members, RCO, Research Service staff, and authorized VA representatives. Research investigators shall be provided reasonable access to files related to their research. The Research Service staff will keep a log of individuals who access the records, other than the research committee members, chairs and Research Service staff. The research service can provide information on who accessed the files, what files were accessed, when the files were accessed, and for what purpose the files were accessed. Research participants are informed of those who have access to their research records in the informed consent and HIPAA authorization.

i. Research Tracking System. The Research Service uses a computerized tracking system, the Managing Institutional Review Board (MIRB) computer program developed by N-Core Systems, Inc., which is maintained by research office staff. MIRB stores information regarding each document received, when it was reviewed, and the results of that review. Additionally, MIRB tracks changes that are needed, when those changes were received and approved, and the date of expiration of initial and continuing review. MIRB tracks IRB committee membership and generates meeting minutes and correspondence.

1. The Research Service also enters data into the Enterprise Project Management Information System (ePROMISE) database system that is provided by VA Headquarters to track research protocols. It indicates which protocols are pending funding, active, final, and/or non-funded. ePROMISE also generates annual

updates of protocol data sheet which is used to produce the annual Research and Development System (RDIS) report to ORD.

2. Each research proposal is given a separate file. Protocols are assigned a unique number by MIRB and receive a unique grant number from ePROMISE for tracking and administrative purposes.

References:

1. Title 38 CFR 16 and 17
2. Title 21 CFR 50, 54, 56, 312, 361, 600, 812, 814
3. Title 45 CFR 46, 160, 164
4. VHA Handbook 1058.01
5. VHA Handbook 1058.2
6. VHA Handbook 1200.01
7. VHA Handbook 1200.05
8. VHA Handbook 1605.1
9. Center Memoranda 151-01
10. Center Memoranda 151-4
11. Center Memoranda 151-05
12. Center Memoranda 151-6
13. Center Memoranda 119-7
14. Pharmacy SOP 25
15. R&D Committee SOP
16. RCO SOP

APPENDIX A

Definitions

1. **Accreditation.** Accreditation of a Human Research Protection Program (HRPP) is the process of obtaining independent recognition that a HRPP affords protection to human subjects by meeting and exceeding the prevailing ethical, professional, and regulatory requirements, and that the HRPP engages in continuous quality improvement.
2. **Accrediting Organization.** The accrediting organization is an independent body that has developed standards of performance to assess compliance with the prevailing ethical, professional, and regulatory guidelines for the conduct of human subject research.
3. **Adverse Event (AE).** An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research.
4. **Affiliated Institution.** An affiliated institution is an academic institution that has a relationship for the purpose of education, research, or enhanced patient care with a VA medical center documented by a formal Affiliation Agreement in conformance with VA requirements (also referred to as “academic affiliate”). In addition, special purpose agreements documented by a memorandum of understanding (MOU) approved by the Chief Research and Development Officer (CRADO) may be developed in research and development (R&D) areas, such as health services or rehabilitation R&D.
5. **Affiliation Agreement.** An Affiliation Agreement is a written agreement documenting the relationship for the purpose of education, research, or enhanced patient care between a VA medical center and an affiliated institution.
6. **Anonymous.** For the purposes of VA research, anonymous means de-identified in accordance with both:
 - a. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR 164.514(b) (VHA Handbook 1605.1), and
 - b. The Common Rule provision that the identity of the subject cannot be readily ascertained by the investigator or associated with the information (38 CFR 16.102(f)).
7. **Assurance (Assurance of Compliance).** For human research, an Assurance is a written commitment to protect human subjects participating in research and to comply with the requirements of 38 CFR Part 16. Assurances are reviewed and approved by the HHS Office for Human Research Protections (OHRP) and various other departments and agencies under the Federal Policy (Common Rule) for the Protection of Human Subjects (56 FR 28001, June 18, 1991) (VHA Handbook 1058.03).
8. **Blinded.** A blinded study design is one comparing two or more interventions in which the research personnel, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects.
9. **Children.** Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted (45 CFR 46.402(a)).
10. **Clinical Investigation.** The FDA considers the term clinical investigation to mean any experiment that involves a test article and one or more human subjects, and that either:
 - a. Meets the requirements for prior submission to the FDA under § 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act; or
 - b. Does not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit (21 CFR 56.102(c)).

11. **Clinical Trial.** A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related intervention to evaluate the effects on health outcomes.
12. **Coded Data.** The term “coded data” means “coded private information” as defined in guidance published by HHS entitled Guidance on Research Involving Coded Private Information or Biological Specimens, currently available at <http://www.dhhs.gov/ohrp/humansubjects/guidance/cdebiol.htm> (see VHA Handbook 1200.12)
13. **Common Rule.** Common Rule means the Federal Policy for the Protection of Human Subjects adopted by Federal departments and agencies conducting or supporting human subject research. The Common Rule is codified for VA at title 38 CFR Part 16.
14. **Control Group.** A control group is the standard by which experimental observations are evaluated. In many clinical trials, one group of patients is given an experimental drug or treatment, while the control group is given either usual care for the illness or a placebo.
15. **Credentialing.** Credentialing is the systematic process of screening and evaluating qualifications and other credentials, including licensure, education, training, and experience, and current competence and health status (see VHA Handbook 1100.19).
16. **Data.** The term data (for the purposes of VHA Handbook 1200.05) means information derived directly from patients or human research subjects or indirectly through accessing databases. It includes information from Deoxyribonucleic Acid (DNA) sequencing. It does not include information derived from research involving animals or other types of research that do not involve human subjects (see VHA Handbook 1200.12).
17. **Database.** A database is a collection of data or information elements organized in a manner to permit systematic retrieval.
18. **Data Monitoring Committee (DMC), Data and Safety Monitoring Board (DSMB), or Data and Safety Monitoring Committee (DSMC).** A DMC, DSMB, or DSMC is group of individuals with relevant expertise that reviews accumulating data from one or more ongoing research studies. The DMC, DSMB, or DSMC independently advises the sponsor or the PI regarding the continuing safety of the research study’s subjects, as well as the continuing validity and scientific merit of the study.
19. **Data Repository.** A data repository is a database or a collection of databases that have been created or organized to facilitate the conduct of multiple research protocols, including future protocols not yet envisioned. It also may have been created for other purposes such as administrative and clinical purposes (VHA Handbook 1200.12).
20. **De-Identified Data.** For the purposes of VA research, de-identified data are data that have been de-identified in accordance with both:
 - a. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR 164.514(b) (see VHA Handbook 1605.1), and
 - b. The Common Rule provision that the identity of the subject cannot be readily ascertained by the investigator or be associated with the information (38 CFR 16.102(f)).Such data may also be known as “anonymous”. ***NOTE: Coded data is data identifiable by the individual(s) who has access to the code. Therefore, coded data are not considered to be de-identified or anonymous.***
21. **Delivery.** In the context of pregnancy, delivery means complete separation of the fetus from the woman by expulsion, extraction, or any other means.
22. **Double-Blinded Study.** A study is referred to as double-blind if both the researcher and the participants are not aware of which treatment each participant is receiving.
23. **Embryo.** An embryo is an organism in the early stages of development, which in humans is the first 6 weeks.
24. **Exempt Research.** Exempt research includes research activities in which the only involvement of human subjects is in one or more of the categories listed in 38 CFR 16.101(b). The exempt status must be determined by the IRB chair

or an IRB voting member designated by the chair. **NOTE:** *Such an exemption applies only to requirements found in 38 CFR Part 16. All other relevant VA and Federal requirements apply.*

25. **Expanded Access.** Expanded access refers to any of the FDA procedures that distribute experimental drugs to participants who are failing on currently available treatments for their condition, and also are unable to participate in ongoing clinical trials.
26. **Expedited Review Procedures for Research.** In contrast to a convened IRB review process, the expedited review process consists of a review carried out by the IRB chair or by one or more experienced voting members of the IRB designated by the IRB chair in accordance with 38 CFR 16.110(b).
27. **Experimental Drug.** An experimental drug is a substance that has been tested in a laboratory and has received approval from the FDA to be tested on people.
28. **External AE.** In the context of a multi-site study, an external AE is an AE experienced by subjects, research staff, or others at another institution engaged in the trial.
29. **Facility.** For purposes of VHA Handbook 1200.05, the term “facility” and “institution” are interchangeable.
30. **Fetus.** A fetus is the product of conception from the time of implantation until delivery.
31. **Health Care Agent.** A health care agent is an individual named by the patient in a Durable Power of Attorney for Health Care (38 CFR 17.32(a)(iii)).
32. **HIPAA Authorization.** The term HIPAA authorization means prior written permission for use and disclosure of protected health information (PHI) from the information’s source person, research subject, or legally authorized personal representative, as required under law, including HIPAA. The written authorization must include all elements of a compliant authorization (see VHA Handbook 1605.1) prior to any disclosure of information.
33. **Human Biological Specimens.** Human biological specimens are defined as materials derived from human individuals, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs, or any other materials that are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures. Bacteria, fungi, or viruses obtained from human biological specimens are not considered human biological specimens, as long as the human material has been removed.
34. **Human Research.** Human research is research involving human subjects as defined in VHA Handbook 1200.05 or one or more identifiable human biological specimens.
35. **Human Research Protection Program (HRPP).** A HRPP is a comprehensive system to ensure the protection of human subjects participating in research. At a local VA facility, the HRPP consists of a variety of individuals and committees including, but not limited to: the VA facility Director, Associate Chief of Staff (ACOS) for R&D, Administrative Officer (AO) for R&D, Research Compliance Officer (RCO), R&D Committee, IRB, other committees or subcommittees addressing human subjects protection (e.g., Subcommittee on Research Safety (SRS), Institutional Biosafety Committee, Radiation Safety Committee, Radioactive Drug Research Committee, Conflict of Interest Committee), investigators, IRB staff, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.
36. **Human Subject.** This definition of human subject includes investigators, technicians, and others assisting investigators, when they serve in a “subject” role by being observed, manipulated, or sampled.
 - a. Title 38 CFR Part 16 defines a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains either:
 - i. Data through intervention or interaction with the individual; interaction includes communication or interpersonal contact between the researchers and the subject; or
 - ii. Identifiable private information (38 CFR 16.102 (f)).

- b. For research covered by Food and Drug Administration (FDA) regulations, human subjects means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. (21 CFR 50.3(g), 21 CFR 66.102(c))
 - c. For research covered by FDA device regulations, subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease (21 CFR 812.3(p)).
37. **In Vitro Fertilization.** In vitro fertilization is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.
38. **Institution.** An institution is any public or private entity or agency (38 CFR 16.102(b)). VHA Handbook 1200.05 distinguishes VA from non-VA institutions (see VHA Handbook 1058.03).
- a. **VA Institution.** A VA institution is any entity that is operated by VA, including but not limited to: VA hospitals, medical centers, clinics, and health care systems; space owned, leased, or rented by VA; and space that is “shared” with a non-VA entity (unless the VA space is leased to a non-VA entity and specifically designated in writing not to be used by VA or VA employees for research). A VA facility may include multiple campuses and satellite components.
 - b. **Non-VA Institution.** A non-VA institution is an entity not operated by VA. Non-VA institutions include, but are not limited to:
 - i. Any entity that is not a legal component of VA or of a VA facility, including a contract research organization (CRO), industry or private sponsor, or public or private research company, foundation, or group.
 - ii. Entities operated under a contract with VA including, but not limited to, contract Community-based Outpatient Clinics (CBOCs), contract nursing homes, contract outpatient clinics. **NOTE:** *Some entities (e.g., CBOCs) are VA institutions when they are part of the VA facility, but non-VA institutions when they are operated under a contract with VA (e.g., a contract CBOC).*
 - iii. Academic institutions, including VA–affiliated medical schools, dental schools, and other academic affiliates.
 - iv. VA-affiliated Non-Profit Research and Education Corporations (NPCs).
 - v. Other Federal, state, or local departments or agencies.
39. **Institutional Official (IO).** The IO is the individual legally authorized as Signatory Official to commit an institution to an Assurance. The IO serves as the official representative of the institution to external agencies and oversight bodies, and provides all written communication with external departments, agencies, and oversight bodies. The Principal Deputy Under Secretary for Health is the IO for VHA Central Office, and VA facility Directors are the IOs for local VA facilities.
40. **Institutional Review Board (IRB).** An IRB is a board, committee, or other group formally designated by an institution to review, approve, require modification in, disapprove, and conduct continuing oversight of human research in accordance with 38 CFR Part 16 and other applicable VA and Federal requirements.
41. **Interaction.** Interaction includes communication or interpersonal contact between investigator and subject (38 CFR 16.102(f)(2)).
42. **Internal or Local AE.** In the context of a multi-center study, internal AEs are those AEs experienced by subjects, research staff, or others at the reporting individual’s own VA facility or VA-approved research site.
43. **International Research.** VA international research is any VA-approved research conducted at international sites (not within the United States (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 sending such specimens or data out of the U.S.

NOTE: For the purposes of VHA Handbook 1200.05, research conducted at U.S. military bases, ships, or embassies is not considered international research.

44. **Intervention.** Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes (38 CFR 16.102(f)(2)). Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured.
45. **Investigational Brochure (IB).** The IB is a comprehensive document summarizing all known information about an investigational agent.
 - a. This includes all basic chemistry, pharmacology, toxicology, pre-clinical and clinical data to date, and summaries of clinical trials and adverse experiences with the investigational agent.
 - b. The sponsor is responsible for keeping the IB updated on a regular basis.
 - c. The IB is usually considered proprietary information of the sponsor and as such the use and distribution of the IB is limited to the study teams.
46. **Investigational Device.** As defined by the FDA, an investigational device is a device that is the object of an investigation (21 CFR 812.3(g)).
47. **Investigational Device Exemption (IDE).** An IDE is an application to FDA that allows an investigational significant risk device to be used in a clinical investigation to collect safety and effectiveness data. If the device is a non-significant risk device, it is considered to have an approved application for IDE after IRB approval is obtained (see 21 CFR 812).
48. **Investigational Drug.** According to VHA Handbook 1108.04, an investigational drug is a chemical or biological drug that is used in a clinical investigation. An investigational drug can be:
 - a. A new chemical compound, which has not been released by the FDA for general use; or
 - b. An approved drug that is being studied for an approved or unapproved use, dose, dosage form, administration schedule, or under an Investigational New Drug (IND) application, in a controlled, randomized, or blinded study (see VHA Handbook 1108.04).

NOTE: Concurrent medications, comparators, or rescue medications used in the investigational trial that are not the drug(s) being studied are not defined as investigational drugs unless they are not commercially approved or not available through commercial channels. Prescription drugs, over-the-counter drugs, nutritional supplements, herbal preparations, and legend items used for diagnosis or treatment and meeting the definition of "investigational drug" are considered investigational drugs.
49. **Investigational New Drug (IND) Application.** An IND is an application to the FDA that allows an investigational drug or biological product to be studied in humans. An IND must be in effect prior to shipment and administration of investigational drug or biological products (see 21 CFR 312).
50. **Investigator.** An investigator is any individual who conducts research involving human subjects including, but not limited to, the PI, co-PI, and Local Site Investigator (LSI). The investigator must uphold professional and ethical standards and practices, adhere to all applicable Federal requirements, and comply with applicable local policies and procedures.
 - a. **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, without compensation (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.
 - b. **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 that team. **NOTE:** *FDA considers Investigator and PI to be synonymous.*

- c. **Co-Principal Investigator (Co-PI).** A Co-PI is when one of two or more PIs share equally in the accountability for a study. A Co-PI must meet the same qualifications of a PI.
 - d. **Site Investigator or Local Site Investigator (LSI).** The Site Investigator or LSI is an investigator at a site participating in a multi-site research project. The LSI oversees scientific, technical, and day-to-day management of the research at the local site.
51. **Legal Guardian.** A legal guardian is a person appointed by a court of competent jurisdiction to maintain and care for the property of an individual, or an individual who the court has declared incompetent due to physical or mental incapacity or age (see VHA Handbook 1605.1).
 52. **Legally Authorized Representative (LAR).** A LAR is 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)).
NOTE: *An individual who is qualified as a 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 or power of attorney) prior to the LAR's signing a HIPAA authorization (see VHA Handbook 1605.1).*
 53. **Minimal Risk.** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (38 CFR 16.102(i)).
 54. **Neonate.** For the purposes of VA research, a neonate is an infant in the first 28 days of life.
 55. **Observational Studies.** Observational studies are non-interventional studies in which individuals are observed and those observations are recorded. Outcomes, including health outcomes, may also be measured by the investigators.
 56. **Office of Research and Development (ORD).** Within VHA Central Office, ORD is the office responsible for the overall policy, planning, coordination, and direction of VA research activities.
 57. **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 subject protections, animal welfare, research safety and security, research information protection, and research misconduct. **NOTE:** *ORD and ORO are two separate offices within VHA. The CRADO reports to the Principal Deputy Under Secretary for Health. The Chief Officer of ORO reports to the Under Secretary for Health.*
 58. **Open-Label.** Open-label refers to when both the researchers and participants know the identity of the drugs or treatments being administered.
 59. **Personal Representative.** A personal representative is a person who, under applicable law, has authority to act on behalf of another individual. This may include power of attorney, legal guardianship of an individual, the executor of an estate of a deceased individual, or someone under Federal, state, local, or tribal law with such authority (e.g., the parent of a minor) (VHA Handbook 1605.1).
 60. **Pilot Studies.** Pilot studies are full-fledged research studies that must be approved by the IRB(s), when human subjects are involved. They are not considered to be activities preparatory to research.
 61. **Pregnancy.** Pregnancy encompasses the period of time from implantation until delivery.
 62. **Preparatory to Research.** Within VHA, activities "preparatory to research" refer to activities that are necessary for the development of a specific protocol. PHI from data repositories or medical records may be reviewed during this process without IRB approval, subject authorization, or a waiver of authorization, but only aggregate data may be

recorded and used in the protocol application (e.g., potential number of subjects meeting study criteria at each site). Within VHA, an activity preparatory to research does not include the identification of potential subjects and recording of data for the purpose of recruiting these subjects or to link with other data. The preparatory to research activity ends once the protocol has been submitted to the IRB for review (see VHA Handbook 1200.12).

63. **Prisoner.** A prisoner is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
64. **Privacy Board.** Under HIPAA, a Privacy Board is a board that is established to review and approve requests for waivers or alterations of HIPAA authorizations in connection with use or disclosure of PHI. The Privacy Board:
- a. Consists of members with varying backgrounds and appropriate professional competency, as necessary, to review the effect of the research protocol on the individual's privacy rights and related interests;
 - b. Includes at least one member who is not affiliated with the covered entity, not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities; and
 - c. Does not have any member participating in a review of any study in which the member has a conflict of interest.
65. **Private Information**
- a. Private information must be individually identifiable in order for the information to constitute research involving human subjects (38 CFR 16.102(f)).
 - b. Private information includes:
 - i. Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and
 - ii. Information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record).
66. **Privileging**
- a. For the purposes of VHA Handbook 1200.05, the terms "privileging" and "clinical privileging" are the same and are defined as the process by which a practitioner, licensed for independent practice (i.e., without supervision, direction, required sponsor, preceptor, mandatory collaboration, etc.), is permitted by law and the facility:
 - i. To practice independently; and
 - ii. To provide specified medical or other patient care services within the scope of the individual's license, based on the individual's clinical competence as determined by peer references, professional experience, health status, education, training, and licensure.
 - b. Clinical privileges must be facility-specific and provider-specific (see VHA Handbook 1100.19).
67. **Program for Research Integrity Development and Education (PRIDE).** PRIDE is the program within ORD that is responsible for training, education, and policy development related to VA human subjects protection. Other VA offices, including ORD services (i.e., ORD's Biomedical Laboratory Research and Development (BLR&D), Clinical Science Research and Development (CSR&D), Health Services Research and Development (HSR&D), and Rehabilitation Research and Development (RR&D) Services), may develop policies for research involving human subjects that have requirements in addition to those in VHA Handbook 1200.05.
68. **Quorum.** A quorum is defined as a majority of the voting members. At meetings of the R&D committee and its subcommittees, a quorum must be established and maintained throughout the entire meeting in order for business to be conducted. Some committees, such as the IRB have additional requirements for the establishment of a

quorum, such as presence of a member whose primary concerns are in nonscientific areas. A member with a conflict of interest cannot:

- a. Contribute to a quorum,
- b. Be present for the discussion of the issue for which they are conflicted, except to answer questions from the committee, or
- c. Be present for the vote on the issue.

69. **Research.** 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 (38 CFR 16.102(d)).

- a. Generalizable knowledge is information that expands scientific understanding or the knowledge base of a scholarly field of study.
- b. Systematic Investigation is a project that is planned in advance and that uses data collection and analysis to answer a question.

70. **Research Compliance Officer (RCO).** The RCO is an individual whose primary responsibility is to review research projects relative to requirements for the protection of human subjects, laboratory animal welfare, research safety, research laboratory security, research information protection, and other areas under the jurisdiction of ORO.

71. **Research Records.** Research records include, but are not limited to, IRB and R&D Committee records, records of all observations, other data relevant to the investigation, progress notes, research study forms, surveys, questionnaires, and other documentation regarding the study (VHA Handbook 1907.01).

- a. **IRB Records.** IRB records include, but are not limited to: copies of all research proposals and amendments reviewed; scientific evaluations, if any, that accompany the proposals; approved informed consent documents; progress reports submitted by investigators; reports of injuries to subjects; reports of complaints from subjects; minutes of IRB meetings; reports of expedited review activities; records of continuing review activities; copies of all correspondence between IRB and the investigators; reports of deviations from IRB-approved protocol; a list of IRB members; written procedures for IRB in the same detail as described in 38 CFR 16.103(b)(4) and (5); and statements of significant new findings provided to subjects as required by 38 CFR 16.116(b)(5).
- b. **Investigators' Research Records.** Research records include the following when relevant to the study: copies of all IRB-approved versions of the protocol and amendments; case report forms and supporting data (including but not limited to signed and dated informed consent forms and HIPAA authorization forms); documentation on each subject including informed consent, interactions with subjects by telephone or in person, observations, interventions, and other data relevant to the research study; reports of adverse events; data analyses; codes and keys used to de-identify and re-identify subjects' PHI; reports (including, but not limited to abstracts and other publications); all correspondence (including, but not limited to, that with the funding source or sponsor) and with applicable oversight entities (including, but not limited to, IRB, R&D Committee, ORO, and FDA); and a master list of all subjects for whom informed consent has been obtained in the study.

72. **Researcher.** A researcher is an investigator.

73. **Sensitive Information**

- a. VA sensitive information is all department data, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, alteration, or destruction of the information.

- b. The term includes information whose improper use or disclosure could adversely affect the ability of an agency to accomplish its mission; proprietary information; records about specific individuals requiring protection under various confidentiality provisions, such as the Privacy Act and the HIPAA Privacy Rule; and information that can be withheld under the Freedom of Information Act (see VA Directive 6500 and VA Handbook 6500).
74. **Serious Adverse Event (SAE)**. A local SAE in human research is an AE that results in death, a life threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.
75. **Sponsor**. For FDA studies, the FDA considers a sponsor to be the person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of their own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators (21 CFR 312.3 and 21 CFR 812.3).
76. **Surrogate**. A surrogate is an individual authorized under VHA policy to make decisions on behalf of a subject who lacks decision-making capacity.
77. **Suspension of IRB Approval**. A suspension of IRB approval is a determination by the IRB Chair, a qualified IRB voting member designated by the IRB Chair, or the convened IRB to temporarily interrupt some or all previously-approved research activities. The suspended activities could include, but not be limited to, recruiting of new subjects for the research. Suspended studies remain open and require continuing review.
78. **Termination of IRB Approval**. A termination of IRB approval is a determination by the convened IRB to permanently halt some or all previously approved research activities including, but not limited to, enrollment of new subjects in research.
- NOTE:** The terms “suspension” and “termination” apply to interruptions related to concerns regarding the safety, rights, or welfare of human research subjects, investigators, research staff, or others. They do not include interruptions in human research resulting solely from the expiration of the IRB approval period (see VHA Handbook 1058.01).*
79. **Test Article**. A test article is 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 Federal Food, Drug, and Cosmetic Act or under §§ 351 and 354-60F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n; 21 CFR 50.3(j)).
80. **Unanticipated Adverse Event (UAE)**. An UAE is an 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 IRB. Such materials may include, but are not limited to: the informed consent form, clinical investigator’s brochure, and product labeling (see VHA Handbook 1058.01).
81. **Unblinding or Breaking the Blind**. Unblinding or “Breaking the Blind” is the formal process of revealing the true identity of the treatment assignment or investigational drug in a double-blinded study.
82. **Usual Care**. Usual care is medical or other treatment or services a research subject would receive if not participating in the research study (e.g., the chemotherapy an oncology patient would receive whether or not the patient was participating in a research study).
83. **VA Research**. VA research is research that is approved by the R&D Committee and conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments),

utilizing VA resources (e.g., equipment), or on VA property including space leased to, and used by VA. The research may be funded by VA, by other sponsors, or be unfunded.

NOTE: *Research conducted by non-VA investigators that does not utilize VA resources and that occurs on space, or with equipment, leased from VA or covered under a use agreement between VA and a non-VA entity is not considered VA research.*