

**Veterans Affairs
Nebraska-Western Iowa
Health Care System (NWIHCS)**

**Institutional Review Board
Standard Operating Policies
and Procedures**

R&D Committee Approved

**VA Nebraska-Western Iowa Health Care System
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Standard Operating Procedures

I. BACKGROUND

A. The Ethical Mandate to Protect Human Subjects

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

1. **The Nuremberg Code.** The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their “research” practices, known as *The Nuremberg Code*. The significance of the Code is that it addressed the necessity of requiring the voluntary consent of the human subject and that any individual “who initiates, directs, or engages in the experiment” must bear personal responsibility for ensuring the quality of consent.

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

3. **The Belmont Report.** Revelations in the early 1970s about the 40-year United States Public Health Service Study of Untreated Syphilis in the Negro Male at Tuskegee and other ethically questionable research resulted in 1974 legislation calling for regulations to protect human subjects and for a National Commission to examine ethical issues related to human subject research (i.e., the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research). The Commission’s final report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, defines the ethical principles and guidelines for the protection of human subjects. The Belmont Report contains three basic ethical principles central to human research that guide the IRB in assuring protection of the rights and welfare of subjects.

These three principles are:

a. **Respect for persons** recognizes individual autonomy and is applied by obtaining informed consent, consideration of privacy and confidentiality, and assuring additional protections for vulnerable populations.

b. **Beneficence** requires that possible benefits are maximized and possible risks minimized for research subjects.

c. **Justice** is evidenced in the equitable selection of subjects with regard to distribution of burdens and benefits.

The Belmont Report also provides important guidance regarding the boundaries and interface between biomedical research and the practice of medicine.

B. The Regulatory Mandate to Protect Human Subjects

The Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects. The IRB complies with the following regulations and guidelines:

1. Department of Health and Human Services (DHHS) Regulations at 45 CFR 46.

In May of 1974, the Department of Health, Education, and Welfare (later renamed DHHS) codified its basic human subject protection regulations at 45 CFR 46, Subpart A. Revised in 1981 and 1991, the DHHS regulations presently include additional protections for fetuses, pregnant women, and human in vitro fertilization (Subpart B), prisoners (Subpart C), and children (Subpart D). The DHHS regulations are enforced by the Office for Human Research Protections (OHRP).

2. Department of Veterans Affairs (VA) Regulations at 38 CFR 16 and the Federal Policy (Common Rule) for the Protection of Human Subjects.

In January of 1991, the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VA at 38 CFR 16, the Common Rule is the same as that codified by the Department of Health and Human Services (DHHS) as Subpart A of the DHHS regulations at 45 CFR 46. DHHS has three additional Subparts in the regulations that are not included in 38 CFR 16; i.e., Subpart B (pregnant women, human fetuses and neonates), Subpart C (prisoners), and Subpart D (children). **All human subject research conducted at NWHCS must adhere to the regulations at 45 CFR 46 and 38 CFR 16.**

In addition, the following the following regulations. . . .

- a. 38 CFR 16 Protection of Human Subjects
- b. 38 CFR 17.33 Regulations for patient rights
- c. 38 CFR 17.85 Treatment of research related injuries to human subjects
- d. 38 CFR 17.45 Medical Hospital Care for Research Purposes
- e. 38 CFR 17.92 Outpatient Care for Research Purposes
- f. Codified by the VA at 38 CFR 16, the Common Rule is identical to Subpart A of the DHHS regulations, but does not include the additional DHHS Subparts B, C, and D

VHA Directive 1200.05 specify VA guidelines for the conduct of human research.

On January 19, 2017, a major revision to the Federal Policy for the Protection of Human Subjects was published and subsequently revised January 22, 2018 and again June 19, 2018 that requires compliance of studies approved by the IRB or determined to be exempt by IRB on or after January 21, 2019. The revised Common Rule also allows for continued compliance with the previous 1991 Common Rule for those studies approved by the IRB or determined to be exempt prior to January 21, 2019. Additionally, studies originally subject to the pre-2018 requirements may transition to the revised Common Rule on or after January 21, 2019. If a study originally subject to the pre-2018 requirements is determined to transition to the revised Common Rule the institution or an IRB must document and date

such determination. Studies that transition to the revised Common Rule must comply with the 2018 requirements on the documented date.

Between July 19, 2018 and January 20, 2019, if the research is determined to transition to the revised Common Rule the institution or IRB could decide to apply two provisions from the revised Common Rule: the revised definition of research that specifies four categories of activity deemed not research or the elimination of IRB review of the grant application or contract proposal. If any study applied either burden reducing provision, that study must be compliant with the revised Common Rule on January 21, 2019. **This paragraph does not apply to VA NWIHCS research.**

3. Food and Drug Administration (FDA) Regulations

When DHHS revised its regulations in 1981, the FDA codified almost identical informed consent regulations at 21 CFR 50 and IRB regulations at 21 CFR 56. Additional FDA regulations that are relevant to the protection of human subjects are:

- a. 21 CFR 50 Protection of Human Subjects
- b. 21 CFR 56 Institutional Review Boards
- c. 21 CFR 54 Financial Disclosure by Clinical Investigators
- d. 21 CFR 312 Investigational New Drug Applications (IND)
- e. 21 CFR 361 Radioactive Drugs
- f. 21 CFR 600 Biological Products
- g. 21 CFR 812 Investigational Device Exemptions (IDE)
- h. 21 CFR 50, Subpart D Additional Safeguards for Children**

i. NOTE: For drug and device studies investigators and IRBs must follow both FDA regulations and VA requirements. FDA regulations supersede VA requirements for human subjects research under FDA jurisdiction unless VA requirements are more restrictive than applicable FDA regulations.

4. **Department of Defense 3216.02** Instructions when DoD supports (i.e. funds) the research. An FWA DoD addendum is approved. DoD 3216.02 Instruction is an Addendum to the IRB SOP and implementation will be triggered when the Initial Review Submission Form identifies DoD supported research. The IRB Administrator will insure implementation and training. The Institutional Official, ACOS/R, and IRB Chairperson have completed CITI training including DoD modules. Certification of their training has been submitted to the DoD as part of the requirement to include the DoD to our FWA. When following Department of Defense (DoD) regulations: Records maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

Summary of relevant DoD requirements:

- *Additional institutional reporting requirements for investigator and/or NWIHCS for: changes in reviewing IRB, when significant changes to the research protocol are approved by the IRB, the results of Continuing Review, non-compliance, if HRPP is under investigation by any Federal*

department, agency, or national organization for cause, unanticipated problems, suspensions must include DoD officials (notify within 30 days). Relevant records are made accessible to DoD to inspect.

- DoD definition of research involving a human being as an experimental subject: an activity that includes both a systematic investigation designed to develop or contribute to generalizable knowledge where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction (as an example a blood draw would not be looking at the effect of the blood draw). In DOD studies where this definition is applicable 10 USC 980 should be reviewed if LAR is involved. If LAR is involved, there must be an intent to benefit the individual participant.
- DoD definition of minimal risk is based upon the phrase, “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” must not be interpreted to include the inherent risk categories of human subjects in their life, (for example, a pilot, soldier in combat zone etc..).
- Special active duty subject payment stipulations apply. (see Initial Review Submission Form)
- Special recruitment procedures apply (officers and non-commissioned officers in supervisory/command positions may not be present at time of recruitment and independent ombudsman may be necessary when recruitment involves a percentage of a unit).
-
- DoD unique limitations on Waiver of Informed Consent for EFIC research 21 CFR 50.24 unless a waiver is obtained from the Secretary of the Army is noted.
- Multi-site studies require a formal agreement that specifies roles and responsibilities of each party. Special requirements for international research apply.
- DoD requirement regarding disclosure for research related injury follow the DoD component is noted,
- DoD research involving pregnant women, prisoners, and children are subject to DHHS Subparts B, C and D. DoD prisoner-subject, prisoner of war prohibitions and requirements noted. For DoD studies, exemption for research involving survey or interview procedures or observations of public behavior does not apply to children is noted. DoD research involving a detainee as a research participant is prohibited unless use of investigational drugs/devices would be offered to US military personnel in the same location for the same condition).

5. The Assurance and IRB Registration Process. The Common Rule requires that every institution engaged in Federally supported human subject research file an “Assurance” of protection for human subjects (38 CFR 16.103(a)). The Common Rule Terms of Assurance are listed on the OHRP website. Each Agency states in their FWA that they accept these terms. Although each Common Rule Agency has the authority to issue its own Assurances, all Common Rule Agencies must recognize Federal-Wide Assurances (FWAs) approved by OHRP in DHHS. The VA uses the OHRP FWA.

The VA Office of Research Oversight (ORO) coordinates IRB registration and FWA filing for all VA facilities. The FWA is signed by the Facility Director, the Network Facility Director, and the Chief Officer, ORO. All VA facilities must register their IRBs and file their FWAs through ORO. There is a VA Addendum to the FWA that provides the place for these signatures. (Appendix A) The Under Secretary for Health established a mandatory training requirement for the FWA. VA Medical Centers can obtain the addendum and filing instructions from the OHRP website (<http://ohrp.osophs.dhhs.gov/>) or from ORO). ORO also provides details on the online training modules on the OHRP website.

The FWA documents should be given to all those engaged in human subjects research in VA. This can be accomplished in a number of ways, such as an attachment to training materials for investigators and IRB members, or posted on a VAMC website location. The FWA documents should be an appendix to the IRB SOP, for example in the section “Local Requirements.”

6. (a) The organization becomes “engaged in research involving human subjects” in a non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention

or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.

(b) Someone is considered to be acting as an agent of the institution in the conduct of research involving human subjects when research that is conducted by VA investigators while on VA time, utilizing VA resources, and/or on VA property including space leased to, and used by, VA. VA investigators include any individual acting under a VA appointment, including full and part-time employees, work without compensation (WOC), or enter Intergovernmental Personnel Act (IPA) appointments. The NWHCS IRB is not responsible for human research conducted at any other institution, except where a Memorandum of Understanding specifies otherwise. **When serving as an IRB for another VA institution, the VA is responsible only for the required actions of the IRB. The relying institution maintains all other oversight responsibility for the conduct of the study.**

II. IRB INSTITUTIONAL AUTHORITY UNDER WHICH THE IRB IS ESTABLISHED AND EMPOWERED [21 CFR 56.109(a)]

A. Authority

The Department of Veterans Affairs was one of 20 departments and agencies that agreed on August 19, 1991 to follow the Federal Policy for the Protection of Human Subjects. This policy is incorporated in [38 CFR 16, 17]. Each VA Medical Center that conducts human research is required to have an Institutional Review Board (IRB) of Record [VHA Handbook 1200.05].

B. Relationship to Research and Development Committee

1. The Research and Development Committee (R&D) is responsible for all research activities conducted under the auspices of NWHCS and is responsible for maintaining high standards throughout the facility's R&D program. VHA Directive 1200.01 establishes the responsibilities and operations of the Research and Development (R&D) Committee.

2. The Research and Development Committee reports through the Chief of Staff to the Facility Director.

3. The Research and Development Committee delegates full responsibility to the Institutional Review Board for scientific and ethical review of all human research. The membership of the Institutional Review Board includes physician-scientists and laypersons qualified to conduct initial and continuing review activities for the types of research typically reviewed at NWHCS. R&D and IRB members are knowledgeable enough to determine when they do not have expertise necessary to conduct adequate review and are required to obtain expert review as appropriate.

4. The Research and Development Committee is comprised of members from various clinical services and research and represents the institution. The R&D Committee oversees the IRB and conducts second level review of some IRB actions, may approve or disapprove IRB actions however may not approve research that has been disapproved by the IRB (38CFR 116.112; VHA Handbook 1200.01 2009) or alter an adverse report or recommendation by the IRB.

5. Cross membership exists between the Research and Development Committee and the Institutional Review Board to facilitate the review process. The R&D Committee and the IRB are independent review bodies. Both committees include a majority of members from outside research service (i.e. medical service, surgical service, nursing service, pharmacy service, psychology service, laboratory service, and the community) who report to supervisors with no direct interests in the institution's research enterprise. The IRB reports to the R&D Committee however the R&D Committee or other institutional officials, including the Facility Director, cannot overrule IRB disapprovals. IRB members may directly contact the Chief of Staff and or the Facility Director to discuss concerns without going through the R&D Committee or through the ACOS/R&D, or any other official or entity.
6. The Research and Development Committee and the Institutional Review Board meet weekly. The IRB members receive copies of all submission materials in time to review them thoroughly prior to the meeting.
7. The Institutional Review Board provides detailed minutes of IRB proceedings to the Research and Development Committee weekly to facilitate R&D 's second level review.

C. Relationship to Nebrasks Educational Biomedical Research Association (NEBRA)

- a. NEBRA was established under Public Law 100-322 and incorporated on February 5, 1992 as a non-profit corporation whose purpose is to provide a flexible funding mechanism for the conduct of approved research at Omaha VA Medical Center. The Facility Director, Chief of Staff and Associate Chief of Staff for Research are required to serve on the Board of Facility Directors. Other required members include those who are not officers or employees of the Federal Government and who are familiar with issues involving medical and scientific research. The NWIHCS IRB serves as the IRB of record for NEBRA.

D. Process for review and modification of IRB SOPs

1. Procedures for Review, Revision and Approval of Policies and Procedures

- a. Changes to regulations, federal guidelines, research practices, or VA or local policies and procedures may require a new SOP or revision of a previously issued SOP.
- b. Each approved SOP will be reviewed no less than three years from the date of approval as described in this policy. The review date is determined as three years from the last date of approval.
 - i. The IRB Coordinator or designee reviews the SOP and provides the revised policy and procedure to designated member(s) of the IRB for review. If the IRB Director or designee determines that significant changes to a policy must be made, the revised policy and procedure may be sent to the ORPP&E team for guidance.
 - ii. The review and approval of the SOP is documented by an IRB Administrator or designee who records the policy and procedure, the date approved (e.g. mm/dd/yyyy) and the member(s) responsible for approval). The approval date is the effective date.

2. Procedures for SOP Dissemination and Training

- a. When new or revised SOPs are approved, they will be disseminated to the appropriate individuals and departments.
 - b. Any new or revised policy or procedure or new regulation is disseminated to the IRB members and staff by the IRB administrator or designee. Record of dissemination and any applicable training is documented by the IRB administrator or designee.
- 3. Procedures for Creating and Using IRB Forms**
- a. Forms are used to ensure that policies are integrated into the daily research and review operations and enable the IRB to manage review, tracking, and notification functions consistently. Forms are not subject to the standards of control cited in sections 1 and 2. Forms include templates, checklists, (electronic) application forms and notifications.
 - b. Forms are created and revised by IRB Coordinator or designee.
 - c. As applicable, forms are implemented in the online system and posted/shared with the field

III. DEFINITION OF THE PURPOSE & INDEPENDENCE OF THE IRB [21 CFR 56.101(a)]

The institution established an independent IRB and empowered it to protect the rights and welfare of human research participants. The purpose of the IRB is to review and approve, require modifications in (to secure approval), or disapprove all human research activities in order to assure that the rights and welfare of individuals involved as subjects of research under Federal auspices are being protected in accordance with federal regulations - VA [38 CFR Part 16, 17], FDA [21 CFR Part 50, 56] and DHHS [45 CFR Part 46 subparts B, C, D].

IV. AUTHORITY OF THE IRB

A. Scope of Authority Defined

Oversees all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency. [38 CFR 16, 17], FDA [21 CFR Part 50, 56] and DHHS [45 CFR Part 46 subparts B, C, D]. The Facility Director must obtain an FWA prior to conducting any human subjects research and is the institutional authority designated on the Federal Wide Assurance 00000556 . The Facility Director is responsible for completing assurance training required prior to signing the FWA initially, and every 3 three years after that. The Facility Director is responsible for ensuring provision of adequate resources to support operations of the IRB and HRPP so that they are in compliance with all VA and other Federal requirements that govern human subject research protection. The Facility Director is responsible for ensuring that the IRB functions independently, and that members have direct access to him/her if they experience undue influence or if they have concerns about the IRB. The Facility Director cannot approve a study that has been disapproved by the IRB. The Facility Director signs and adheres to the MOU between VHA Central Office and NWHCS delineating the respective roles and responsibilities of each organization. The Facility Director signs and adheres to the MOU between NEBRA (VA NPC) and NWHCS delineating the respective roles and responsibilities of each organization. The Facility Director ensures subject outreach and fosters an institutional culture that supports the ethical conduct of all research.

B. Statutory Basis for IRB Authority

1. The Facility Director gives the IRB full authority:

- a. to approve, require modifications in to secure approval, and disapprove all research activities overseen and conducted by the organization...
 - b. to suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.
 - c. to observe, or have a third party observe the consent process and the conduct of research.
2. The statutory bases for these authorities are as follows:
- a. Statutory provisions for protection of VA patient rights. *U.S.C. (United States Code) Sections 7331 through 7334*
 - b. VA (Department of Veterans Affairs) regulations pertaining to protection of patient rights. [38 CFR 17.34 and 17.34a]
 - c. VA (Department of Veterans Affairs) regulations pertaining to rights and welfare of patients participating in research. [38 CFR 16 *Federal Policy for the Protection of Human Subjects*]
 - d. VA (Department of Veterans Affairs) requirements for the protection of human subjects in research. VHA Handbook 1200.5 June 29, 2017 (Protection of Human Subjects)
 - e. FDA (Food and Drug Administration) regulations pertaining to rights and welfare of patients participating in research involving investigational drugs and devices. [21 CFR 50, 56]
 - f. DHHS (Department of Health and Human Services) regulations pertaining to rights and welfare of patients participating in research supported by DHHS. [45 CFR 46 subparts B,C,D] [Insert State laws regarding research as applicable].

V. THE IRB'S RELATIONSHIP TO:

A. Institution Administration

The NWIHCS Research and Development Committee reports through the Chief of Staff to the Facility Director. The Facility Director is the institutional official responsible for all research activities conducted under medical center auspices, is the signatory for assurances (FWA), identifies Research Service as the entity responsible for developing and implementing applicable policies and procedures, appoints IRB members, and is responsible for oversight of the HRPP such that research is conducted ethically and according to applicable laws, regulations and guidelines. The Facility Director completes educational requirements required by ORD and oversight bodies (e.g. OHRP- FWA) and completes the Annual Facility Director Certification for submission to ORO. The Facility Director reviews the minutes of the Research and Development Committee. The Facility Director is responsible for providing the IRB with adequate resources.

B. Other Committees and Department Chairpersons Within the Institution

The IRB is a Sub-Committee of the Research and Development Committee. The IRB may require projects to be reviewed and approved by the Radiation Safety Sub-Committee, IACUC, Safety Committee, Bio-hazard Sub-Committee, or by ad hoc reviewers.

C. The Investigational Pharmacy
(Located in 3C-123/3C-135/3D-141)

Policies and Procedures

(1) VHA Handbook 1108.04, "Investigational Drugs and Supplies," Feb 29, 2012

Note: investigators and the facility must follow VHA Handbook 1108.04

The Investigational Pharmacy is a critical element of the NWHCS HRPP and is responsible for receipt, storage, security, dispensing and disposition of investigational drugs. The point at which study drug is stored, dispensed and disposed of is an obvious point for a gatekeeper functionary to minimize risk for patient injury and non-compliance in a high vulnerability area.

The investigational pharmacist maintains a drug log that includes the following factors:

- (1) Name, dosage form and strength of the drug.
- (2) Manufacturer or other source (Sponsor).
- (3) Amount, date and quantity received.
- (4) Lot or ID number and expiration or retest date – Documentation provided by the Sponsor that the expiration or retest date is monitored centrally to maintain blinding or ensure continued stability is acceptable in lieu of recording actual date(s).
- (5) Serial number (if applicable) and date of prescription dispensed
- (6) Patient's name or other identifier.
- (7) Quantity and date dispensed and balance remaining.
- (8) Date Protocol approved by MIRB and R&D Committee.
- (9) Name of authorized prescriber.
- (10) Pharmacist initials.
- (11) Final Entry Log for when drug therapy for the study ends. This entry documents the date of termination of the use of the drug, the quantity remaining, the action taken to dispose of the balance on hand, and the agent or individual responsible for drug destruction or return.

The investigational pharmacist does not fill a prescription without seeing a copy of the signed consent form and copy of the CWAD (Electronic medical record clinical alert) which identifies research subjects, the study drug they are taking, the investigator and coordinator contact numbers, that informed consent was obtained prior to initiation of study procedures, the date the consent form was signed, and that a copy of the consent form was given to the patient. In addition, the investigational pharmacist monitors VA Form 10-9012 (Investigational Drug Information Record) scanning into the medical record. The Investigational Pharmacy review provides reports to the IRB for every Continuing Review. These reports identify research subjects, specify the version of the consent form signed and specify the date the consent form was signed. Discrepancies are identified, written clarifications are obtained when required, and, if indicated, corrective action is taken (e.g. one-on-one training; re-consenting subjects; inviting investigators and study staff to IRB meetings for discussion of significant issues).

The ACOS/R&D is responsible for dissemination of Pharmacy Benefits Management (PBM) Drug Safety Bulletins to the IRB and investigators so that appropriate action is taken in order to assure the safety and welfare of research subjects who may be affected by the alert. The IRB reviews the alert, follows specific instructions contained in the alert, and follows required actions to protect subjects to their resolution. Additionally, the IRB Administrator sends copies of all PBM alerts to investigators in a blast e-mail. The Investigational Pharmacist assists the IRB and provides them with information about

studies for which the PBM alert may be relevant. PBM alert reviews and related actions are documented in IRB minutes.

A computerized listing of all active drug studies will be maintained. This list contains the name of the investigator, study title, and all drugs associated with that study to include the investigational drug(s), comparator drug(s), rescue drug(s), and any adjunct or background drug(s). (1058.01 June 17, 2015) This list can be electronically searched to ensure that investigators, AO/R&D, IRB, and R&DC can be efficiently and reliably notified of Pharmacy Benefits Management (PBM) Drug Safety Bulletins and National PBM Communication Drug Safety Alerts. The maintenance of this computerized list will be facilitated through the addition of specific requirements on IRB Initial Review, Continuing Review, and Modifications to Approved Research submission forms. Each form will now include a section for investigators to list all investigational, comparator, rescue, and adjunct medications or any changes to existing study regimens.

D. Research Investigators and Study Staff

The **Principal Investigator (PI) or Local Site Investigator (LSI)** certifies that he/she will conduct the study according to applicable laws, regulation, ethical standards and guidelines governing the protection of human research subjects. The Principal Investigator is required to be qualified by training, and assumes ultimate responsibility and oversight for the protocol to conduct research according to sound research design, assures adequate resources are available, selects and oversees trained study staff and delegates duties prospectively and consistent with Scopes of Practice to research team members, assures that VA human research training requirements are met, weighs risk benefits for subjects, implements fair recruitment, responds to subject complaints or requests for information, develops an informed consent process, minimizes risk and develops plans to monitor safety and detect harm, reports safety findings and unanticipated problems, discloses conflicts of interest, adheres to IRB Conditions of Approval, federal, sponsor and organizational policy in order to conduct the study appropriate to human subject protections. Investigators are required to submit complete protocols and relevant study related materials listed in IRB Submission Forms to the IRB for review, including continuing/continuing reviews and status updates as required by the IRB... Investigators have access to HRPP, IRB SOPs and IRB Submission Forms – all of which provide regulatory and organizational guidance and all of which are listed on the Research website. Investigators are not authorized to initiate research, including screening activities until they have received written required written approvals.

All study staff, as required by VA regulations must be credentialed and privileged and have appropriate licensure prior to conducting approved research activities. Study staff must have an approved Scope of Practice in place for each investigator they work under. All Principal Investigators and research staff must have a VA employee appointment (with or without [WOC] compensation status) prior to initiating research activities. Co-investigators communicate with the IRB through the Principal Investigator.

Promptly Reporting Changes in Principal Investigator (PI) or Local Site Investigator (LSI): this means promptly reporting any changes in the PI or LSI to the IRB. Changes in the PI or LSI must be reviewed and approved by the IRB prior to the initiation of the change to ensure the new individual meets the criteria for conditions of approval.

Promptly Reporting Changes in Other Study Staff:

(a) If named in the protocol replacement of study staff represent a change in the protocol. Such a change must be reviewed and approved by the IRB prior to initiation of the change to ensure the new individual meets the criteria for conditions of approval.

(b) If not named in the protocol (e.g. a study coordinator being replaced by another study coordinator) the change does not represent a protocol change and does not require prospective IRB and approval. These types of study personnel changes should be reported promptly to the IRB but no later than at Continuing Review.

Only students and other trainees (including residents and fellows), including VA employees, from schools with an academic affiliation agreement consistent with current VHA policy or that have been appointed to a VA training program that has no external sponsorship (e.g. VA Advanced Fellowship), may serve as investigators within a VA facility, or use data, or human biological specimens that have been collected within VA for clinical, administrative, or research purposes. **NOTE: A waiver may be obtained from the CRADO under special circumstances.**

(1) A VA investigator sufficiently experienced in the area of the trainee's research interest must serve as PI and is responsible for oversight of the research and the trainee. The PI is responsible for ensuring the trainee complies with all applicable local, VA and other Federal requirements.

(2) In conducting the research, the trainee must comply with all VA and other Federal and local institutional requirements, including those related to research, information security, and privacy.

(3) If the trainee does not complete all aspects of the research prior to leaving VA, the VA employee serving as the PI must ensure the protocol is completed or terminated in an orderly fashion, and in accordance with all applicable local, VA, and other Federal requirements.

(4) When the trainee leaves VA, the VA employee serving as the PI is responsible for ensuring all research records are retained by VA.

The IRB generally communicates with external sponsors through the investigator however the IRB is authorized to contact sponsors directly if appropriate to human subject protections. Where applicable (i.e. if the proposed research has significant impact on other NWHCS Services), investigators may be required by the IRB to obtain letters of cooperation from NWHCS Services and top management officials as a condition of approval.

E. Other Medical Center Services

The medical center provides facility management, clinical and administrative support (e.g. medicine, surgery, nursing, lab, radiology, engineering, human resources, material acquisition, information management, E-mail etc.) The R&D Committee and IRB include membership from services critical to the research process. Investigators insert clinical alerts (**CWADs**) in the electronic medical record when applicable to provide information about research subjects to other providers. A CWAD is an electronic medical record research clinical alert that describes the study, study drug, documents the date informed consent was obtained and documents that a copy was given to the subject. The Investigational Pharmacist requires a copy of the CWAD prior to dispensing study drug. **(Note: CWAD is the hospital acronym for C – crisis note, W – clinical warning, A – allergies, D – advanced directive. If you enter any one or combination of these they pop-up in the electronic record in the upper right hand corner to alert other providers who may access the medical record).** The IRB determines if representatives from other medical center services need to be involved with the research

(e.g. to authorize, to review, to provide expertise, to serve as sub-investigators or to serve as medical monitors) in order to maximize human subject protections.

F. Clinical Trials

Clinical trials are a kind of clinical research designed to evaluate and test interventions. Clinical trials are also called interventional studies. Clinical trials are defined at 38 CFR 16.102(b) as research studies in which one or more human subjects are (control) to evaluate the effects of the interventions on biomedical or behavioral health-related Investigational and approved drugs, biologics, and devices used in clinical trials may also be regulated by the FDA.

For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web (38 CFR 16.116(h)), unless the IRB waived documentation of informed consent. The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol. Certain information that should not be made public may be redacted as determined by the Federal department or agency. OHRP has determined that informed consent forms should be posted to either <https://ClinicalTrials.gov> or <https://Regulations.gov> (Docket ID: HHS-OPHS-2018-0021). Paragraph 17j. of VHA Directive 1200.05 specifies which entity is responsible for posting the consent form during the allotted time.

For ORD-funding clinical trials, Principal Investigators are responsible for registering their trials with and submitting summary results to <https://ClinicalTrials.gov>, as a condition of funding. For all other clinical trials supported or conducted at the VA, clinical trials that fall under Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), must also register and report summary results at <https://ClinicalTrials.gov> as specified in the law (https://www.research.va.gov/resources/ord_admin/clinical_trials/).

G. Other Institutions and Multi-Site Research

The NWIHCS IRB cannot serve as the IRB of record for a non-VA institution (**except for DOD, DOE and NPC sites**) without written permission of the Chief Research and Development Officer (CRADO), delegated to the Director, ORPP&E and the ORO Chief Officer and written concurrence from the Office of General Counsel (OGC) in VA Central Office. (VHA Handbook 1058.03 (6)(e))

The NWIHCS IRB is responsible for the protection of the rights and welfare of human research subjects enrolled in research under the IRB's purview. If conducting human research studies involving more than one engaged institution, each institution is responsible for safeguarding the rights and welfare of human subjects entered at his site, and for complying with all applicable local, VA and other Federal requirements. The IRB has the authority to suspend or terminate a project conducted at another site if the IRB is the IRB of Record for the other site. The IRB may agree to function as the IRB of Record for another institution or may utilize another FWA institution's IRB under special circumstances - a written cooperative agreement is required. The agreement should address:

- a. Institutional agreements, if applicable to allow NWIHCS to function as the IRB of Record.

- b. Delineation of duties and responsibilities for research review units and research staff at both FWA institutions.
- c. Responsibilities and relationship of investigators and research staff to IRBs at participating institutions.
- d. How reports of Serious Adverse Events/Unanticipated Events involving risks to subjects from other sites are reported to all participating sites.
- e. The frequency with which communication should occur.
- f. Investigator and research staff credentials.
- g. Provisions for emergency care.
- h. Consideration of the community's mores when research takes place in a different community.

For all studies involving off-site research procedures at other institutions the role of participating institutions, IRBs, and off-site research personnel (including how they communicate with each other) must be provided to the IRB. The IRB evaluates whether adequate plans are in place to minimize potential risks due to lack of communication or misunderstanding of responsibilities between research staff and between institutional oversight bodies. Protocols, consent forms and HIPAA authorizations should clearly separate VA research from non-VA research and the IRB must only approve the VA research.

For a VA multi-site study, (1) not only the PI, but also all LSIs, must obtain such approvals from the relevant local facilities' subcommittees, and other approvals according to the respective applicable local, VA and other Federal requirements, and (2) 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).

H. Regulatory Agencies

The IRB is subject to regulation and inspection by all governmental regulatory agencies (e.g. ORO, FDA, OHRP, VA, GAO).

I. Sponsors

The sponsor is the person or entity who takes responsibility for and initiates a clinical investigation. The sponsor may be a pharmaceutical company, a private or academic organization, or an individual. An investigator-sponsor is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug and/or significant risk device is being administered or dispensed. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor. Only one individual in a study should be designated as a sponsor-investigator. The majority of NWHCS FDA regulated research is sponsored by external organizations. (1) NWHCS requires written assurances from sponsors that research is conducted according to applicable laws and regulations, good clinical practices (GCP) and ethically. (2) Sponsors are required to follow NWHCS and VA CRADA publication policies (i.e. VA and Sponsor have the right to make publicly available the results of their research).

All NWHCS research, including externally sponsored research requires prospective IRB review and approval prior to the conduct of any research activities (including recruitment and screening activities). The IRB and investigator may agree as appropriate, to additional sponsor requirements (e.g. investigational article storage/disposal, special reporting responsibilities, for multi-center studies, use of specific case report forms, etc.).

Externally sponsored research protocols must be conducted under a written organizational agreement(s) (e.g. protocol, contract, grant notification, memorandum of understanding etc.) with the sponsor or funding entity. Research conducted in international settings will include prospective approval of the CRADO, delegated to Dir, ORPP&E, according to VHA Directive 2005-050.

J. International Research

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

All individuals who participate as subjects in research at international sites must be provided appropriate protections that are in accord with those given to research subjects within the U.S., as well as protections considered appropriate by local authority and custom at the international site (38 CFR 16.101(g)). Facility Director certification is required. [Information on the applicability to the European Union General Data Protection Regulation \(EUGDPR\) is pending.](#)

a. **Definition of VA International Research.** VA international research is defined as any VA-approved research conducted at international sites (i.e. not within the U.S., its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research that entails sending such specimens or data out of the U.S. This definition applies regardless of funding source (funded or unfunded) and to research conducted through any mechanism of support including MOUs, CRADAs, grants, contracts, or other agreements.

1. Sending such specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA investigator on sabbatical at an international site) is considered international research. It also includes a VA's serving as a coordinating center for an international research project.

2. International research includes multi-site research involving non-U.S. sites where VA is the study sponsor, a VA investigator is the overall study-wide PI, VA holds the Investigational New Drug (IND), or the VA manages the data collection and the data analyses.

3. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator (i.e., the PI for the study as a whole is not a VA investigator).

4. Before approving international research involving human subjects research, the IRB must ensure that human subjects outside of the U.S. who participate in research projects in which VA is a collaborator receive equivalent protections as research participants inside the U.S. (see OHRP guidance at <http://www.hhs.gov/ohrp/international/index.html>). **NOTE:** The VA medical Facility Director must approve participation in the proposed international research (see guidance at: <http://www.research.va.gov/resources/policies/default.cfm>).

5. All international research must also be approved explicitly in a document signed by the VA medical Facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO.

b. **Multi-Site Research**. Multi-site research is covered under this definition if any of the following apply:

- (1) VA is a sponsor;
- (2) VA functions as the coordinating center;
- (3) VA subcontracts to a foreign site;
- (4) The PI for the total study is a VA investigator; OR::
- (5) The VA investigator is specifically collaborating with an international investigator and the VA investigator sends data or human biological specimens outside the U.S., or receives them from outside the U.S.

NOTE: *This requirement does not apply if VA is only one of the participating sites and the research does not meet the preceding conditions.*

c. **Facility Director Permission.** Permission must be obtained from the Facility Director or designee, prior to initiating any VA-approved international research. This applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including agreements, MOU, Cooperative Research and Development Agreements (CRADA), grants, or contracts. The Facility Director, or designee, will not grant permission for an international research study involving prisoners as research subjects.

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

e. **PI Responsibilities.** In addition to the PI responsibilities delineated elsewhere in this document, the PI is responsible for:

- (1) Obtaining approval from the facility in writing before initiating an international research study.
- (2) Conducting research in compliance with this Handbook, and all other applicable VA and other Federal requirements including those for protecting human subjects, tissue banking, use of databases, Federal criminal laws, and the Standards of Ethical Conduct for Employees of the Executive Branch.

I. Sponsor Contracts - VA Cooperative Research and Development Agreement (CRADA)

Effective March 26, 2008 the Office of Research and Development (ORD) required use of VA Cooperative Research and Development Agreements (CRADAs) to formalize non-governmental Sponsor/VA/NPC research collaborations. Required CRADAs signatories are: (1) the Institutional Official - VA Facility Director, (2) the non-profit research corporation Executive Facility Director (functions as contracts officer), (3) the Investigator and (4) the Sponsor. VA CRADAs include VA required language regarding human subject protections, including data safety monitoring, immediate reporting, informing subjects, survivability of requirement to report, publications, indemnification and payment for subject injury.

VA is required to provide treatment for research related injury (RRI) for all research subjects, sponsors cannot bill subject's insurance companies for RRI but are responsible for costs incurred for treatment of injury reasonably related to subject's study participation, except for negligence or willful misconduct of the subject or protocol administration failure.

Treatment of Research-Related Injuries – Details of VA and sponsor responsibilities

VA has the authority, is required and will provide medical care for research related injury to all research participants except for (1) subject noncompliance, (2) willful misconduct of the subject, or (3) contracted research with an individual or non-VA institution. These policies extend to non-Veteran participants enrolled in VA-approved research projects (inpatient care is contracted for non-Veterans). Necessary medical care will be provided in a VA Medical Center except in situations where the (a) VAMC is unable to provide the specialized care that is required; (b) cost of VAMC care is significantly greater than community care; (c) the subject is a non-Veteran. The Facility Director must provide reasonable reimbursement for emergency treatment in a non-VA facility.

Sponsor cannot bill subject's insurance company for RRI; but is responsible for costs incurred for treatment of injury reasonably related to subject's study participation; except for negligence or willful misconduct of the subject or protocol administration failure. CRADA and ICF address sponsor responsibilities.

VA stipulated and required CRADA language includes an article regarding human subject protections requirements, including safety data reporting requirements that survive study closure and termination of the CRADA. If sponsors request significant changes that alter the intent of a VA approved CRADA template the contract officer submits change requests to the VA Office of General Counsel STAR attorney for review and approval. The Research Non-profit Corporation Executive Facility Director (contracts officer) is required to complete and maintain CITI Human Research Training, regularly attend IRB meetings (non-voting) and ensure that VA CRADAs are consistent with VA and IRB requirements. The contract officer ensures that sponsors do not alter VA required human subject safeguard language incorporated in CRADA model templates. The contract officer reviews recruitment incentives included in CRADAs for appropriateness to human research protection. Incentive payments to VA employees for identifying and/or enrolling subjects are not allowed.

The IRB (not the sponsor) has the authority to determine if a study is approved or disapproved at NWHCS. A sponsor does not have any authority to approve or disapprove studies at NWHCS. If the IRB and a sponsor reach an impasse the sponsor or the IRB/R&D Committee may choose not to conduct or to discontinue studies. In such circumstances the IRB shall assure that provisions for subject safety are appropriate to human subject protections.

J. Reports to ORO Central Office

The Facility Director must report the following research events to ORO as indicated in the following:

(1) **Assurance Changes.** Proposed changes to the facility's Federal-wide Assurance (FWA), or other human research Assurance, must be submitted to ORO prior to submission to OHRP and in accordance with VHA Handbook 1058.03.

(2) **IRB Changes.** The proposed addition or removal of the IRB(s) of record designated in a facility's FWA must be submitted to ORO prior to submission to OHRP and in accordance with VHA Handbook 1058.03. Any change in IRB membership rosters must be reported to ORO in accordance with VHA Handbook 1058.03.

(3) **Substantive MOU Changes.** Any substantive change in an MOU with an affiliate institution or other entity related to the designation of IRB(s) or other human research protection arrangements must be reported to ORO within 5 business days.

K. Research Participant Outreach Program

a. Contact telephone numbers for research study staff and IRB Administrator are incorporated in the consent form. An informational brochure entitled, "Volunteering in Research – Here are some things that you need to know" is available to prospective research participant.

c. The HRPP surveys research participants annually. The survey (see sample survey below) is mailed along with a return addressed stamped envelope. Results of the research participant survey are submitted to the IRB and R&D Committee for review and action as appropriate.

L. ACOS for Research

The Facility Director has delegated authority to the ACOS/Research to implement and to maintain the HRPP. Research cannot be initiated at NWIHCS until the local investigator has obtained written notification that the research can be initiated from the ACOS/Research. This notification occurs only after the research project has been approved by all applicable R&D Committee sub-committees, and after the R&D subcommittees' notification of approvals have been approved by the R&D Committee. The ACOS/Research is also responsible for notifying the investigator of approval after Continuing Review by the Research and Development Committee and sub-committees.

VI. MEMBERSHIP OF THE IRB

A. Committee Composition

The IRB has members and alternates that are appointed in writing by the Facility Director (IRB Chair and members for 3 years and may be re-appointed for 3 year terms indefinitely). Committee composition is reviewed annually according to the following criteria: (1) professional representation, (2) diversity, (3) institutional knowledge, (4) gender representation, (5) voting status, (6) training and background, (7) potential conflicts of interest, (8) if one member's primary concerns are in scientific areas, (9) if one member's primary concerns are in non-scientific areas, (10) if community members are not associated with the VAMC or affiliated university or are not part of the immediate family of a person who is affiliated with the VAMC or affiliated university, (11) if IRB membership is appropriate given the research being reviewed, (12) if membership includes representatives with an interest in or experience with vulnerable populations either as members or ad hoc consultants, (13) if alternate members have appropriate training and backgrounds to serve as replacements, (14) if ad hoc reviewers are utilized when IRB members do not have the expertise necessary to adequately review research, and if (15) the number of IRB meetings and the frequency of meetings are adequate for

the number and types of studies.

The IRB Roster includes members and specific alternates who have comparable qualifications to those of the primary member. The Roster designates if a member is considered a scientist or non-scientist, and if the member is considered affiliated or non-affiliated with NWHCS. The non-scientist members represent the perspective of research participants. The Committee Roster is not updated on an annual basis. The roster is updated when there is a change in membership.

B. Chair

1. Selections and Appointment

The Research and Development Committee recommends the Chair, and the Facility Director appoints the Chair for a three-year term. The Chair must hold a paid VA appointment. The Chair has expert knowledge in human subject protections. The Chair must be a highly regarded and respected leader in order to promote respect for the IRB's advice and counsel throughout the medical center and external to the medical center.

2. Length of Term/Service

The Chair is appointed in 3-year increments and may be reappointed for 3 year terms indefinitely.

3. Duties

The Chair has primary responsibility for conducting Committee business. They direct Committee proceedings in accordance with institutional and federal requirements. The Chair mentors Committee members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are protected. They function as a role model and conducts business fairly and impartially. They are the signatory official for official IRB minutes and official IRB correspondence. They may delegate signing authority to Committee members. The Chair must not simultaneously chair a research sub-committee or the R&D Committee.

4. Annual Performance Evaluation

The ACOS for Research considers the following criteria when evaluating the IRB Chair: (a) knowledge of human research protection regulations and guidelines, is the IRB functioning according to regulations and guidelines, (b) appropriate use of expert consultants; (c) assessments of external reviewers from FDA, OHRP, ORO; (d) compliments and complaints from research participants, investigators, sponsors and others; (e) IRB member turnover; (f) dedication and sincerity to patient advocacy role.

5. Removal

The Chair may be removed by the Research and Development Committee with the concurrence of the Facility Director. The Facility Director is responsible for suspending or terminating membership of any individuals who are not fulfilling their member responsibilities or obligations.

C. The IRB Members

1. Selections and Appointment

The Facility Director is responsible for appointing the IRB Chairperson (or Co-chair, or Chair and Vice Chair) and IRB voting members. Employees who by virtue of their titles of their positions (e.g. ACOS) to serve as ex-officio members are not required to

be appointed by the Facility Director. The Facility Director is responsible for suspending or terminating the IRB membership of any individuals who are not fulfilling their member responsibilities or obligations. The selections are recorded in the R&D Committee minutes. The appointments are officially approved when the Facility Director signs the R&D Committee minutes and members may be reappointed indefinitely. The Facility Director is the final signatory authority for all Research and Development Committee minutes. Members are appointed to a 3-year term and may be reappointed indefinitely. The IRB Membership Roster is updated as required by the IRB Administrator and updates are submitted to OHRP and ORO. RCOs may act as a consultant to the IRB but may not serve as a member (either voting or non-voting) and may attend IRB meetings.

2. Requirements to Be an IRB Member

- a. The IRB must have at least five voting members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution(s) for which it reviews research.
 - (1) The IRB must be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
 - (2) The IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable local, VA and other Federal requirements, and standards of government ethics and professional conduct and practice. therefore include persons knowledgeable in these areasIf an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration must be given to the inclusion of one or more individuals on the IRB who are knowledgeable about and are experienced in working with these subjects. **NOTE: IRBs serving VA should also consider including a Veteran or Veteran's representative.**
- a. Each IRB must include at least one voting member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. Members whose training, background, and occupation are within a behavioral or biomedical research discipline should be considered a scientist, while members whose training, background, and occupation are outside of a behavioral or biomedical research discipline should be considered a nonscientist.
- b. Each IRB must include at least one voting member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. Retired VA employees who are receiving VA retirement benefits are considered affiliated for purposes of VA IRB membership.

NOTE: Veterans who receive their care at the facility, but have never been employed by VA, would not be considered affiliated.

- c. An IRB cannot have a member participate in the IRB's initial or continuing review of any project in which the member has a conflict of interest, except to provide information requested by the IRB.
- d. An IRB may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals are not allowed to be voting members of the IRB.
- e. VA facilities must maintain accurate membership rosters for their designated IRB(s) of Record and submit the roster(s) to ORO as required by VHA Handbook 1058.03. The roster must list IRB members identified by name, earned degrees, representative capacity, indications of experience such as board certifications, licenses, etc., sufficient to describe each member's primary anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution (e.g., full-time employee, part-time employee, member of governing panel or board, paid or unpaid consultant).
- f. VA facility research office staff including, but not limited to, the ACOS/R&D, the AO for R&D, and IRB administrative staff may not serve as voting members of the facility's IRB. They may serve as ex officio, non-voting members or attendees; however, they and the IRB must be sensitive to any potential, actual, apparent, or perceived conflicts of interest and appropriately manage such conflicts.
- g. Research Compliance Officers (RCOs) may act as consultants to the facility's IRB, but may not serve as members of the IRB. RCOs may attend IRB meetings when requested by the IRB or as specified by the IRB's SOPs. RCOs must be aware of and manage any potential, actual, apparent, or perceived conflicts of interest that arise because of their role. **NOTE:** RCOs are further discussed in VHA Handbook 1058.01.
- h. The Privacy Officer (PO) and the Information System Security Officer (ISSO) serve in an advisory capacity to the facility's IRB as either non-voting members or as consultants.
- i. Facility Directors, their administrative staff, COS, other facility senior administrators such as Associate or Assistant Directors or Chief Nurse, and NPC Administrative Staff may observe IRB meetings, but may not serve as members of the facility's IRB.
- j. If alternate members are appointed to the facility's IRB, the IRB's written procedures must describe the appointment and function of alternate members, and the IRB membership roster must identify by name the primary member(s) for whom each alternate member may substitute. The alternate members must have similar member qualification(s) of the primary member they replace.

3. Length of Term/Service

Members serve terms in three-year increments and may be re-appointed. Due to the long learning curve and extensive training requirements the institution strives to keep IRB member turnover at a minimum.

4. Duties

Committee members are responsible for assuring that the rights and welfare of research subjects are protected, that risks are minimized and that benefits outweigh risks. Members vote to approve, require modifications (in order to secure approval) or disapprove submissions. These actions include: (a) initial reviews, (b) continuing reviews, (c) amendments, (d) NWHCS serious adverse events, (e) sponsor serious adverse events (f) unanticipated protocol deviations, (g) advertisements, (h) consent form revisions (i) investigator brochure updates (j) protocol deviations, (k) minutes of previous meetings (l) investigator changes, (m) general policy issues and (n) non-compliance. The Committee has the authority to suspend or terminate an investigator's research privileges if it is determined he/she is non-compliant. Serious or continuing noncompliance is reported to the Research and Development Committee, Facility Director, VA Headquarters, and relevant federal oversight agencies (e.g. FDA, and OHRP, ORO).

5. Attendance Requirements and Training

Members are requested to attend as many meetings as possible and to notify the IRB Coordinator and/or Chair when the cannot attend. An alternate member may only substitute for his/her designated member. The IRB ensures that initial and continuing education requirements for the IRB Chair, IRB members, and IRB alternate members are met.

6. Annual Performance Evaluation

The IRB Chairperson considers the following criteria when evaluating IRB members: (a) thoroughness in reading of IRB meeting material; (b) level of participation in discussion; (c) meeting attendance; (d) does member provide appropriate representation for his/her professional background; (e) knowledge of human research protection regulations and guidelines; (f) dedication and sincerity to patient advocacy role.

7. Removal

The Research and Development Committee may remove members with the concurrence of the Facility Director. The Facility Director is responsible for suspending or terminating membership of any individuals who are not fulfilling their member responsibilities or obligations.

D. Requirements for Research Involving Prisoners (Sub-Part C)

The NWHCS IRB rarely reviews research involving prisoners. In order to consider research involving prisoners the IRB must, (a) have a majority of its members not otherwise associated with the prison, (b) include a prisoner or prisoner advocate who can adequately represent the interests of prisoners unless the research has already been reviewed by an IRB that included a prisoner advocate. VA CRADO approval is required in addition to IRB Approval for research involving prisoners.

It is more often that a "prisoner review" is required for a subject who becomes incarcerated during an ongoing protocol and the continuation of that subject is either important for the study outcome or for the health of the subject.

E. Use of Individuals with Special Expertise

The IRB and/or R&D Committee is authorized and required to enlist services of expert reviewers when additional expertise is necessary for appropriate scientific review of human research protocols without requiring any other institutional approvals. Both Committees have a membership with expert knowledge and skills that enable them to ascertain if additional expertise is necessary. The expert reviewers submit written evaluations and may attend IRB meetings, however are not authorized to vote. The IRB is authorized to compensate ad hoc expert reviewers as appropriate. IRB minutes document utilization of ad hoc expert reviews. Conflict of Interest policies apply to expert reviewers, and disclosures must be submitted for review. In general, if members cannot identify an established expert the appropriate Division Chiefs at NWHCS or affiliate medical schools will be contacted and asked to identify expert reviewers with the appropriate expertise. When an expert consultant review is required, the agenda item to be reviewed will be labeled pending review by the expert consultant.

The IRB encourages the facility Research Compliance Officers to attend meetings and serve as non-voting consultants. The IRB reserves the right to invite the VISN RCO, if applicable, as a consultant if VISN issues arise.

F. Audits

The Facility Director is responsible for ensuring appropriate auditing of local human subjects research studies to assess compliance with all applicable local, VA, and other Federal requirements including, but not limited to, ORO requirements and in accordance with VHA Handbook 1058.01. The IRB accepts RCO audits to fulfill auditing requirements. The IRB may request the RCO (or other appropriate auditors) to conduct more focused audits of one or more aspects of the study. The criteria used to increase the frequency of audits or to audit focused aspects of the study would be related to study specific issues. (e.g. involvement of vulnerable populations, level of risks, experience of study staff, involvement of FDA approved articles for which there has been a new safety warning issued or for which there is limited human use, or change in the labeling that indicates increased risks, issues of noncompliance, unanticipated problems involving risk to subjects or others, privacy/information security, need verification from non-study staff of study team practices).

Findings of RCO audits are reported to the IRB as required by ORO. The reporting time frame varies depending on the nature of the findings. For example, if it involves apparent serious or continuing non-compliance it is reported within 5 business days. If it involves non-serious, non-continuing, non-compliance it is reported promptly. The IRB reviews actions taken and ensures that corrective actions are implemented and completed as appropriate.

VII. MANAGEMENT OF THE IRB

A. Compensation of IRB Members

IRB community members are compensated by NEBRA to attend IRB meetings. The IRB meets second Thursday of the month (with exceptions for holidays, weather, etc.) and meetings last approximately three hours.

B. Liability Coverage for IRB Members

IRB members, including the unaffiliated member are officially carrying out the VA mission and are protected from liability under the US Torts. All IRB members have official VA appointments approved by a Human Resources Management Service, NWIHCS. Clarification - the IRB Unaffiliated Members must have a WOC appointment to provide liability coverage for their IRB work related activities and therefore, are still considered unaffiliated with the institution.

C. IRB Administrative Support Staff

The organization employs one full time IRB Administrator, one full time Assistant Coordinator and one part-time Administrative Assistant devoted exclusively to support IRB activities. Their tour of duty is 8:00AM until 4:30PM and they are available to assist HRPP personnel as needed. Additional staff support from the Research Service is provided as needed, and to conduct quality assurance activities.

1. IRB Administrator Duties:

- (a) Directing and overseeing all IRB support functions and operations
- (b) Training, supervising and evaluating IRB Staff
- (c) Developing and implementing procedures to effect efficient document flow maintenance of all IRB records
- (d) Maintain the official roster of IRB members
- (e) Schedule IRB meetings
- (f) Oversee the distribution of pre-meeting materials
- (g) Prepare minutes of IRB meetings
- (h) Prepare and distribute IRB Action Letters to investigators
- (i) Report changes in IRB membership to OHRP and ORO
- (j) Maintain IRB documentation and records in accordance with regulatory requirements
- (k) Assist new IRB members with orientation and training
- (l) Facilitate communication between investigators and the IRB
- (m) Maintain the database of IRB records
- (n) Serve as a resource for study staff on general regulatory information, and provide guidance about forms and submission procedures
- (o) Train investigators and research staff
- (p) Maintain training documentations and reference materials related to human subject protection requirements.
- (q) Drafting reports to the IRB, R&D, ACOS and other HRPP members
- (r) Assist in evaluation, audit, and monitoring of human subject research as directed by the IRB, the R&D Committee, or the ACOS for Research in order to improve performance
- (s) Keep manuals and SOP's up to date
- (t) Assist with Accreditation Visits and sponsor monitoring visits
- (u) Coordinate and assist during regulatory inspections and site visits
- (v) Copying study materials for distribution to IRB members

D. IRB Member Information on File

The IRB Administrator maintains information files for all IRB members. These files are

stored in paper form in the IRB office and are electronically maintained in the MIRB database.

- (1) Name.
- (2) Earned degrees.
- (3) Representative capacity (e.g. physician, non-scientist, ethicist, community member).
- (4) Indications of experience, such as board certifications, licensures, certifications, etc.
- (5) For community members, past or present association with the VA (including academic affiliates).
- (6) For community members, confirmation that no part of the community member's immediate family is affiliated in the past or in the present with the VA or its academic affiliates.
- (7) Documentation of the voting status of each member.
- (8) Documentation of alternate status.
- (9) Committee member appointment letters

E. Training of IRB Members, Investigators, and other HRPP Staff

Human research training for IRB members, investigators and research staff is specified by VA and is required.

1. Orientation - IRB members receive comprehensive reference materials including VA [38 CFR 16,17], VA [VHA Handbook 1200.05], FDA [21 CFR 50,56], DHHS [45 CFR 46], the 2006 FDA Information Sheets, the Institutional Review Board Guidebook (DHHS), The Belmont Report, the NWHCS HRPP, and the NWHCS IRB Standard Operating Procedures. Human research subject training for research staff is implemented in accordance with VA requirements.

2. IRB Member Training – In addition to required training the NWHCS HRPP, IRB Standard Operating Procedures and “Protecting Study Volunteers in Research” by Cynthia Dunn, M.D. and Gary Chadwick, Pharm.D. (Note: this reference book includes HHS and FDA regulations governing human research are provided to IRB members. Members are encouraged to independently seek out training opportunities and to discuss complex scientific and ethical issues with each other (e.g. The IRB Forum).

3. New Member Training - Individual training is conducted by experienced IRB members the Research Compliance Officer and the IRB Administrator. Codes of federal regulations, The Belmont Report, the Initial Review Submission Form, the Submission Form and the Consent Form Template are key review tools that are used to discuss scientific and ethical review. A member is considered an “experienced” IRB member after having attended 26 convened IRB meetings.

4. Required Training, Continuing Education

- a. All individuals regardless of employment or pay status involved in conducting VA human research including anyone who has contact with subjects or reviews research involving human subjects (i.e. investigators, study coordinators, research assistants, trainees, ACOS/R, AO/R, IRB staff, IRB and R&D voting members, ex-officio and non-voting members and members of other research committees that review research involving human subjects) are required to successfully complete training in ethical principles on which

human research is to be conducted. Training modules on accepted good clinical practices are available through the CITI program, but not required. All other applicable VA and VHA training requirements (i.e. privacy and information security training) at the local and national level must be met. Training must be completed before anyone conducts human subject research. **REQUIRED** - Collaborative Institutional Training Initiative (CITI) or approved ORD alternatives are required. (<http://www.citiprogram.org>) Research Service will accept the completion of the CITI group called "VA Only." Investigator/study staff based at the university affiliate must log in to CITI, affiliate themselves with VA and complete required human research training.

- b. Research study staff conducting human research are **REQUIRED** to also complete NIH Conflict of Interest Training once. (<http://grants.nih.gov/grants/policy/coi/index.htm>)
- c. Training must be updated every 3 years thereafter.
- d. At Initial Review, the IRB reviews human research training status of study staff. Study staff forward certificates to the IRB office to document training. Training documentation is filed, tracked and followed up on by IRB/R&D staff.
- e. ORD Training Website – <http://www.research.va.gov/pride/training/default.cfm>

5. Principal Investigator Training - Submit proof to the IRB that required human research training is completed. Study cannot commence until Principal Investigator completes required training. In addition to mandatory training, research educational and submission materials are available in the Education Apple under Research on the computer desktop. Other material including, "Protecting Study Volunteers in Research" by Cynthia Dunn, M.D. and Gary Chadwick, PharmD (Note: includes HHS and FDA regulations governing human research) are available in the IRB Office. Two investigators have successfully completed ACRP requirements and are Certified Clinical Research Investigators. All investigators are encouraged to complete investigator certification and complete Good Clinical Practices training (e.g. the ACRP or AAPP GCP training courses). Under certain circumstances the IRB and/or the R&D Committees may require an investigator to attend GCP training. Review of research qualifications of research staff are conducted at Initial Review and Continuing Review.

6. Coordinator, Sub-Investigators and Other Human Research Staff Training - Submit proof to the IRB that required human research training is completed. Study cannot commence until sub-investigators and other human research staff complete required training.

7. Monitoring of Training

- Research Service maintains training logs, ISO and PO provide research service with a list of research employees whose privacy or information security is overdue. Research Service follows up.
- CITI training must be completed by study staff prior to conducting research activities and renewed as required.
- Research staff track training and ensure annual updates are completed. Scopes of Practice additions/deletions are tracked weekly. 
- Training logs are maintained.
- E-mail reminders are sent by NWIHCS Research Staff to human research study staff in advance of the CITI training expiration date and follow-up reminders are initiated as the expiration date draws near.
- Non-responders and those whose training has expired are contacted by IRB Administrator and as appropriate by higher levels of supervisors (e.g.

AO/Research, ACOS/Research).

- Study staff who do not complete required human research training are reported to the IRB/R&D for additional action as warranted.

8. HRPP Strategies to Disseminate New Information - **New** information, training opportunities, new and/or revised HRPP/IRB SOP policies and procedure, submission forms and templates are disseminated to IRB members and research staff in multiple ways and are available in the Education Apple under Research on the computer desktop. The IRB Administrator is responsible for e-mail groups for IRB members, IRB alternate members, Investigators, HRPP Officials and Research Coordinators/Assistants have been established and are maintained by the IRB Administrator. New information may be forwarded via Outlook with “read confirmation” as appropriate and documentation in minutes as necessary. As appropriate, hard copies of information may also be forwarded to members of the mail groups. Research Investigator/Coordinator meetings are held regularly throughout the year – attendance records and minutes are maintained. Changes in procedures and requirements are discussed.

9. The Research Service Library - Contains regulatory, instructional and reference materials from multiple sources. Much of the material is available on-line at R&D, ORO, OHRP and FDA websites. Key laws and references are:

DHHS

- 45 CFR Part 46 (HHS) Revised November 13, 2001 Effective 12/13/ 2001
Sub-Part A (Basic HHS Policy for Protection of Human Research)
Sub-Part B (Additional Protections for Pregnant Women, Human Fetuses and Neonates in Research)
Sub-Part C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects)
Sub-Part D (Additional Protections for Children Involved as Subjects in Research)

FDA

- 21 CFR Part 50 (Protection of Human Subjects) (FDA)
Part 56 (Institutional Review Boards)
Part 312 (Investigational New Drug Application)
Part 600 (Biological Products: General)
Part 812 (Investigational Device Exemption)
- FDA 2006 Information Sheets

VA

- 38 CFR Part 16-17 (Department of Veterans Affairs)
VHA Handbook 1200.05 05/02/2012 (VA Manual Requirements for The Protection of Human Subjects in Research)
- ORD Website (includes HIPAA guidance)
- NWHCS Guidebook for Investigators and Coordinators
- ORO Web Site (includes regulatory guidance and best practices information)

STATE LAWS

- Virginia Human Research Law Chapter 5.1 Virginia Statute 32.1-162.20
- Virginia laws for disease reporting at 12 VAC 5-90-80 and 12 VAC 5-90-90 Section 32.1-36
- Virginia privacy laws regarding patient health record privacy at 32.1-127.1:03
- Virginia laws regarding genetic information testing at 38.2-508.4

- Virginia laws regarding child abuse at 18.2-371.1
- Virginia laws regarding elder abuse at 31.1-55.3

F. Credentialing and Privileging

All VA research staff must be employees if conducting human research (exempt or non-exempt). Care providers (MD, DNP, RN, etc...) must be credentialed and privileged (if applicable) as required by current local, state, VHA and ORD requirements. Research staff (including volunteers) may only perform those activities in a research study for which they have the relevant:

a. **Credentials.** Each member of the research staff who is a provider must be appropriately credentialed, except individuals providing secretarial support who should undergo the Human Resource Management (HRM) process for administrative personnel.

b. Privileges

(1) If the local facility where the research is to be performed requires privileging to perform a given duty (e.g., a procedure) in the clinical setting, the individual must be privileged at that facility to perform the duty before the individual can perform that duty in the research setting.

(2) If the local VA facility requires privileging to perform a given procedure, it is not sufficient for only the supervisor of the person performing the research procedure to be privileged for that procedure. The person performing the research procedure must be privileged for the procedure.

c. **Research Scope of Practice or Functional Statement.** Each member of the research team must have a research scope of practice statement that has been approved by the individual's immediate supervisor and the ACOS for R&D, and that defines the duties the person is allowed to perform for research purposes. A research scope of practice statement must be developed for all research personnel (clinical and non-clinical). The research scope of practice statement must be consistent with the occupational category under which the individual was hired, and it must not include any duties for which the individual is not qualified. Current scopes of practice for all research personnel must be retained by the Research Office.

NOTE: A duty (e.g., a procedure) cannot be added to a scope of practice statement unless the individual meets all criteria to perform the duty in the clinical setting (e.g., the individual must be privileged for a procedure if privileging is required for that procedure in the local clinical setting).

(1) If research personnel are involved in more than one study, the research scope of practice statement may be written to cover multiple studies (i.e., personnel do not need a research scope of practice statement for each protocol but they do need one for each investigator for whom they conduct study activities).

(2) Licensed independent practitioners will have a scope of practice for research in addition to a copy of their clinical privileges.

d. **License, Registration, and Certification.** The employee must have all required licenses, registrations, or certifications to perform a given procedure, intervention, or other activity in the research setting and practice only within the scope allowed by such licenses, registrations, or certifications.

G. Use of Expert Consultants

The IRB is required to enlist services of ad hoc expert reviewers when additional expertise is necessary for in depth scientific and/or ethical review of human research protocols. IRB can obtain this review and authorize payment for such review as appropriate without requiring any other institutional approvals. The IRB has a membership with expert knowledge and skills that enable them to ascertain if additional expertise is necessary. Investigators also may submit external reviews of their protocols. The ad hoc expert reviewers submit written evaluations and may attend IRB meetings, however are not authorized to vote. The IRB is authorized to compensate ad hoc expert reviewers as appropriate. IRB minutes document utilization of ad hoc expert reviews. Conflict of Interest policies apply to expert reviewers, and disclosures must be submitted for review. In general, if members cannot identify an established expert the appropriate Division Chiefs at NWIHCS and [name of affiliate if appropriate] will be contacted and asked to identify expert reviewers with the appropriate expertise. When an expert consultant review is required, the agenda item to be reviewed will be deferred pending review by the expert consultant.

H. Conflict of Interest in Research

INTRODUCTION:

Conflicts of interest arise in situations where one party owes a duty of loyalty to another or may compromise, or have the appearance of compromising, professional judgment in the design, conduct, oversight or reporting of research. Researchers and members of committees who oversee research are required to disclose potential conflicts of interest. It is the policy of NWIHCS to insure balance, independence, objectivity and scientific rigor in all peer reviewed research activities conducted under the auspices of this institution. This institution's main obligation is first and foremost to protect the rights and welfare of research subjects.

The Standards of Ethical Conduct for Executive Branch Employees apply to all VA employees, including those involved with the conduct or oversight of research activities under the auspices of this institution's Human Research Protection Program.

Like all VA employees, VHA employees conducting VA research approved by the Research and Development Committee, must comply with the Federal criminal code and the Standards of Ethical Conduct for Executive Branch Employees. The obligation to follow applicable ethics laws and regulations also applies to without compensation (WOC) employees and student trainee's conducting VA research.

Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In research, a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings.

Definitions:

AFFECT THE FINANCIAL INTEREST – Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE – An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD – A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21 and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER – An entity with which you serve as officer, Facility Director, trustee, general partner, or employee.

Responsible Official:

The Conflict of Interest Officer is the institutional official responsible for reviewing potential conflicts of interest in research and is appointed by the Facility Director. The Conflict of Interest Officer (CIO) reviews and evaluates investigator disclosures in consultation with the ACOS/R, R&DC Chairperson, and/or the Office of General Counsel when necessary. Recommendations are submitted to the R&D Committee and/or relevant Subcommittees to minimize conflicts and to manage associated risks. The R&DC and/or relevant sub-committees make the final determination.

INVESTIGATOR CONFLICT OF INTEREST

Who must complete a “Research Financial Conflict of Interest Statement”?

The duties and responsibilities of a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), Local Site Investigator, study chair or site principal investigator (hereinafter “Investigators”) require them to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. The Conflict of Interest Statement must be filed prior to Initial Review of a study protocol, Continuing Review of a study protocol and, prior to being added to a study protocol.

Conflicts of interest arising from a significant financial interest and significant other potential conflicts of interest must be reviewed and a management strategy must be fully developed and in place prior to approval and initiation of the research or expenditure of funds. Non-compliance with management plans adopted in accordance with conflict of interest rules may result in suspension or termination of the study or of research privileges.

“Research Financial Conflict of Interest Statement” Disclosures:

1. INCOME AND COMPENSATION. Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?

2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, Facility Director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected by this study? B. Covered Relationships: Could this study affect the

financial interest of you, your spouse, close relative, household member or general partner? C. Relationships in the Past Year: Have you, within the last year, served as an officer, Facility Director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study? D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?

3. INTELLECTUAL PROPERTY. With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?

4. NON-PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?

5. SPECIFIC TYPES OF COMMERCIAL INTERESTS. A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? Note: This does not include stock controlled through a diversified mutual fund or a blind trust. B. Sector Mutual Funds: Do you, your spouse, or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States.

Other conflicts of interest include but are not limited to:

Duties of loyalty to peers;
Appointments;
Promotions;
Tenure;
Grants;
Supervisory Relationships;
Publications as they relate to the above.

R&DC/Subcommittee Considerations for Investigator Conflict of Interest:

- Considers the COI report and recommendation and evaluates the potential impact on the research project.
- Considers if conflicts are real (i.e. would change behavior and require a management strategy) or apparent (i.e. would not change behavior but may still need to be disclosed and/or managed in order to preserve the public trust);
- Considers if the conflict could result in coercion and undue influence that could impact safety and data integrity;
- Considers if potential for harm to subjects or others exist that may result in the need for additional protections to minimize risk;

The R&DC/Subcommittees make determinations and approve a conflict of interest management strategy that minimizes risks as applicable. In making this determination, they consider the nature of the research, the magnitude of the interest and the degree to which the conflict is related to the research, the extent to which the interest could be directly and substantially affected by the research, and if there is potential for harm to research subjects or others and/or if there is a potential for risk to the integrity of research data.

Management Strategies for Investigator Conflict of Interest:

- Do not participate in the study;
- Divestiture of significant financial interests;
- Reduction of the financial interest;
- Separation of responsibilities for financial decisions and research decisions. Investigators holding a significant financial interest cannot as a management strategy delegate the conduct of research to trainees or other employees over whom the investigator has direct supervision;
- Disqualification from participation in the portion of the research that would be affected by significant financial interests;
- Modification of the research plan or of the role(s) of particular research staff (e.g. designation of the person who seeks consent);
- Monitoring of research by independent reviewers;
- Severance of relationships that create conflicts;
- Public disclosure and/or disclosure in consent forms of significant financial interests.

R&DC/SUB-COMMITTEE MEMBERS CONFLICT OF INTEREST

Individuals responsible for review of research must disclose any potential, actual, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research and must also comply with all applicable VA and other Federal requirements regarding conflict of interest.

Committee members are expected to disclose all potential conflicts that would be perceived by a reasonable outsider as a conflict of interest. For example:

1. Member or family member is involved in research under review;
2. Member is reviewing a protocol of their supervisors or employees;
3. Possible impact of decisions on members own work;
4. Personal or professional agendas (e.g. publications, promotions).

Management Strategies for R&DC/Subcommittee Members Conflict of Interest:

Committee members holding a financial interest or other conflict of interest as defined above must disclose this interest for each project being reviewed, not vote, and recuse themselves from the meeting. This COI policy applies to all types of events reviewed. Members of the R&DC/sub-committee are reminded at the beginning of convened meetings to recuse themselves if they have a conflict.

Recusal means that the member is present at the convened meeting, declares a Conflict of Interest, leaves the room, does not participate in final deliberations, does not vote, and cannot be counted toward a quorum. If a quorum is lost, review of the project will be deferred until such time that a quorum exists. Recusal is recorded in R&DC/sub-committee minutes and R&D

minutes for each project. The member recused is identified by name in correspondence to the investigator.

If members request an ad hoc review, the ad hoc expert reviewers must submit the Research Financial Conflict of Interest Statement to the Conflict of Interest Officer and R&DC/sub-committee prior to ad hoc expert review. If there are potential conflicts of interest, the reviewer will not be used.

INSTITUTIONAL CONFLICTS OF INTEREST

Top management, R&DC/sub-committee members, investigators and study staff are made aware of existing policies and of potential for conflicts of interest in their own activities.

Examples of potential institutional conflicts may include:

1. Pressure or desire to protect the institution at the expense of protecting subjects;
2. Pressure or desire to protect investigators or employees at the expense of protecting subjects;
3. Non-disclosure of serious non-compliance to avoid potential liability;
4. Institutional or community values which undermine subject protections;
5. Pressure for speedy reviews;
6. Financial pressures;
7. Pressures from research sponsors (e.g. excessive enrollment incentives)

Mechanisms to identify potential institutional conflicts include:

1. Annual independent financial audit of NEBRA ;
2. Reporting and complaint procedures;
3. Observations from institutional officials;
4. Reports from research subjects;
5. Reports of oversight agencies and accreditation surveys;

Mechanisms in place to manage institutional conflicts include:

1. Training programs for all research personnel, R&DC/subcommittee members, and institutional officials;
2. Policies and procedures insure that appropriate firewalls and internal controls are in place to protect the R&DC/subcommittees from institutional or other hierarchical types of influence;
3. Annual review of policies and procedures include consideration of conflict of interest. As conflicts are identified policies and procedures will be revised to minimize and manage such conflicts;
4. Wherever there is the appearance of institutional conflict of interest, our policy is that the studies should preferably be conducted elsewhere. Where this is not feasible, outside observers with no connection to NWIHCS, NEBRA, or the study sponsor may be engaged to oversee the human subject protection process.
5. Whenever a member of the review unit feels he/she has been subject to undue influence, or the attempt at the same, the episode should be reported to the R&DC/subcommittee, which will determine appropriate action, designate officials to investigate, and take corrective action as appropriate.
6. Institutional conflicts that cannot be managed locally are referred to the VISN Director for review

I. Research Conflict of Interest Statement

NW|HCS uses the Research Conflict of Interest Statement approved by the VA Office of Technology Transfer (OGE Form 450 Alternative VA) as required by VA.

VIII. IRB RECORD KEEPING & REQUIRED DOCUMENTATION

[21 CFR 56.108(a-b) and 56.115(a)(6), 38 CFR 16.103(a-b), 16.108, 45 CFR 46.103(b)(4) and 46.103(b)(5) and 46.108] FDA (21 CFR), VA (38 CFR) and DHHS (45 CFR) require that an Institutional Review Board (IRB) operate according to written Standard Operating Procedures (SOPs) to ensure protection of the rights and welfare of individuals involved as subjects of research. There is significant overlap between FDA, DHHS and VA guidelines which at times are addressed individually in these SOPs. The requirements do not differ significantly. **Records will be maintained according to VA Directive 6300 and Record Control Schedule (DAA-0015-2015-0004).**

A. IRB Membership Roster

The IRB membership roster includes member names, alternate names, specialty and VAMC relationship. Individuals with cultural diversity, knowledge of community values, experience with vulnerable populations, medical expertise, and who are respected by their colleagues are represented in Committee membership. The R&D Committee conducts the IRB membership review annually and old and new rosters are maintained.

B. IRB Agenda and Minutes

The IRB agenda is prepared for each IRB meeting as submitted items are added to the database. Common agenda categories include the following:

- Conflict of Interest Disclosure Reminder - Members
- Minutes
- Old Business
- New Business
- Quality Improvement
- Compliance
- Education
- Review of Non-Scripted Changes
- Initial Review
- Previously Tabled Protocol (Initial)
- Continuing Review
- Study Closure
- Dissemination of Study Results
- Consent Form Revision
- PI Change
- Notification
- Protocol Deviations
- Advertisement
- Amendments
- Investigator Brochures Update
- NWIHCS Serious Adverse Events

- Safety Supplements Update
- Notification of National Pharmacy Benefits Management (PBM) Bulletins and Communication Drug Safety Alerts

Agendas are filed in the IRB office and Minutes in the R&D Office.

For each reviewed protocol item, the agenda documents:

ITEMS REVIEWED:(Items submitted for review will vary based on the study design and action reviewed) * *Common examples:*

- VA Form 9012 (Investigation Drug Information Record)
- FDA Form 1572, FDA IND#, IDE#, HDE#, 510K#
- Conflict of Interest Disclosure
- Protocol
- Investigator’s Brochure and Package Insert
- Correspondence from investigator and sponsor
- Research staff credentials and scopes of duty
- Consent Form
- Project Data Sheet
- Questionnaires, Surveys, Research Participant diaries, data collection instruments
- Literature reviews
- Requests for Exemption from IRB review (101)
- Requests for Waiver or Alterations of informed consent (116)
- Requests for Waiver of Documentation of informed consent (117)
- Significant and Non-significant risk device determination
- Summary of IRB discussions/IRB Analysis Checklist
- Completed IRB Submission Forms (Initial, Continuing, Amendment, SAE)

C. IRB Minutes

Minutes are required to document relevant discussion of the above reviewed items and to document the actions of the IRB. Minutes are required to include, separate deliberations for each action; votes for each protocol as numbers for, against, or abstaining; the names of IRB members who left the meeting (recusal) because of a conflicting interest along with the fact that a conflicting interest is the reason for the absence; attendance of members or alternate members including those who participated through videoconferences or teleconference, and documentation that those members received all pertinent material before the meeting and were able to actively and equally participate in all discussions.

Required actions include:

- Minutes/IRB Documentation are required to document that regulatory criteria for IRB approval are considered (46.111, 56.111, 38.111).
- Voting decisions including scripted and non-scripted conditional approvals; tabling; disapprovals;
- maintenance of a quorum;
- alternate members and who they are substituting for;
- recusals for conflicts of interest;
- the basis for waiver of the requirement for IRB review (exemption - pre-2018 Rule- 3838 CFR 16.101b1-6; 2018 Rule- 38 CFR 16.104(d)(1-8));
- the basis for requiring modifications in research (amendments);
- the basis for disapproving or suspending/terminating research;
- rationale for significant risk/non-significant risk device determination and subsequent approval or disapproval decisions;

- justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the informed consent document;
- rationale for conducting continuing review of research that otherwise would not require continuing review;
- determinations required by the regulations and protocol-specific findings justifying those determinations for waiver or alteration of the consent process (46.116d 1-4) and for waiver of the requirement to obtain a signed consent form (46.117c);
- the degree of risk,
- the approval period appropriate to the degree of risk,
- IRB determinations regarding payments to subjects,
- use of vulnerable populations,
- use of non-Veterans as participants,
- specimen banking,
- if medical records need to be flagged,
- and determinations relevant to 5 day reporting requirements.
- IRB minutes document that Waiver of HIPAA authorization is met.

Meeting minutes document discussion of: (1) controverted issues and their resolution, (2) risk and potential benefit analysis, (3) informed consent process, (4) documentation of informed consent, (5) risk evaluation/assessment and safeguards for physical, psychological, social/legal, economic, privacy and confidentiality risks including measures to protect SSNs when real SSNs, scrambled SSNs, or the last four digits of SSNs will be used in the study, (Note: special precautions to protect SSNs does not apply if the only use of SSNs is on the informed consent form or the HIPAA Authorization) (6) subject selection including justification for use of non-Veterans (7) need for DSMB or other data safety monitoring, (8) use of vulnerable subjects and additional safeguards, (9) approval of use of waiver or alteration of the HIPAA Authorization, (10) Protocol deviations - (a) are evaluated to determine whether they represented non-compliance and (b) whether non-compliance was serious or continuing and (c) IRB management of non-serious or non-continuing non-compliance, (11) Unanticipated Problems –IRB decisions whether an event was an unanticipated problem involving risks to subjects and others. In the circumstance should research participants include children or prisoners, appropriate documentation of the required special membership quorum, protocol specific findings required by VA policy (VHA Handbook 1200.5 Paragraphs 19, 20, 21) and applicable regulations (Prisoners 45CFR Part 46 Subpart C Pregnant Women 45CFR Part 46 Subpart B and Children 45CFR Part 46 Subpart D) will be documented in IRB minutes. Minutes are prepared for each IRB meeting. Minutes of the previous meeting minutes are reviewed and approved at a future meeting unless deferred for specific reasons. Minutes also reflect final approval of minor stipulations and the name of the IRB member or qualified staff assigned for final review with authority to issue final approval. Once approved by the members at a subsequent IRB meeting, IRB minutes may not be altered by anyone including higher authority. All IRB minutes are reviewed by the R&DC.

D. Maintenance/Retention of Submitted Documents and Correspondence

The IRB requires that a complete set of all materials relevant to review of the research including R&DC correspondence and correspondence to researchers regarding IRB actions be maintained in study files. The IRB records include for each protocol's initial and continuing review, the frequency for the next continuing review (as applicable). The IRB and investigators will keep study records in accordance with VA policy, and as required by the protocol, federal and state laws. CV's and training records for study staff are located in the R&D office in a secure filing cabinet until they are indexed and archived at the approved long-term storage facility designated by the research office. CV's and training records for

IRB members are maintained in the IRB Administrator's office in a secure filing cabinet until they are indexed and archived at the approved long-term storage facility designated by the research office. All records must be maintained in a VA secure environment.

The original IRB Approved Consent Form is stamped and provided to the investigator and a copy is filed. The IRB requires that the stamped version of the consent form be used to consent subjects. If the investigator leaves the VA facility the original research records must be retained at the institution and archived.

E. Access to IRB Records

All IRB records are kept in secured locked areas and may be accessed by authorized individuals and entities on a need to know basis. Access to IRB records is limited to the ACOS and AO for Research, the IRB Chairperson and members, IRB Administrator and office staff, authorized VA representatives (e.g. Research Compliance Officers, Privacy Officers, Information Security Officers), and officials of the Federal and State regulatory agencies, including the Office of Research Oversight, the OHRP, the FDA, DoD as relevant, and other accrediting agencies.

Should researchers or their study staff need to review IRB files, the IRB staff will pull what is requested and provide a copy to the requestor. In the unlikely situation that an investigator and/or their research staff request permission to review their IRB record folders this may be done ONLY in the full-time presence of an IRB staff person.

All other access to IRB records is limited to those who have legitimate need for them as determined by the Facility Director, the R&D Committee, VA Central Office or if required to do so by law.

Employees, contractors, volunteers, students, and others will protect information contained on printouts and other media by keeping VA sensitive information in locked files or cabinets when not in use. Research Service works with the ISO and PO and ensures privacy and information security training is completed for all staff.

Logical access controls are employed to permit only authorized access to VA computer systems and restrict users to authorized transactions, functions, and information. Research Service authorizes and monitors access to shared drives for research studies. Research Service shared drives are configured to restrict access to only appropriate staff.

Research Service uses recycle bins for disposal of VA Sensitive Information. Use of shredders is not authorized by Research Service.

F. Long Term Record Retention

The IRB and investigators will keep a complete set of all research study records. The IRB and investigators will keep study records in accordance with VA policy (Record Control Schedule DAA-0015-2015-0004) and as required by the protocol, federal and state law. If the investigator leaves NWHCS the research study records (electronic and/or paper) remain at NWHCS.

Research records are stored in secure research locations within the medical center and at a VHA approved professional off-site storage facility. Currently, research records are boxed, labeled and sent to the storage facility (Business Associate Agreement on file). A

“Certificate of Destruction” will be issued by the record storage facility and filed in the IRB office. All Research records must be made accessible for review and copying by authorized officials of oversight agencies (e.g. FDA, OHRP, ORO).

Record Storage and Destruction Policy

Purpose: Research Service at NWHCS follows the VA Record Retention Policy for the storage and destruction of research records (subject and regulatory documents).

Transferring of Records

If an investigator leaves the VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the investigator leaves one VA facility to go to another 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 ACOS/R, PO, ISO, RCOs, and research sponsor. *(Note: The investigator is not the grantee, nor does the investigator own the data)*

G. NWHCS IRB Data Management System

The IRB utilizes a sophisticated electronic management system to record and track IRB, R&D, IACUC, and SRS actions. The system records and tracks all committee review items, events, discussion, votes, and correspondence. The ACOS/Research and the AO control access to and authorizes use of the IRB data management system.

H. Education and Training Records

Education and training records are maintained by the Research Administrative Office.

I. Communications to and from the IRB

Formal communications from the IRB are written and all determinations are conveyed in writing. Copies are filed in the IRB’s investigator project file and are maintained in an electronic database. The Chair or designee assigns and authorizes the use of a signature stamp to individuals composing the IRB minutes and correspondences to investigator.

IX. FUNCTIONS and OPERATIONS OF THE IRB

A. What Requires Review by the IRB?

If there is any element of research in any activity involving human subjects, the activity (including screening procedures and subject recruitment) must have a NWIHCS staff member be either the Principal Investigator (PI) or a Local Site Investigator (LSI) for that study and undergo IRB review before it can start. No study can be initiated until a determination by an appropriate **authority** that the study does not constitute human subjects research, is exempt or has satisfied all requirements for approval and has received approval by the convened IRB or expedited reviewer (when appropriate). Activities considered research involving human subjects must meet the definitions of research and human subject as defined in VA, DHHS or FDA regulations. The IRB makes determinations if studies meet the regulatory definitions of human research. The criteria that the IRB uses to make determinations are listed in IRB SOP under the Section entitled, "VA, DHHS and FDA DEFINITIONS - IS ACTIVITY SUBJECT TO THE HRPP?" If an investigator is unsure whether IRB review is required he or she is request a determination. VA does not allow classified research (e.g. classified government research for Central Intelligence Agency) involving human subjects to be approved by IRB or R&D Committee or performed in VA facilities.

B. Scheduling of Meetings

The IRB meets the second Thursday of the month. Scheduled meetings will be canceled or re-scheduled for federal holidays, lack of a quorum or for cause at the direction of the Chairperson. Complete minutes of the IRB meeting are provided to Research and Development Committee members.

Guests

Guests (e.g. – students, visitors, potential members, etc.) may be allowed to attend IRB meetings at the discretion of the IRB Administrator and/or HPA. Guests must agree to the same standards of conduct, conflict of interest, and confidentiality as IRB members and staff. Requests for guests to attend should be made in advance by contacting the IRB Administrator. A nondisclosure agreement may be required.

C. Pre-meeting Distribution to Members of Agenda and Study Materials to be Reviewed

The IRB requires that all members receive all submission materials including minutes of the previous meeting in time to conduct a thorough review at convened meetings of all agenda items in order to determine if the research meets regulatory criteria for approval based upon 45 CFR 46.111, 21 CFR 56.111, 38 CFR 16.111 and for review of modifications to previously approved research in order to determine whether modified research (i.e. amendments) continue to fulfill the regulatory criteria for approval. One copy of the protocol, investigational brochure, approved consent form and any newly proposed consent form, amendment, advertisement, serious adverse event, continuing review, completed investigator submission forms or other material to be reviewed must be received in the IRB Office by Wednesday in order to be reviewed the following Tuesday. IRB staff prepare a written agenda, make copies of materials submitted by the investigator, and make copies of the previous week's IRB minutes for distribution to IRB members by 2:00 PM Friday. The layperson's materials and, if necessary, other member's materials are sent via courier to members' homes. The courier is the same courier that the VA Medical Center uses for CBOCs and has completed VA Privacy Training. The schedule may be adjusted

for holidays, weather or other unanticipated circumstance. Members are given a minimum of four days to review materials.

D. Review Process – Emsure Members Receive Review Material

1. All Members Receive Complete Study Documentation for Review
Members receive personal copies of all study materials to be reviewed.
2. Ad Hoc Reviewers receive complete Study Documentation for Review
Ad hoc reviewers receive personal copies of all study materials necessary to conduct a thorough review.
3. Role of any Subcommittees of the IRB
There are no subcommittees of the IRB . Research protocols/amendments that involve radiation or bio-safety issues/risks receive Radiation and/or Safety sub-committee approval prior to final approval by the IRB and Research and Development Committees.

E. Use of Primary and Secondary Reviewers

The primary and secondary reviewer system is utilized to lessen the Chairperson's burden so that he does not have to verbally present every agenda item at IRB meetings. IRB members are assigned agenda items to present during the IRB meeting. Primary/secondary reviewers present agenda items as assigned except Non-scripted changes, Initial Reviews and Previously Tabled Initial Reviews. Those agenda items are presented by the Chairperson. The IRB administrator establishes the presenter schedule. Reviewers are responsible for, (1) presentation of reviewed agenda items submitted and leading the discussion at convened IRB meetings. All members of the IRB receive a complete copy of the IRB submission, all IRB members review submitted materials and all members actively participate during IRB meetings.

X. IRB Review / Operations

The IRB reviews all submitted items at a convened meeting. Reviews and determinations are documented in Committee minutes and IRB submission forms. Written notifications of review, approval, disapproval or actions required are sent to the investigator. Reviewed items along with a file copy of the written notification are filed in the protocol folder and kept in the IRB office. The Principal Investigator (PI) signs submission forms. Sub-investigator may sign if the PI is unavailable. (e.g. vacation, sick leave, etc.)

The IRB developed and implemented the use of data collection tools for investigator submissions. The primary data collection forms are:

- (a) Initial Review Submission Forms
- (b) Continuing Review Submission Form
- (c) Consent Form Template
- (d) Modification to Approved Research IRB Submission Form
- (e) 5 Day Reporting Form
- (f) Non-5 Day Reporting Form
- (h) HIPAA Authorization Template
- (i) Waiver of HIPAA Authorization (full and partial for recruitment)

- (j) Conflict of Interest Disclosure
- (k) Data Repository SOP
- (l) Exempt Submission Form

A. Conducting Reviews – IRB Review Process [21 CFR 56.108(a)(1) and 56.109(a-f)]

The IRB reviews and has the authority to approve, require modifications in (to secure approval) or disapprove all human research activities conducted under the auspices of NWHCS and NEBRA . If warranted, the IRB may request information about other IRB reviews of the research. IRB actions and investigator correspondence are recorded in the minutes and filed electronically in the IRB database and in paper files. The primary purpose of the IRB is to protect the rights and welfare of NWHCS human research subjects. In order to secure IRB approval, the IRB must receive adequate information from the investigator and sponsor to determine:

1. that the research staff has appropriate qualifications and resources to conduct and monitor the study
1. that the protocol has scientific merit
2. that risks are minimized
3. that the risk-benefit ratio is appropriate (i.e. no research can be approved if potential risks outweigh potential benefits)
4. that selection of subjects is equitable
5. that provisions for safety monitoring are appropriate (should include plans for identification and reporting of adverse events and include safety assessment plans as applicable)
6. that provisions for privacy and maintaining confidentiality of data are appropriate
7. that vulnerable populations are afforded additional safeguards.

B. Initial Reviews

To facilitate the IRB's review of a new research project, the Principal Investigator is required to submit the following items to the IRB for review :

- Protocol and Consent Form
- Any relevant grant applications
- Complete DHHS approved protocol and consent form (when one exists)
- Initial Review Submission Form including Study Personnel List
- Amendments (if applicable)
- Investigational Drug or Device Brochure
- FDA approved medication – include Package Insert, PDR or Medline information
- VA Form 9012 – Investigational Drug Form (as applicable)
- FDA form 1572 (if applicable)
- Conflict of Interest Disclosures for appropriate research staff
- VA Project Data Sheets
- Scopes of duty for research staff
- Serious Adverse Event (SAE) reports (if applicable)
- Advertisements (if applicable)
- Literature review (as appropriate)
- Questionnaires, survey instruments, data collection forms (if applicable)
- Research Privacy and Data Security Plan

- Authorization to Transport and Utilize VA Sensitive Information Outside Protected Environments (if applicable)
 - Request for HIPAA Waiver of Authorization (if applicable)
 - HIPAA – Request for HIPAA Waiver for Recruitment Purposes (required if an investigator plans to access medical records or other protected health information (PHI) in order to identify potential subjects for recruitment purposes without having first obtained written informed consent)
 - Common Rule Waiver of Informed Consent for Recruitment Purposes (required if an investigator plans to access medical records or other protected health information (PHI) in order to identify potential subjects for recruitment purposes without having first obtained written informed consent [or for studies subject to the 2018 requirements, IRB approval of access to prospective subject's identifiable information or identifiable biospecimens without informed consent/waiver of informed consent under specific conditions.](#))
 - Waiver of Informed Consent (116d if applicable)
 - Waiver of Documentation of Informed Consent (117c if applicable)
 - Data Repository SOP (if applicable)
 - Once received, the IRB administrator and/or staff will perform an administrative review to ensure that all required documents have been submitted and to determine whether the research study may be eligible for expedited review. The IRB reviewer assigned to review the study will make the final determination regarding whether the study is eligible for expedited review or if it must be reviewed at a convened meeting of the IRB.
- **Expedited Review Eligibility**
- In order for a study to be eligible for initial review/approval by expedited review, all research activities must fit into one or more of the expedited review categories published in the Secretary of HHS Expedited Review List (see Appendix G). The expedited review procedure cannot be used if the research meets one or more of the following criteria:
 - The research poses more than minimal risk to human participants (see definition for minimal risk).
 - The research is classified.
 - The identification of the participants and/or their responses would reasonably place the subjects at risk of criminal or civil liability or be damaging to the participants financial standing, employability, insurability, reputation, or be stigmatizing. An exception can be made when reasonable and appropriate protections are implemented so that there are no greater than minimal risks related to invasion of privacy and breach of confidentiality.

Research subject to the pre-2018 Requirements and FDA Regulated Research

For both FDA regulated research and research that is subject to the pre-2018 Requirements, the assigned reviewer must first determine that all proposed research activities meet the definition of minimal risk. Once that determination has been made, the assigned reviewer must confirm that all proposed activities fit into one or more of the categories on the expedited review list (see Appendix G).

Research subject to the 2018 Requirements

[For research that is subject to the 2018 Requirements, it is presumed that all activities included on the expedited review list are minimal risk activities and thus eligible for expedited review. If](#)

the assigned reviewer believes that a proposed study activity that is found on the expedited review list is greater than minimal risk and thus requires convened board review, the assigned reviewer must document the rationale for determining that the activity is greater than minimal risk on the reviewer form and then inform the IRB Administrator that the study needs to be scheduled for review at the next available convened board meeting.

C. Limited IRB Review

Limited IRB review is a type of review required in 38 CFR 16. The purpose of this type of review is to ensure privacy/confidentiality protections are in place to reduce the chance of inappropriate disclosure in exempt research that involves the collection or use of sensitive, identifiable data and that "broad consent" was obtained for the use of stored identifiable data or biospecimens (collected solely for the purpose of research), and (if appropriate) documented according to an approved protocol.

- For exemption categories 2 and 3, the requirement for limited IRB review is triggered when:
 - The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects; AND
 - Any disclosure of the human subjects' responses outside the research would reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.
- For exemption categories 7 and 8, limited IRB review is always required. These categories are only available for use when broad consent will be (or has been obtained).
- A limited IRB review procedure will be conducted using expedited review procedures, and will consist of the review of exempt human subjects research by the IRB Chair, Vice Chair, or by an experienced reviewer designated by the Chair or Vice Chair from among the IRB members (as a designated expedited reviewer) IAW the requirements set forth in 38 CFR 16/21 CFR 56.110. In conducting limited IRB review, the reviewer may exercise all of the authorities of the IRB except that s/he may not disapprove the research. A research activity may be disapproved only after review by the convened
- For exempt studies involving access to PHI (e.g., from medical records), the required Privacy Board review may be integrated with limited IRB review by the same assigned IRB reviewer.
- Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly report to the IRB (i.e. within 5 business days).
- All exempt protocols initially reviewed and approved by limited IRB review procedure are not reviewed for continuation by the IRB.

D. Expedited Review Process

Only experienced voting IRB members are authorized to perform reviews using the expedited review process. An experienced member is one who has previously served on an IRB (VA or non-VA) for at least one year. A master letter signed by the IRB Chair which designates the IRB members authorized to perform expedited reviews is kept on file and is updated when changes in membership occur that affect the listing.

- Although the research may be eligible for review using the expedited review procedure, if the Chair or Expedited Reviewer decides the research should be reviewed at a convened meeting, the IRB Administrator will schedule the research for review at the next available convened IRB meeting.
- The Expedited Reviewer must ensure that all IRB approval criteria, including any applicable waivers, are met prior to granting approval to a study under this process. For initial reviews, the expedited reviewer documents his/her review using the reviewer form for new applications.
- During the review, the Expedited Reviewer may contact the investigator directly with any comments or requested modifications. The Expedited Reviewer may also relay any comments or requested modifications to the IRB Administrator who can contact the investigator.
 - The investigator is asked to provide any additional information requested by the Expedited Reviewer **within 5** workdays. If the investigator is unavailable, this deadline can be extended at the discretion of the Expedited Reviewer and the IRB Administrator.
- The Expedited Reviewer makes an approval recommendation or an approval determination, within x working days of receiving the project action for review unless the Reviewer has questions for the investigator. If questions were forwarded to the investigator, the Expedited Reviewer makes an approval recommendation/determination within x working days of receiving an adequate response from the investigator. An adequate response will include a cover memo detailing the changes made, as well as clean and track changes copies of all revised documents. The Expedited Reviewer will then make an approval recommendation or determination on the applicable checklist and forward it to the IRB Administrator along with the completed Reviewer Form.
 - For initial review of new Project Applications, the Expedited Reviewer provides an approval recommendation to the IRB Chair by selecting one of the following recommended actions:
 - Approval. Changes can be suggested but are not required. The expedited review category or categories under which the expedited review occurred is specified as is a continuing review period if the study requires continuing review, (generally one year unless the Reviewer determines a shorter review period is required). Requiring a shorter time period can be based on such factors as the experience of the study team, an unusual study design or consenting process, vulnerability of study populations, projected rate of enrollment, and other factors based on study design and execution.
 - Modifications Required for Approval. The expedited review category or categories under which the review occurred is specified. The Expedited Reviewer stipulates the specific modifications to be made on the reviewer checklist and forwards these to the IRB Administrator via an approved method. The IRB Administrator then relays these modifications to the investigator via encrypted e-mail or by uploading the information to SharePoint and providing the link to the investigator.

- Deferral for review by the convened IRB. The IRB Administrator schedules the project for review at the next regularly scheduled meeting of the convened IRB. The Expedited Reviewer serves as the Primary Reviewer at the convened meeting, unless the Expedited Reviewer is unavailable, in which case another voting member is assigned to be the Primary Reviewer by the IRB Chair. A copy of the Expedited Reviewer's comments is included in the materials sent to all IRB members with the meeting agenda package.
- The Expedited Reviewer may not disapprove a study. If the expedited reviewer feels that the study cannot be approved, he/she must refer the study for review by the convened IRB.
- The IRB Chair signs off on the Expedited Reviewer's recommendation. The date the IRB Chair documents his/her concurrence is considered the date of final IRB approval for research studies undergoing initial review via expedited review.
- For initial approvals that are conducted by expedited review, the approval letter must contain the expedited review categories that the study is eligible for as well as information on the continuing review expiration date if the study requires continuing review..

E. Expedited Review Report

- All IRB members are informed of expedited approvals via an expedited review report that is disseminated at the convened IRB meeting.
- For actions pertaining to Initial approvals, the report entry will include the assigned IRB number; name of the project, name of PI, date of approval, and expedited review category under which the action was approved.

F. Continuing Reviews

The IRB is required to conduct continuing review of non-exempt human subjects research at intervals appropriate to the degree of risk, but not less than once per year, except in the following cases:

Research subject to the 2018 requirements that meet one of the following categories:

- Research eligible for expedited review
- Research that has progressed to the point that it involves only one or both of the following, which are part of an IRB-approved study:
 - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
 - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care
- Research reviewed by the IRB in accordance with the Limited IRB review provisions

The IRB must document the rationale for conducting continuing review of a research study that is subject to the 2018 Requirements and falls into one of the categories of research that does not require continuing review. The required documentation is included on the continuing review reviewer form that the reviewer completes for both expedited and convened board reviews.

FDA-regulated research, research subject to the pre-2018 Requirements, and research that does not meet the criteria stated above require continuing review at intervals appropriate to the degree of risk, but not less than once per year.

Continuing review approval of research must occur **on or before** the date when approval expires. When continuing review is not completed prior to the expiration of the current approval period, there is an automatic lapse of IRB approval. All research must stop unless the IRB Chair determines that it is in the best interest of individual participants to continue the research interventions or interactions.

For research requiring continuing review, continuing Review is allowed to stop only when (1) the research is permanently closed to the enrollment of new participants, (2) All participants have completed all research-related interventions, and (3) collection and analysis of private identifiable information has been completed. The IRB is not allowed to find an over-riding safety concern or ethical issue such that it is in the best interests of individuals to enroll in expired research. This must be done under emergency use of a test article.

The Subject Lists are submitted by the Investigator and by the Investigational Pharmacist and are secured in the IRB Office. The information is cross-referenced by the IRB office staff prior to the meeting. Discrepancies are reported to the IRB during the review of the projects. The Subject Lists are filed with the Continuing Review event.

G. Continuing Review Process

For research that requires continuing review, the IRB Administrator sends out an initial reminder notification to the Principal Investigator 45 days prior to the expiration date of the study. The reminder email includes the date by which all materials must be received by in order to ensure review prior to the continuing review expiration date.

The Principal Investigator is required to submit the following items to the IRB, if applicable:

- Continuing Review Submission Form including investigator protocol summary
- Copy of approved consent form and any newly proposed consent document
- Conflict of Interest Disclosures for appropriate research staff
- Copy of approved Study Personnel List, if no staffing changes are being made
- Protocol Summary (Electronically generated chronology of all previous IRB actions)
- Status report on the progress of the research

H. Continuing Review by Expedited Review

Once the continuing review packet is received, the IRB administrator and/or staff will perform an administrative review to ensure that all required documents have been submitted and to determine whether the research study may be eligible for continuing review by expedited review. In order to be eligible for continuing review by expedited review, the study must either (1) have been eligible for expedited review during its initial review and approval and continues to be eligible for expedited review or (2) at the time of continuing review submission, the study meets expedited review category 8 or 9 which allow continuing review by expedited review.

If it is determined that the study is eligible for continuing review by expedited review, the continuing review packet will be routed to an assigned reviewer for expedited review. The IRB reviewer assigned to review the study will make the final determination regarding whether the study is eligible for expedited review or if it must be reviewed at a convened meeting of the IRB. The expedited reviewer is responsible for ensuring that all initial approval criteria continue to be met. The expedited reviewer completes the continuing review reviewer form to document their review.

The expedited reviewer may contact the investigator directly with any comments or requested modifications. The Expedited Reviewer may also relay any comments or requested modifications to the IRB Administrator who can contact the investigator. The investigator is asked to provide any additional information requested by the Expedited Reviewer within x workdays. If the investigator is unavailable, this deadline can be extended at the discretion of the Expedited Reviewer and the IRB Administrator. If the action being considered is a continuing review, the study approval expiration date must be taken into consideration as it cannot be extended.

The expedited reviewer has approval authority for continuing review and can make one of the following determinations which are documented on the continuing review reviewer form:

- Approval. Changes can be suggested but are not required. The expedited review category or categories under which the expedited review occurred is specified as is a continuing review period if the study requires continuing review, (generally one year unless the Reviewer determines a shorter review period is required). Requiring a shorter time period can be based on such factors as the experience of the study team, an unusual study design or consenting process, vulnerability of study populations, projected rate of enrollment, and other factors based on study design and execution.
- Modifications Required for Approval. The expedited review category or categories under which the review occurred is specified. The Expedited Reviewer stipulates the specific modifications to be made on the reviewer checklist and forwards these to the IRB Administrator via an approved method. The IRB Administrator then relays these modifications to the investigator via encrypted e-mail or by uploading the information to SharePoint and providing the link to the investigator.
- Deferral for review by the convened IRB. The IRB Administrator schedules the project for review at the next regularly scheduled meeting of the convened IRB. The Expedited Reviewer serves as the Primary Reviewer at the convened meeting, unless the Expedited Reviewer is unavailable, in which case another voting member is assigned to be the Primary Reviewer by the IRB Chair. A copy of the Expedited Reviewer's comments is included in the materials sent to all IRB members with the meeting agenda package.
- The Expedited Reviewer may not disapprove continuation of a study. If the expedited review feels that the study cannot be approved, he/she must refer the study for review by the convened IRB.

I. Continuing Review by Convened Board Review

If the study is not eligible for expedited review, the continuing review of the protocol will be placed on the agenda for the next available meeting of the convened IRB. If the approval period will lapse prior to the next regularly scheduled convened meeting, the IRB Administrator will consult with the IRB Chair to determine if an unscheduled meeting should be called to review the action.

The study will undergo continuing review in accordance with convened board review procedures.

Continuing Review Expiration Date

The continuing review approval expiration date is the last date the study can be conducted without further IRB approval.

For new projects requiring review by the convened IRB, the date of the convened meeting at which the project is “Approved Contingent Upon Required Minor Modifications” or, if there are no modifications, “Approved”, establishes the date by which the expiration period will be calculated for the approval period specified by the IRB.

For new projects undergoing expedited review, the date the Chair approves the New Project Application after any required modifications (if any) were made, is the date by which the expiration date will be calculated for the approval period.

For approved projects undergoing continuing review, the new continuing review approval period will be set by one of the following depending upon the type of review being conducted:

For reviews by the convened Board, the date by which the expiration period will be calculated for the new approval period is the date the Application for Continuing Review is either “Approved” or “Approved Contingent upon Minor Modifications.”

For reviews conducted by expedited review procedures, the date by which the expiration period will be calculated for the new approval period is the date the Application for Continuing Review is “Approved” by the Expedited Reviewer.

As an option, when continuing review occurs annually and the IRB performs and completes the review within 30 days before the original expiration date of the current IRB approval period, the IRB can retain the original anniversary date (day and month) as the date for the next IRB approval expiration date of the study. This includes studies reviewed via expedited procedures and by the convened IRB.

When the IRB approves the research with conditions at the time of continuing review before the expiration date of the preceding approval period, IRB approval does not lapse even if the investigator needs additional time to satisfy some or all of the conditions. The IRB will establish a date by which the investigator must respond to the conditions and will then determine if the conditions are met or other action needs to be taken. If the investigator does not respond in a timely manner, the IRB may take additional action, such as suspension of enrollment and/or study activities.

J. Lapse in Approval (STUDY EXPIRATION).

If a PI has not provided continuing review application materials to the IRB, or the IRB has not approved the continuing review application by the IRB approval expiration date, the IRB approval automatically lapses and all research activities must stop, including data analysis of personal identifiable information. No enrollment of participants can occur.

If the continuing review application is not approved by the IRB approval expiration date, all research activities must stop.

The PI must immediately submit to the IRB Chair a list of participants for whom stopping or interrupting interventions or interactions would cause harm. The IRB Chair will consult with the Associate Chief of Staff for Research to determine whether it is in the best interests of individual participants to continue participating and document the consultation and determination in writing to the PI.

The IRB will notify the PI, the sponsor funding the project, affected participating sites, of lapses of study approval. Correspondence will be prepared by the IRB administrative staff to be reviewed and signed by the IRB Chair. Correspondence will be sent by encrypted email with a read receipt requested.

If the lapse occurred due to non-submission of the continuing review applications by the PI, the PI may submit the request for continuing review application, along with a justification for the delay in submission, up to 30 days after the expiration of approval date in order for the review to still be conducted by the IRB. After the 30 days have elapsed, the project or site will be considered noncompliant and the Board will proceed in accordance with reporting per the requirements outlined for reporting Serious and Continuing Noncompliance in this policy and consider the study or site for termination. If study or site termination is not in the best interest of participants, the study may be continued until the participants have safely completed the study or can be withdrawn but no new enrollment can take place.

If the PI wants to re-open a study that lapsed and it has been over 30 days since the lapse occurred, a new PI study application must be submitted, or the PI can consult with the IRB Administrative office regarding any documentation that may be required, in addition to the continuing review application, for the review to take place.

If the PI submitted all the required documents by the expiration date, but the approval period lapses, all the actions outlined above must still take place. The IRB will review the submitted materials as soon as practicable.

K. Research Status Updates

The research office will send out a data call on an annual basis requesting a status update on all open non-exempt human subject research studies that do not require continuing review. The research status update form will be sent out to all PIs at the start of the new fiscal year. Responses that indicate that the study should be closed will prompt a request for the PI to submit a study closure report. Investigators failing to respond will be re-contacted once the suspense date has passed for an update. Failure to respond by the suspense date will not be considered a lapse in approval.

L. SAE Events

(Requirement - all IRB members receive personal copies of all study materials to be reviewed at convened IRB meetings)

Items submitted for review include but are not limited to:

- 5 Day Reporting Form or Non- 5 Day Reporting Form
- On-site SAE#
- Off-site Sponsor SAE# (Note: only the Investigational Pharmacist receives personnel copies of sponsor SAEs)
- Date of event
- Description of event
- SAE relationship to study (related or not related)
- Is the event/risk anticipated or unanticipated
- Risk section of currently approved ICF
- Incorporation of new risks into a revised ICF (if indicated)
- Subject notification plans if indicated
- Med Watch Report, Discharge Summary – attach appropriate source documents

M. Modification to Approved Research (Amendments)

It is the policy of the IRB that amendments or modifications in research projects may not be initiated without prior review and approval by the IRB, except where necessary to eliminate apparent immediate hazard to human participants

Amendments or modifications in projects determined to be exempt from IRB review must be reviewed to ensure that the amendment does not change the regulatory category for the research. Exempt determination should be made by the R&D Committee or an electronic determination tool.

The Principal Investigator is required to submit the Modification to Approved Research IRB Submission Form including a justification for the amendment (signed), a complete description of the proposed changes, a summary of changes, and amended protocol as appropriate. Items submitted for review include but are but are not limited to:

- Protocol change (e.g. inclusion/exclusion, administrative, new information for subjects, therapy changes, scientific changes)
- Consent Form Change
- Advertisement
- Investigational Brochure and Safety Update Summary
- DSMB/Interim Safety Reports and Update Summary
- Investigator Change
- Reports of Unanticipated Problems involving risks to subjects or others
- Protocol Deviations
- Other

Minor modifications to previously approved research may be reviewed and approved using expedited review procedures. All other modifications to research that was originally approved by the convened IRB must be reviewed by the convened IRB.

If the proposed amendment or modification involves the informed consent or conveying new information, the PI must indicate whether participants who have already consented to participate need to be re-consented and/or informed.

The date when the current IRB approval period for a project expires is not changed based on the approval date of an amendment.

N. Emergency Use Reports

Instances of Emergency Use must be carefully documented in writing by the investigator and must be received by the IRB within 5 days of use of an emergency article. Reviews of the emergency use are documented in IRB minutes and filed in IRB's investigator project file.

O. Emergency Use Notification and Reporting Procedures

Physicians must report to the IRB in writing any unapproved emergency use of test articles within five working days. Prospective use of test articles without IRB approval is addressed in detail in *Section XVII EXEMPTION FROM PROSPECTIVE IRB REVIEW*. This section will be carefully referenced to assure that federal regulations are met. In its review of emergency use if it is anticipated that the test article may be used again the IRB will request submission of a protocol and consent document for review to obviate successive emergency uses. If insufficient details are provided by the Principal Investigator additional information may be requested.

P. Statements of Significant New Findings Provided to Subjects

The "new findings" statement is included in the consent form template provided to investigators. The Committee verifies that this statement is included in the approved consent form. The method and urgency of conveying significant new findings varies depending on safety specifics. For example, if new information indicates that study medication is harmful then subjects will be contacted immediately. In less urgent cases, for example a change in principal investigators, written notification may be appropriate. A phone call in addition may be appropriate. A revised consent form and re-consenting all affected subjects may be necessary. All actions are filed in the IRB's investigator project file.

XI. VOTING REQUIREMENTS

A. Quorum Required to Transact Business

Greater than 50% of IRB voting members must be present to achieve a quorum. Quorums can be lost if a member or members have to leave a meeting early or absent themselves due to conflicts of interest. In such circumstances affected projects would be deferred until a quorum was re-established or postponed until the next meeting. The IRB Administrator is responsible for monitoring and ensuring the required quorum is maintained during IRB meetings, including special IRB membership requirements if research involves pregnant women, prisoners and children. Should the IRB Administrator not be present at a convened meeting the Chairperson or designee will assume this role.

B. Diversity Requirements of Quorum

At least one licensed physician must be present for review of protocols utilizing FDA regulated test articles, at least one member whose concerns are in non-scientific areas must be present, and at least one member who represents general perspective of participants is present. A non-affiliated member should be present at every meeting however business may be conducted without this member.

C. Percent Needed to Approve or Disapprove a Study

Definition of Voting Status and Quorum Implications:

Approvals, Modifications in order to secure approval Tabling, and Disapprovals must be by a majority (>50%) consent of voting members present who did not abstain. Members for, against, abstained, recused, and excused are recorded in IRB minutes and in the IRB Action Letter provided to investigators.

For:	Present at the convened meeting, participates in final deliberations and votes for approval.
Against:	Present at the convened meeting, participates in final deliberations and votes for disapproval.
Abstained:	Present at the convened meeting, participates in final deliberations and chooses not to vote. Counted towards the quorum.
Recused:	Present at the convened meeting, declares a Conflict of Interest, leaves the room, does not participate in final deliberations and does not vote. <u>Absent from the quorum.</u>
Excused:	Present at the convened meeting however has left the room for personal reasons during final deliberations and does not vote. <u>Absent from the quorum.</u>

IRB policy requires that the names of IRB members who abstained, were recused or were excused are recorded in IRB and R&D Minutes and in the IRB Action Letter to investigators.

D. Full Voting Rights of all Reviewing Members

Each voting member has one vote.

E. Proxy Votes (Written or Telephone)

No proxy votes are allowed.

F. Prohibition Against Conflict-Of-Interest Voting

Voting members who have conflicts of interests are required to recuse themselves from deliberations leave the room, and not vote. Conflicts of interest

include circumstances where financial, professional, or other personal issues are involved.

G. Remote Participation Option

If members cannot be physically present at the meeting, some or all members may participate in the meeting by conference call or videoconference; however, voting members cannot participate in the meeting discussions or voting by email. (1) Members participating by conference call or videoconference receive all relevant materials prior to the meeting and be able to participate actively and equally in all discussions. (2) Minutes 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.

XII. IRB REVIEW PROCESSES

In order to approve research, the IRB requires and ensures that all Criteria for Approval (16.111) are met.

A. What the convened IRB Reviews

The IRB only reviews non-exempt human subjects research. IRB conducts Initial Review and determines if the research has satisfied all relevant criteria for approval and conducts subsequent Continuing Review, when required. IRB of record approval of a study (i.e. initial review, continuing review and review of modifications to previously approved research when the modification affects a criterion for approval) means there is a PI or LSI for the study, and the IRB has determined that the research has satisfied all relevant Criteria for Approval (16.111), and is consistent with applicable VA and other Federal regulatory and ethical standards, and may be conducted at NWIHCS within the constraints set forth by the IRB and by other applicable local, VA, and other Federal requirements. The IRB ensures that any significant new findings that may affect the subject's willingness to continue participation are provided to the subjects.

1. Ensures risks to subjects are minimized by using procedures consistent with sound research design by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risks, and when appropriate by using procedures already performed for diagnostic or treatment purposes. Ensures risks to subjects are reasonable in relation to potential benefits, if any, to subjects, and the importance of the knowledge that may reasonably expected to result. IRB considers only risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive, even if not participating in the research.) IRB does not consider potential long-term effects of applying knowledge gained in the research as risks within purview of its responsibility.
2. Waivers: (a) waiver or alteration of the informed consent process; or (b) waiver of documentation of informed consent, (c) Waivers of HIPAA Authorization (full or partial)
- 2.5 Recruitment: For studies subject to the 2018 requirements approval requests for access to potential subject's identifiable biospecimens without informed consent/waiver of informed consent under specific conditions.

3. Determines that a valid IND or IDE is present prior to approving research during Initial Review by reviewing the protocol and the investigator's answer to Initial Review Submission Form questions 7, 8, 9 on page 2 of the Form. The IRB's procedures to decide whether an IND or IDE is required are in IRB SOP Section XV Device Studies and Investigational Drug Studies.
4. Determines if research qualifications of staff and resources (e.g. staff, space, beds, funds, time, admission/inpatient study authorization, approval from other medical center officials if warranted) available to the investigative team at all study sites are appropriate to human subject protections. Specifically, the IRB evaluates whether the investigator has enough time to complete the research within the agreed research period and considers the availability of medical and or psychological resources that participants might require as a consequence of the research. According to Title 38 CFR 17.85 "Treatment of Research Related Injuries to Human Subjects," VA must provide necessary medical treatment to a research participant injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. The informed consent form template includes language explaining VA's authority to provide medical treatment to research subjects injured by participation in a VA research project. Conducts periodic Continuing Review of projects when required, and specifically looks for indications of insufficient resources (e.g. continuing failure to submit required information in a timely manner, continuing failure to respond appropriately or in a timely manner to IRB stipulations, excessive and recurring numbers of protocol deviations, high staff turnover, poor record keeping, other medical center staff complaints or research subject complaints).
5. Conducts scientific and ethical review at Initial and Continuing Review and specifically evaluates protocol study design, study purpose and setting, scientific rationale including review of study plan, hypothesis, experimental procedures, and study duration. Ensures equitable selection of subjects and is cognizant of special problems of research involving vulnerable populations. Ensures when appropriate there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Evaluates potential risks and benefits to subjects in conjunction with potential scientific merits of the protocol. Determines need and type of monitoring (e.g. DSMB, interim analysis) and provision of special services to participants (e.g. counseling, hospitalization, follow-up). Insures that the consent form includes all required elements, accurately describes procedures, risks and benefits, and specifies alternative treatment options. Seeks expert review if members do not have sufficient expertise to adequately review a protocol. Expert reviewers may attend IRB meetings or provide written comments but they cannot vote. Ensures research is relevant to the health of Veterans.
6. (a) Approves, (b) Modifications Required in Order to Secure Approval (Scripted Changes, Non-Scripted Changes), (c) Tables, or (d) Disapproves all submissions and provides written explanations to the investigator within one week of the IRB meeting. Modifications Required – Scripted Changes involve minor scripted stipulations that may be verified by an experienced IRB member to secure approval without full committee review. Modifications Required – Non-Scripted Changes involve minor stipulations with no substantial risk-benefit concern impacting subject safety. This category of approval often involves the requirement that additional non-scripted clarifications be provided to the Full Committee for review. For example, if reviewing the consent form the Committee wants the investigator to "list the consequences" or if the Committee recommends, "remove or improve." Tabled

submissions involve significant deficiencies that require substantial modifications in order to secure approval and require complete IRB re-submission for full Committee review. Disapprovals require fundamental changes in the protocol in order to secure approval and require a complete IRB submission. If responses to Modifications in order to secure approval or Tabled items are not received within 3 months, the IRB may require a comprehensive, start from the beginning re-submission or if appropriate, may initiate a study suspension or closure.

7. Determines if potential benefits outweigh potential risks to subjects and assures that subjects are fully informed about potential risks, benefits and alternative treatments (other than research). Evaluates physical risks, psychological risks, social risks, economic risks, legal risks, privacy of subjects risks (in collaboration with PO), and confidentiality of data risks (in collaboration with the ISO). Reviews subject safety monitoring plans (DSMB, interim analysis) to assure that risks are minimized. Ensures that data and privacy of individuals from whom research data is obtained are protected during and after study completion.
8. Ensures informed consent will be sought from each prospective subject or LAR and appropriately documented. Ensures federally required basic and additional elements (as applicable) of informed consent are included in the consent form and ensures that the consent form is consistent with the protocol, investigator brochure, meets all regulatory requirements and ensures language is not coercive. Ensures information is presented in understandable language at an 8th grade level and does not include any exculpatory language that waives or appears to waive a subject's rights or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. IRB contact telephone numbers are incorporated into the consent form. Provides to Principal Investigators a VA Informed Consent Form template that has been modified by the IRB and includes required statements. IRB modifications are written in red ink on the submitted consent form. All Consent Form versions submitted to the IRB are reviewed and filed. Only the most recently approved version of the informed consent form may be used to consent subjects. The IRB does not approve a HIPAA authorization, but ensures in conjunction with the PO that the protocol and informed consent form are consistent with the HIPAA authorization. The IRB may approve waivers (partial and full) of HIPAA Authorization.
9. For research requiring continuing review, determines at Initial Review the frequency of Continuing Review appropriate to degree of risk but not less than once per year (e.g., 12, 9, 6, 3 months) and includes Continuing Review requirements in IRB Approval Letters. The Continuing Review "clock" starts on the date of the convened IRB meeting at which the IRB approved the protocol if no modifications were required; OR the date at which the investigator meets all of the modifications required by the IRB. The expiration date is the last date that the research is approved. An approval date and a version is affixed to the approved informed consent document. The IRB may review within 30 days prior to expiration and still retain the anniversary date. If approval expires all research activities must stop, except those activities which will harm a subjects, and the investigator must immediately submit to the IRB Chair, a list of subjects who could be harmed by stopping study procedures. There is no grace period to extend conduct of research beyond the expiration date.

Studies involving: (a) limited experience in humans (e.g. Phase I, II), (b) use of vulnerable subjects, (c) significant risk devices, (d) sensitive survey issues, (e) use of narcotics or other research articles with potential for abuse, (f) inexperienced

investigators or investigators with previous incidences of non-compliance, (g) off-site research, (h) investigator-initiated research where the NWHCS IRB may be the only safety review board etc. are examples of research that may require more frequent (than 12 month) Continuing Review. Continuing Review is allowed to stop only when (1) the research is permanently closed to the enrollment of new participants, (2) All participants have completed all research-related interventions, and (3) collection and analysis of private identifiable information has completed (4) research approved under expedited categories unless a justification for the CR is provided by the IRB.

10. Identifies Drug, Device, Radiation, Biohazard, and Chemical/laboratory hazards. Procedures that are determined to pose chemical, radiation or biohazard risks not encountered in ordinary medical care require appropriate institutional review and approval (e.g. Radiation Safety Officer, NWHCS Safety Officer, Sub-committee on Research Safety). Assures that appropriate risk statements are incorporated in the consent form. Assures that plans for storage, security and dispensing of investigational items are appropriate to subject protection.
11. Ensures additional safeguards are in place to protect Vulnerable Populations (such as children, prisoners, pregnant women, those who lack decision making capability, or economically or educationally disadvantaged persons). Documents why an individual or population is vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of subjects who are likely to be vulnerable. Individuals or populations that may be temporarily or permanently vulnerable include, but are not limited to, those who:
 - a. Are susceptible to coercion or undue influence (e.g. the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).
 - b. Lack comprehension of the research and its potential risks (e.g. educationally disadvantaged, dementia, schizophrenia, depression).
 - c. Have increased susceptibility to harm from the procedures of the specific study under review (e.g. individuals who would have to answer study survey questions about their sexual assault).
 - d. Are at risk for economic, social, or legal consequences from the study (e.g. individuals who would have to answer study survey questions about their drug use or HIV status).

The IRB is required to assure that the following specific requirements are fulfilled for research involving children, pregnant women, prisoners, and those who lack decision making capability

- For research conducted on pregnant women the IRB is required to determine that requirements outlined in Subpart B of the DHHS regulations and VHA Handbook 1200.5 are met.
- For research conducted on children the IRB is required to determine that requirements outlined in Subpart D of the DHHS regulations and VHA Handbook 1200.5 are met. **Facility Director certification is required.**
- For research conducted on prisoners the IRB is required to determine that requirements outlined in Subpart C of the DHHS regulations and VHA Handbook 1200.5 are met. **Dir, ORPP&E approval is required.** Special IRB membership is required – prisoner's representative will be present at IRB meeting.

12. Determines at Initial Review and Continuing Review which projects may require independent verification from sources other than the investigator that no material

changes have occurred since previous IRB review. The IRB has the authority to observe, audit and verify records and/or the informed consent process to insure that only approved research activities are being conducted. The IRB criteria used to make these determinations include the following:

- Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in Continuing Review reports or from other sources (e.g. sponsor study monitors).
- Projects conducted by investigators who previously have failed to comply with the regulatory requirements and/or requirements of the IRB.
- Complex projects involving unusual levels or types of risks to subjects.

13. Requires that any modifications or updates in previously approved research activities (e.g. Amendments, Updated Safety Information, Investigational Brochures, Serious Adverse Events, Unanticipated Problems Involving Risks to Subjects or Others, protocol deviations, recruitment procedures, consent form modifications, investigator changes, premature completion of a study, or other relevant issues, etc.) be promptly reported to the IRB for re-evaluation and the IRB determines if Criteria for Approval of research are still met. Proposed changes in approved research during the period for which the IRB approval had already been given cannot be initiated without IRB approval. Changes in approved research that were initiated without IRB review and approval to eliminate apparent immediate hazards to the participants must be promptly reported to the IRB. The IRB determines whether the change was consistent with ensuring the participants continued welfare. The IRB ensures that any significant new findings that may affect the subject's willingness to continue participation are provided to the subjects. The IRB working with the Privacy Officer ensures that protocol amendments are consistent with consent forms and HIPAA authorization. For studies requiring continuing review, the date of continuing review is not changed based on the approval date of the amendment unless the IRB specifies that the date of continuing review is changed. If there is an amendment or modification to the protocol that affects the informed consent form, there must be an analogous amendment or modification to the informed consent form and as applicable the HIPAA authorization. Similarly, if there is a modification to the consent form and/or HIPAA authorization that affects the protocol then there must be an analogous amendment to the protocol.

The IRB requires that the members receive and review sufficient information about proposed modifications to previously approved research in order to determine whether the modified research continues to fulfill the criteria for approval. The IRB reviews new information in order to determine, (1) if risks are minimized, (2) if the risk-benefit ratio has changed, and (3) if the importance of the knowledge that may be reasonably expected to result has changed. If yes, (1) the IRB may require modifications (to secure approval) and (2) the IRB may require that new information be provided to subjects. The IRB requires submission of complete Amendments and Investigator Brochures including a summary of changes. Where appropriate, previously approved Consent Forms and proposed modified Consent Forms are submitted. The investigator must submit a justification for protocol modifications and consent form modifications.

14. Ensures when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the subjects. The IRB systematically evaluates whether research submitted for initial review, continuing review, or review of modifications have adequate data and safety monitoring plans (see Initial Review Submission Form and Continuing Review Submission Form). The monitoring may occur at specific points in time, after a specific number of participants have been enrolled, or upon recognition of harm. The monitoring might

compare the character, incidence and severity of actual harm to that expected, comparing the magnitude and probability of benefits to that expected, or to determine the causality of unexpected harm. The IRB, DHHS or FDA might require specific monitoring by the investigator, the sponsor (medical monitor, data monitoring committee (DMC), interim analyses) or independent monitoring board (DSMB) and a plan for reporting safety findings to the IRB, the IRB will ensure that these requirements are fulfilled. At Initial Review, the IRB requires the investigator to identify DSMBs and to describe other plans for data safety monitoring. For studies that do not have or are not required to have a DMC and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, the IRB may suggest the creation of a DMC.

- a. Prospective Studies.** The investigator is required to describe the data and safety monitoring plan for prospective studies when submitting to the IRB. This Plan must include, but is not limited to, the following:
- (1) What safety information will be collected including SAEs (see VHA Handbook 1058.01);
 - (2) How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects);
 - (3) The frequency of data collection including when safety data collection starts;
 - (4) The frequency or periodicity of review of cumulative safety data;
 - (5) If not using a Data Monitoring Committee (DMC) and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring;
 - (6) Provisions for the oversight of safety data (e.g., by a DMC);
 - (7) Conditions that trigger an immediate suspension of the research, if applicable.

- b. Retrospective Studies.** The investigator is required to describe the safety and monitoring plan for retrospective studies when submitting to the IRB. (e.g. pre-existing data and biological specimens). When applicable, the Plan needs to include, but is not limited to, the following:
- (1) A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being;
 - (2) A procedure to determine when and how to notify individual subjects or their health care providers of findings that may affect the subjects' health.

NOTE: The data and safety monitoring plan may vary depending on the potential risks, complexity, and nature of the study. The use of an independent DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are high-risk, vulnerable populations are included, or when required by the funding organization, FDA, sponsor, or other relevant entity.

15. For studies requiring continuing review, determines at Continuing Review the focus and review cycles for Continuing Review. The focus of Continuing Review (refer to Continuing Review Submission Form for specific reporting/assessment details) will be:
 - a. To assure that federally established criteria, organizational criteria and IRB Conditions of Approval are being met. The Continuing Review Submission Form solicits specific information from investigators. The IRB determines if the risk-benefit ratio is favorable, assesses need for special safeguards to protect subjects, reviews the adequacy of ongoing protections for potentially vulnerable individuals and determines if the study may continue and assigns a new Continuing Review interval based on risk assessment. In addition, the IRB determines which projects needed verification from sources other than the investigators that no material changes have occurred since the previous IRB approval. The IRB considers specific criteria (See

Section VIII Item D of the IRB SOP). OHRP and FDA provide guidance on what to consider at Continuing Review. Based upon that guidance the NWHCS IRB considers the following elements:

Protocol Summary: Please attach a protocol summary (1 page – usually part of the initial protocol) and a progress report (see below).

Progress Report: The main purpose of this report is to determine whether new information or unanticipated risks were discovered since the previous IRB review. The report should include the following:

1. Number of subjects entered into the study;
 2. Summary of subject experiences (benefits; adverse events) and any unanticipated problems involving risks to subjects or others since the last IRB review;
 3. Number of withdrawals of subjects from the research and reasons for withdrawals since the last IRB review;
 4. Any complaints about the research since the last IRB review;
 5. Summary of relevant recent literature, interim findings, and any other new information (especially information about risks associated with the research) since the last IRB review;
 6. A current risk/benefit assessment;
 7. Any amendments or modifications to the research since the last IRB review;
 8. Any relevant multi-center trial reports (e.g. data safety monitoring board reports);
 9. A copy of the current informed consent document and any newly proposed consent document.
- b. To assess safety related issues for indications (e.g. SAEs, protocol deviations, subject withdrawals, unanticipated events, non-reporting of reportable events, inconsistencies with Investigational Pharmacy consent form audits, commonalities or oddities) that may suggest increased risk, reduced potential benefit, investigator/coordinator error, or evidence that the NWHCS population is different than others.
- c. To determine if any new information regarding the test article requires an Amendment or Consent Form Revision, and/or to determine if new Safety Information that may affect a research subject's well-being, medical care or willingness to remain enrolled in the study needs to be communicated to research subjects.
- d. To determine if there is any significant change in the risk-benefit ratio and to approve, require modifications in (to secure approval) or disapprove the project.
- e. To determine a new Continuing Review date based on degree of risk but no later than 12 months for research requiring continuing review. There are no provisions for grace periods, continuing review and re-approval of research must occur on or before the date when IRB approval expires. The Continuing Review "clock" starts on the date of the convened IRB meeting at which the IRB reviewed the protocol/research with modifications required in order to secure approval. The expiration date is the last date that the research is approved. If Continuing Review does not occur by the expiration date (i.e. within the time frame set by the IRB) all research activities must stop unless the IRB or IRB Chair, in consultation with the VA Chief of Staff, found that it was in the best interest of individual participants to do so.

The Continuing Review date is set early enough (6 weeks before the prior 12 month approval expires) to allow time for submission delays. If Continuing Reviews are not received on time a TABLE Warning Letter (“black flag” letter) is sent. The TABLE Warning Letter sets a final review date on or prior to the approval expiration date.

f. How to manage studies because Continuing Review was not completed within the timeframe set by the IRB:

- Approval of research projects not reviewed within the timeframe set by the IRB will automatically expire. All research activities must stop unless the IRB or IRB Chair, in consultation with the VA Chief of Staff, found that it was in the best interest of individual participants to do so.
- The IRB promptly notifies the principal investigator of the expiration. The R&D Office may in addition notify the investigator.
- New enrollment of participants must not occur. (Note: the IRB is not allowed to find an over-riding safety concern or ethical issue involved such that it is in the best interests of the individual to enroll in expired research. This must be done under the requirements for emergency use of a test article.)
- Once notified by the IRB the principal investigator must immediately submit to the IRB Chairperson a status report of all enrolled subjects and list of research participants for whom expiration of the research would cause harm. The IRB or IRB Chair, with appropriate consultation with the VA Chief of Staff, determines if it is in the best interest for the participants to continue in the research. If study approval expires the IRB will determine and approve notification of subjects as warranted. The expiration of Continuing Review will be reported to the sponsor. When follow-up of participants for safety reasons is deemed necessary participants are informed and any subsequent adverse events that may occur will be reported to the IRB and sponsor. Such expirations of IRB approval not involving safety concerns, are not required to be reported as a suspension/termination of IRB approval when following VA regulations.
- Once research activities are stopped, IRB review and re-approval must occur prior to re-initiation of the research.
- The IRB ensures that any significant new findings that may affect the subject’s willingness to continue participation are provided to the subjects.

16. Assures that all IRB members receive all pertinent materials necessary to conduct an appropriate review: At a minimum these include:

- a. Initial Review - Initial Review Submission Form, protocol, investigator brochure, proposed consent form and if applicable, VA Form 9012 - Investigational Drug Information Record, Conflict of Interest Disclosure, FDA Form 1572, Radiation Safety and Bio-hazard reviews.
- b. Continuing Review – Completed Continuing Review Submission Form, current approved consent form, electronic protocol history that provides chronological and detailed descriptions of all previous IRB actions. All members have access to the complete protocol file prior to and during the IRB meeting. One member receives a copy of the complete protocol including any modifications previously approved by the IRB. ***Critical element*** - All members receive an IRB computer generated protocol history that includes complete details of every previous IRB review.
- c. IRB Process - investigator submissions must be received in the IRB office by Wednesday for review the following Tuesday. Materials are distributed (including IRB minutes of the previous meeting) to members on Friday and

couriered to the home of the community member or others as necessary. Adjustments to the schedule may be made due to federal holidays, weather, IRB training, etc. Schedule adjustments will be made and approved by the IRB Chairman or Co-chair. IRB members will have ample time allotted to review IRB packets (4 to 5 days, minimum)

17. Requires documentation of informed consent unless a specific waiver or alteration is granted by the IRB or unless specific criteria for exception from Informed Consent are met for emergency use of a test article. Assures that the informed consent form, (a) incorporates potential risks including the consequences of such risks if applicable, (b) does not overstate benefits and understate risks, (c) includes all foreseeable risks and discomforts associated with the research treatments and procedures and, (d) assures that storage and release of identifiable private information is appropriate to human subject protections, (e) ensure language in the informed consent is consistent with the protocol and when applicable, work with the Privacy Officer to ensure it is consistent with the HIPAA authorization. Documentation of informed consent includes, the signature and date of the subject or the subject's LAR, the signature of the witness and the date of the subject's or LAR's signature was witnessed, when applicable, and if use of facsimile is approved by the IRB, the subject may submit the signed and dated informed consent form to the investigator or designee by facsimile. (Clarification - Email communications do not constitute documentation of informed consent.)
18. Conveys IRB findings (including consent form approvals or modifications required) in writing to the Principal Investigator, to the Research and Development Committee, and if required to a sponsor or regulatory agency within one week of the IRB meeting. IRB "actions required" are clearly written on notification letters. IRB consent form "actions required" are marked in red ink on the consent form.
19. Assures that the use of stored specimens conforms with VA requirements. Specimens must be used only for the specific tests/analyses outlined in the approved research protocol and informed consent and destroyed when the specific test/analyses are complete. Reuse of the specimens must be consistent with the protocol and consent under which they were collected and reuse must only occur through a VA-approved protocol.
20. Requires that new findings potentially impacting subjects' willingness to participate in studies are conveyed to subjects. The Committee assists investigators in determining the urgency of the situation and the manner in which information needs to be conveyed to subjects. Significant new information may require re-consenting of all affected subjects. Re-consenting is not required for subjects that have completed their active participation in a study, or for subjects who are still actively participating when the change is deemed not to affect their safety or willingness to participate. For example, changes in telephone numbers or investigator names may be communicated to subjects via a written notification.
21. Reviews research involving deceased persons. Research involving deceased persons is not subject to state and federal laws governing human research activities. However, when research involves the use of protected health information (PHI) the requirements in 45 CFR 164.512 (i) (iii) shall be met.
22. Identifies all active research data repositories at NWHCS and ensures that all of the administrative and oversight requirements set forth in VHA Handbook 1200.12, §13, are met.

B. Categories of Actions by the IRB

Categories Table

All categories of IRB submissions must first undergo review by the full committee at a convened meeting. The Committee will determine at that point what action to take. The range of actions and basis for those actions are described below and summarized in this table:

<u>IRB Action</u>	<u>Material Resubmitted</u>	<u>Review of Resubmission</u>
Approved	---	---
Modifications Required to Secure Approval – Scripted	Minor scripted changes	Designated IRB Reviewer
Modifications Required to Secure Approval-- Non-Scripted	Minor non-scripted changes require clarification	Full Committee
Tabled	Full resubmission	Full Committee
Disapproved	New protocol	Full Committee
Deferral	More material needed	Full Committee

1. Approved

Meets the regulatory criteria for IRB approval (45 CFR 46.111, 21 CFR 56.111, 38 CFR 16.111). The date of approval is the date of the convened IRB meeting at which approval was granted.

2. Modifications Require to Secure Approval– Scripted: Designated IRB Member or the IRB Administrator Reviews Investigator Response

Meets the regulatory criteria for IRB approval (45 CFR 46.111, 21 CFR 56.111, 38 CFR 16.111). Minor changes and/or minor additional information are required. The Committee defines “minor” as involving no substantial risk-benefit concern impacting subject safety. This category of approval often involves the requirement that additional specific language stipulated by the IRB (“scripted”) be inserted in the consent form. It also might include a request for additional minor documentation. An experienced IRB **voting member** (defined as a voting member having attended more than 26 IRB meetings and completed required training requirements) designated by the Chairperson assures that IRB requirements have been met. The experienced IRB voting member has the complete submission material available and assures that stipulated changes are made in order to secure IRB Approval. The experienced IRB voting member is knowledgeable and authorized to re-submit material for Full Committee Review any new information that unexpectedly arises that falls out of the scope of “minor.” The date of IRB Approval is the date the conditions were determined to be met. For the purpose of determining the date of continuing review for studies requiring continuing review, the date of the IRB Action, “Modifications Required to Secure Approval” is used. Written notifications to IRB members regarding when conditions were determined to be met are listed in the IRB Agenda, section entitled, “Stipulations Met and Final Approval Letter Issued.”

3. Modifications Required to Secure Approval – Non-Scripted – Full Committee Reviews Investigator Response

Meets the regulatory criteria for IRB approval (45 CFR 46.111, 21 CFR 56.111, 38 CFR

16.111). Minor changes and/or minor additional information are required. The Committee defines “minor” as involving no substantial risk-benefit concern impacting subject safety. This category of approval often involves the requirement that additional non-scripted clarifications be provided to the Full Committee for review. For example, if reviewing the consent form the Committee wants the investigator to “list the consequences” or if the Committee recommends, “remove or improve.”

4. Tabled – Full Committee Reviews Investigator Response

Does NOT meet the regulatory criteria for IRB approval (45 CFR 46.111, 21 CFR 56.111, 38 CFR 16.111). Significant modifications are necessary in order to secure IRB Approval. The IRB TABLES submissions in which inadequate information is provided for the IRB to determine if regulatory criteria of approval are met.

5. Disapproved

Contains a fundamental scientific, or ethical flaw which precludes approval and/or the risk benefit ratio is inappropriate to the safe conduct of human research.

C. IRB Communication to the Investigator

The IRB provides written communication to the investigator for all IRB actions within one week of the meeting. Verbal and informal lines of communication (e.g. telephone, E-mail) are always open. The IRB and IRB staff encourage research staff to ask questions. IRB sponsored Coordinator/Investigator Meetings are an effective tool to disseminate information to research staff.

D. Vulnerable Populations

covered under subparts B, C and D of 45 CFR 46. Vulnerable populations include individuals covered under subparts B, C and D of 45 CFR 46.

Examples of Subjects Requiring Special Consideration

- members of a group with a hierarchical structure such as employees, students, or active Service members,
- subjects who are economically or educationally disadvantaged,
- subjects who are homeless,
- patients with limited or no treatment options such as those who are terminally ill or in a nursing home,
- subjects at risk for social, economic, or legal consequences who have to answer research survey questions about their employment or student practices, drug use or HIV status,
- subjects who may have increased susceptibility to harm such as those who are asked sensitive questions about disturbing situations such as a sexual assault.

General Steps Followed by Investigators and the NWHCS IRB to Determine Need for Additional Protections:

For individuals or populations that may be temporarily or permanently vulnerable the investigator and the NWHCS IRB considers those who:

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

General Procedures Followed by the Investigator and NWHCS IRB Regarding Approval of Additional Safeguards:

If the investigator and IRB determine that a vulnerable individual or population may be enrolled, an IRB approved plan of additional safeguards is required. The investigator is required to provide to the IRB a written plan describing additional safeguards that will be implemented. The IRB will review the plan and determine if it is adequate to protect subjects' rights and welfare. (Note: Instructions to investigators are incorporated in the Initial Review Submission Form)

E. Communicating IRB Findings and Actions to Investigator and Institution

Ref: [21 CFR 56.108(a)(1) and 56.109(e)]

Letter(s) regarding all IRB determination are signed by the Chairperson or other voting member who have reviewed the research. The official IRB determination letters are forwarded to the investigator along with relevant study information including approved consent forms, PO reviewed HIPAA authorizations determined to be legally effective, and Conditions of Approval. The Chair or acting Chair authorizes the individual(s) recording meeting minutes to forward IRB approved determination letters to investigators. The assigned minutes takers are authorized to use the Chair's or Acting Chair's signature stamp, or sign for them on the IRB approved determination letters. Approval, Modifications Required to Secure Approval (non-scripted and/or scripted modifications required), Table, Disapproval for all IRB reviews including initial and continuing review, modifications to a previously approved research, serious adverse events, etc.) are communicated in writing to the Principal Investigator within one week of the IRB meeting. IRB correspondence to investigators regarding its findings and actions provides reasons for its determinations and requested changes and/or additional information as appropriate. The IRB sends written requests on official IRB letterhead requesting additional information or clarifications. If a response is not received within 3 months the IRB may impose additional requirements as warranted.

F. Determination of Continuing Review Frequency

Determining which Studies require Review more often than Annually **[21 CFR 56.108(a)(2) and 56.109 (f)]**

For studies that require continuing review, The IRB requires Continuing Review of **certain** research at intervals appropriate to the degree of risk, but not less than once per year. The IRB may determine that certain studies require risk assessment more often than annually. IRB minutes specify the review requirements (e.g., 12 months, 9 months, 6 months, 3 months). The IRB assures that appropriate safeguards have been included to protect the welfare of subjects likely to be vulnerable to coercion or undue influence and may ask investigators or sponsors to address this issue in detail. Investigators are required to identify use of vulnerable populations and to explain extra precautions taken to prevent coercion. Examples of studies which may be considered for special attention and requiring review more often than annually may involve:

1. Withdrawal of therapy, whether or not it is replaced by experimental treatment, when there is significant risk of morbidity or mortality.
2. Any invasive surgical procedure (including arterial catheterization), even if the experimental procedure replaces a standard surgical procedure that is thought to involve higher risk.
3. Significant risk of serious impairment.
4. Risks when there are no potential clinical benefits for the subject and/or there is limited use in humans (e.g. Phase I or Phase II studies).
5. Use of potentially Vulnerable subjects.
6. Significant Risk Device studies.
7. Use of narcotics or other articles with potential for abuse.
8. Inexperienced investigators or experienced investigators with previous incidences of non-compliance.
9. Off-site research.
10. Investigator-initiated research where the NWIHCS IRB/R&D may be the only safety review bodies with responsibility for protecting subjects.

G. Verification from Sources other than the Investigator

Verification that no Material Changes have Occurred since Previous IRB Review – Ref: [21 CFR 56.108(a)(2)]

In certain cases, in conjunction with risk-benefit assessment, the IRB may require verification from sources other than the Principal Investigator that no material changes have occurred since previous IRB review. This may be necessary at times, for example, in cooperative studies, other multi-center research or for non-compliance investigations. The IRB recognizes that protecting the rights and welfare of subjects may sometimes require that the IRB solicit independent verifications.

At Initial Review and at Continuing Review the IRB considers various kinds of information in its risk-benefit assessment. Some examples of considerations that might trigger the need for independent verification are:

1. Probability and magnitude of anticipated risks to subjects.

2. Likely medical condition and mental status of the proposed subjects.
3. Probable nature and frequency of changes that may ordinarily be expected in type of research proposed.
4. Limited use of research test articles in humans.
5. Use of vulnerable populations.
6. Prior experience with the principal investigator and research team.
7. Prior oversight experience that the IRB has with the research drug, device, product or procedure.
8. Investigator initiated projects involving more than minimal risk.
9. Reports of investigator audits by regulatory authorities.
10. Sponsor monitor reports.
11. Suspected serious non-compliance.
12. Complaints.
13. Suspected scientific misconduct.
14. Lack of expertise of IRB members to adequately review research.
15. Other factors that the IRB deems relevant.

In making determinations about independent verification, the IRB may prospectively at Initial Review or retrospectively at Continuing Review require independent verification. Some examples of types of independent verifications from sources other than the investigator (e.g. Research Compliance Officer, AO Research, IRB Administrator, non-research VAMC unit manager, ORO official, expert scientific reviewer, etc.) may include:

1. Audits of investigator's performance.
2. Audits of investigator's study records.
3. Observation of the informed consent process.
4. Review of CPRS medical record entries.
5. Reviews of investigational pharmacy reports at Continuing Review.
6. Monitoring of significant device storage and dispensing procedures.
7. Audits of sponsor monitoring reports.
8. Request additional information from research participants, staff or sponsor officials as warranted.
9. Require additional independent safety monitoring and interim reports of the findings throughout the study.

10. Require the Principal Investigator and/or research coordinator to seek additional training.
11. Require the Principal Investigator to secure the professional services of individuals with specialized expertise to monitor subject safety and provide reports deemed necessary to the IRB.

XIII. IRB CONDITIONS OF APPROVAL

(Note: A printed copy of IRB Conditions of Approval is mailed to investigators with each Initial and Continuing Review Approval Letter)

1. Do not initiate any research until you obtain written IRB approval and written notification from the NWIHCS Associate Chief of Staff for Research that research can be initiated/continued. Adhere to ethical principles defined in the Belmont Report of April 18, 1979: (1) Respect for persons, voluntary consent, privacy, confidentiality, (2) Beneficence - maximize possible benefits to the subject and minimize possible harms, (3) Justice - equitable selection of subjects.

Do not request SS numbers by telephone. You can obtain and use SSNs only when real SSNs are required to meet the specific aims of the research and such use is approved by the IRB.

Use IRB approved subject recruitment material. Initial contact by the research team must be made in person or by letter prior to initiating any telephone contact. All telephone contacts must be limited to topics outlined in IRB approved protocols and informed consent forms.

Research records must be maintained according to the VHA Records Control Schedule. Contact IRB for additional information regarding hard copy and electronic storage instructions. If the investigator leaves NWIHCS the records are maintained at NWIHCS . Copies of relevant information may be transferred to an investigator's new VA facility with appropriate approval of the privacy officer and information security officer.

2. The investigator will conduct the study according to the protocol, sound study design and (GCP) guidelines, applicable laws and regulations and will report to the IRB and sponsor significant findings that could affect the safety and well-being of research subjects. The investigator will prepare and maintain all study records including accurate case histories (e.g. case report forms and signed, dated consent forms along with Master Lists of research subjects for whom informed consent has been obtained as required by the IRB and accounting of disclosures).

The investigator will create a Health Record and a progress note in CPRS for all research subjects (Veterans or Non-Veterans) when the research requires use of any clinical resources such as: radiology, cardiology (e.g. electrocardiogram, stress test etc.) clinical laboratory, pharmacy etc. or if the research intervention may lead to physical or psychological Adverse Events.

3. Do not initiate any unapproved changes (e.g. Amendments, Consent Form modifications, Advertisements) without IRB review and approval except where necessary to eliminate apparent immediate hazard to human subjects. Changes

in approved research initiated without IRB approval to eliminate apparent immediate hazard must be reported promptly to the IRB and sponsor. Do not initiate any modifications of research determined to be EXEMPT by the IRB without IRB re-review. Report changes in your employment or credentialing and privileging status to the IRB. Changes in Principal Investigator (PI), Local Site Investigator (LSI) and other study staff named in the protocol (e.g. medical monitor) require prospective IRB review and approval. Other study staff changes (e.g. study coordinator not named in the protocol) should be promptly reported but no later than at Continuing Review).

4. Informed, written consent is required of each human subject or his legally authorized representative (LAR) unless specifically waived by the IRB/sponsor prior to conducting any research activities (including screening activities,, unless approved by the IRB). The investigator or a designee who has knowledge about the study, appropriate training and scope of practice obtains informed consent using an IRB approved and date stamped consent form. The research subject or (LAR) and witness if required by the IRB must sign and date the consent form. **NWIHCS follows Federal law regarding who can serve as a legally authorized representative.**

Order of Priority

- (a) Health care agent appointed by person in a Durable Power of Attorney for Health Care**
- (b) Legal guardian or special guardian**
- (c) Next of kin 19 years or older in the following order:**
 - i. Spouse**
 - ii. Child**
 - iii. Parent**
 - iv. Siblings**
 - v. Grandparent**
 - vi. Adult grandchild**

A separate HIPAA authorization, or waiver approved under normal IRB review procedures is required if the study involves use of Protected Health Information. Surrogate HIPAA authorization may be obtained by a personal representative (i.e. a legal guardian or individual who has power of attorney). NOTE: A “LAR” for the purposes of research informed consent is not synonymous with HIPAA’s “personal representative.” Ensure that the protocol HIPAA authorization and consent form are consistent.

Surrogate consent for inclusion of vulnerable subjects who lack decision making capability must be specifically approved in advance by the IRB if the patient lacks decision-making capacity or has been declared incompetent. If decision making capacity fluctuates it may be necessary to re-consent some subjects. Even if an LAR gives consent, subjects with limited decision-making capacity should assent if able to do so and no subject should be forced or coerced to participate. Only the approved IRB /date stamped consent form should be used.

Provide a copy to the subject or LAR signing the form and keep the original for your files. Document a CWAD (clinical alert) in medical record as appropriate and remove the CWAD at Study Closure. CWAD documentation in the medical record is not required if (1) participation in the study involved only one encounter (e.g. one blood draw); (2) participation in the study involved the use of a questionnaire or previously collected specimens or (3) identification as a

participant in minimal risk studies would place the subject at greater than minimal risk. The CWAD should document: (1) that subjects are enrolled in a research project, (2) the study drug they are taking, (3) the investigator and coordinator contact numbers, (4) the date of informed consent, (5) that informed consent was obtained before any study procedures were conducted, and (6) that a copy of the consent form was given to the subject.

5. Report to the IRB within 5 business days all NWHCS SAEs unless the IRB has specifically approved an exception in which such reporting is not required (e.g. minimal risk chart review protocols, protocols using data generated for clinical care, in which interventions for clinical care were not part of the research). The FDA defines Serious Adverse Events as: (1) death, (2) life-threatening, (3) hospitalization-initial or prolonged, (4) disability, (5) congenital anomaly, (6) required intervention to prevent permanent impairment or damage, (7) serious and unexpected severity or frequency of expected events.

6. Report to the IRB within 5 business days all Unanticipated Problems involving risks to subjects and others (i.e. events that are unforeseen, caused harm or placed a person at increased risk of harm, and are related to the research procedures). Such events can occur in clinical and non-clinical research and may involve individuals not directly involved in the research. Examples may include: (1) unresolved complaints or violent or illegal behavior, (2) loss of consent form or research data, (3) breach of confidentiality, (4) unexpected injury or death to subject or others, (5) unexpected pregnancy or incarceration involving research subject, (6) pharmacy or lab errors, (7) inability to conduct specified safety assessments, (8) interim analysis indicates subjects have lower rate of response than anticipated, (9) protocol deviations that placed subjects at increased risk, (10) any serious problem that puts subjects or others at increased risk.

7. Promptly disclose all Conflicts of Interest (e.g. financial, professional/academic, personal) if you have not already done so and report new potential conflicts should they develop throughout the course of the study. Conflicts of interest can occur under a variety of circumstances, can be overt or covert and arise in situations where one party owes a duty or loyalty to another.

8. Report Emergency Use of unapproved test articles or use of test articles without informed consent to the IRB within 5 days.

9. Provide a copy of each subject's Consent Form, Investigational Drug Information Record-VA Form 9012(s) and CWAD (medical record flag/clinical alert) to the Investigational Pharmacist prior to your request to receive, store and dispense study medication (the Investigational Pharmacist is the official responsible for the storage and dispensing of investigational drugs).

10. For studies requiring continuing review, submit Continuing Review information to the IRB by the date specified and inform the IRB when your study is completed (federal law requires that every project must be reviewed a minimum of once per year). If the Continuing Review does not occur within the timeframe set by the IRB, submit a list of subjects for whom stopping research activities would cause harm, and stop all research activities unless the IRB or IRB Chair, in consultation with the VA Chief of Staff, found that it was in the best interest of individual subjects to do so. Study results should be disseminated to

the IRB and to subjects as appropriate as they become available.

11. The Principal Investigator assumes ultimate responsibility for this study and is responsible for training and oversight of his/her research staff. Investigator performance and your research program are subject to review by the NWHCS IRB, RCOs, sponsors, as well as by federal regulatory agencies (e.g. FDA, OHRP, ORO). Completion of human research training is required for investigators and research staff every three years. All sponsor contracts must be reviewed and approved by the NEBRA Executive Director and the VA Facility Director.

12. When a previously enrolled research subject becomes a prisoner or becomes pregnant, the principal investigator should promptly notify the IRB of this event and cease research interventions. Additional regulatory requirements apply and re-review of the research is required.

13. Investigators and coordinators are encouraged to contact the ACOS for Research, AO for Research, IRB Chairperson, Research Compliance Officer or IRB Administrator to discuss concerns or suggestions. Investigator appeals of IRB decisions should be submitted to the IRB for review.

14. NWHCS IRB is not connected with, has no authority over and is not responsible for human research conducted at UNMC, Creighton or other institutions. Separate consent forms, HIPAA authorizations, initial reviews, continuing reviews, amendments, and reporting of serious adverse events are required if the same study is conducted at multiple institutions.

15. Report Information Security and Privacy Incidents, including the loss of confidential or Privacy Act protected data to the Information Security Officer (ISO), the Privacy Officer (PO), your Supervisor, R&D Committee Chair and ACOS/Research within 1 hour.

16. PROTECT VA SENSITIVE INFORMATION

Definition of VA Sensitive Information:

“VA sensitive information” is data that requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, alteration, or destruction. The term includes (1) information whose improper use or disclosure could adversely affect the ability of an agency to accomplish its mission, (2) proprietary information, (3) records about individuals requiring protection under various confidentiality provisions such as the Privacy Act and the HIPAA Privacy Rule, and (4) information that can be withheld under the Freedom of Information Act (FOIA). Health information de-identified in accordance with VHA Handbook 1605.01 Appendix B would not be considered sensitive information.

ACTION REQUIRED:

- Don't leave hard copies/charts with VA sensitive information in open areas for others to see or take.
- Don't store VA sensitive information on unencrypted computers or unencrypted storage devices (e.g. thumb drives).
- Don't transport, use or store VA sensitive information off-site unless you obtain written permission (contact the IRB Administrator). Use “Request for Issuance of USB Flash Drive and/or Authorization to Transport & Utilize VA Sensitive

Information Outside Protected Environments.”

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- Don't transmit VA sensitive information in unencrypted e-mails (contact ISO if you need PKI encryption software installed on your machine) and refer external requests for information to the PO.

17. Investigators are responsible for the research protocol and therefore are responsible for:

1. Disclosing conflicts of interest
2. Ensuring adequate resources
3. Ensuring qualified research staff
4. Promptly reporting changes in investigators (PI and LSI) and study staff
5. Overseeing the research staff
6. Ensuring complete information in the research protocol and that research is scientifically sound.
7. Obtaining written approvals before initiating research
8. Implementing the study as approved including use of investigational drugs and devices when applicable.
9. Maintaining investigator's research records
10. Obtaining informed consent (designating responsibility for obtaining informed consent, using most IRB approved current consent form, circumstances under which informed consent must be obtained, ensure consent process clearly defines usual care from research risks, documentation of informed consent)
11. Ensuring consistency of informed consent form, protocol, and HIPAA authorization
12. Ensuring HIPAA authorization (or waiver) is obtained
13. Performing subject outreach
14. Ensuring appropriate telephone contact with subjects
15. Obtaining IRB approvals for all changes to the research protocol/consent form
16. Submitting continuing review materials for studies requiring continuing review
17. Reporting problems and SAEs
18. Reporting deviations and complaints
19. Completing appropriate actions at research project completion
20. Transferring and/or archiving research records per VA requirements
21. Maintaining a Master list of all subjects for whom informed consent has been obtained
22. Ensuring appropriate research laboratory test reporting (research lab test results cannot be used for diagnostic, treatment or prevention of disease unless the lab has been accredited and meets all requirements)
23. Ensuring requirements of multi-site studies
24. Creating a VHA health record when the research requires use of any clinical resources or if the research intervention may lead to physical or psychological AEs

18. Investigator Responsibility to Maintain Research Records

It is the investigator's responsibility to maintain 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.

(1) Research records include the following when relevant to the study:

- (a) Copies of all IRB-approved versions of the protocol and amendments.

- (b) Case report forms and supporting data, including, but not limited to, signed and dated informed consent forms and HIPAA authorizations.
- (c) 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,
 - 5. Other relevant study data including, but not limited to:
 - a. Progress notes,
 - b. Research study forms,
 - c. Surveys, and
 - d. Questionnaires.
- (d) Reports of adverse events.
- (e) Data analyses.
- (f) Codes and keys used to de-identify and re-identify subjects' PHI.
- (g) Reports including, but not limited to, abstracts and other publications.
- (h) 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.
- (i) A Master List of all subjects for whom informed consent has been obtained in the study. This means the investigator must maintain a Master List of all subjects from whom informed consent has been obtained unless the IRB (a) granted a waiver of documentation of informed consent (117c) and (b) the IRB determines that including the subjects on such a Master List poses a potential risk to subjects from a breach of confidentiality.

(2) Documents must be maintained in a secure environment and be accessible so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements.

(3) An Accounting of Disclosure must be maintained for each and every disclosure of information from this study to a non-VA entity. (Note: The facility Privacy Officer can assist in providing a mechanism to account for this disclosure)

What Are the Penalties for Non-Compliance?

Non-compliance may result in suspension of approval of a particular project. Serious and continuing non-compliance may result in suspension of your privilege to conduct research at NWHCS .

XIV. WHAT TO REPORT TO THE IRB, INSTITUTIONAL OFFICIALS AND OTHER REGULATORY AGENCIES

A. Unanticipated Problems Involving Risks to Participants or Others *[21CFR 56.108(b)(1) and 56.115(a)(1)]*

This policy applies to all human subjects research conducted in the VA, as well as investigators, IRB members and staff, R&D members and staff, and institutional officials. Others who may report possible unanticipated problems include participants, participant's family members, an affiliate university, the VA patient relations offices, sponsors and other auditors,

and others not involved with the research project but having information about a possible unanticipated problem.

Members of the research community are required to report and the IRB is required to review reports of unanticipated problems involving risks to subjects or others (e.g. adverse events, complaints from participants or others, protocol deviations, new safety information, DSMB/data monitoring committee reports as well as any other event that influences the risk benefit analysis of the research. The IRB determines whether these reports were unanticipated problems involving risks to participants or others and takes required actions including notifications of subjects, suspension, termination and reporting to relevant institutional officials/entities (e.g. VA/ORO and DoD) and oversight agencies (e.g. DHHS, FDA)

Definitions

Adverse Event (AE) - is any untoward physical or psychological occurrence in a human subject participating in research.

Related AE, Death or Problem – is an AE, death or problem that may reasonably be regarded as caused by or probably caused by the research.

Serious Adverse Event (SAE) - is an untoward occurrence in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect., or that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome.

Serious problem - A serious problem is a problem in human research or research information security that may reasonably be regarded as:

- (1) Presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or
- (2) Substantively compromising a facility's HRPP or research information security program.

Unanticipated and Unexpected Problems – The terms refer 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.

UPIRTSO – add definition

Sponsor Serious Adverse Events Review Policy:

Sponsors of FDA-Regulated studies generate numerous IND Safety Reports to Investigators and require submission of all of these reports to the IRB. The individual reports (both initial and follow-up) generally do not provide enough information for the IRB to perform a meaningful analysis. The IRB relies on receipt of sponsor safety reports or notifications, DSMB reports, or Data Safety Committee reports as these groups have access to all pertinent data required to perform a meaningful analysis. The NWIHCS IRB ensures that an adequate data safety monitoring plan is in place prior to approval of each study. Sponsor AE reports lacking meaningful analysis do not constitute problems. The NWIHCS IRB Chair or his designee (Investigational Pharmacist, experienced IRB member) will review these reports according to

VHA Policy, and an acknowledgement of receipt will be provided to the Investigator for his study files.

Examples of materials provided to and reviewed by IRB: - Unanticipated Problems. As warranted, the IRB may review relevant reports such as 5 Day Reporting Form, Non-5 Day Reporting Form, notifications from others, protocol, investigational brochure, consent documents, IRB Continuing Reviews, Electronic Protocol Histories and protocol material deemed relevant. The IRB assesses reports of potential sources of unanticipated problems such as:

- complaints or violent or illegal behavior,
- loss of research data,
- breach of privacy or confidentiality,
- reports of injury or death involving participant or others including work related injury to personnel involved in human research
- a research participant becomes unexpectedly pregnant
- a research participant is incarcerated,
- interruptions of participant enrollments due to concerns about safety, rights and welfare of participants, research staff, or others,
- pharmacy or lab errors,
- scientific reports,
- interim data analyses including sponsor analyses describing a safety problem,
- DSMB, data monitoring committee findings describing a safety problem for which IRB/investigator action might be warranted,
- VA National Pharmacy Benefits Management Bulletins/Communications (PBM Safety Alerts)
- inability to conduct specified safety assessments,
- findings of scientific or ethical misconduct,
- sponsor monitor reports,
- protocol deviations, exceptions or violations, including changes to research without prior IRB approval in order to eliminate apparent immediate harm,
- compliance reports,
- internal and external adverse events that are unexpected involve new/increased risks, and related to research,
- any problem or deficiency involving substantive harm, or genuine risk of substantive harm, to the safety, rights, or welfare of human research participants, research staff, or others,
- any problem reflecting a deficiency that substantively compromises the effectiveness of the HRPP,
- any other information that influences the risk benefit analysis

Reporting Requirements:

IRB Reporting Requirements – Regarding review of serious unanticipated problems and serious adverse events: If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is unanticipated and related to the research, the IRB Chair or designee must report the problem or event directly (without intermediaries) to the Facility Director within 5 business days after the determination. The report must be made in writing, with a simultaneous copy to the ACOS/R and the R&D Committee. The Facility Director must report the problem or event to ORO within 5 business days after receiving such notification. A simultaneous determination is required regarding the need for any action necessary to prevent an immediate hazard to subjects including whether or not a protocol or informed consent modification is warranted and if previously enrolled subjects need to be notified.

Institutional Reporting Requirements – Facility Director is responsible for notifying within 5 business days after being informed of a reportable event, the Office of Research Oversight Regional Office (ORO), with a copy to the VISN Facility Director and ORD and to PO and ISO if report involves unauthorized use, loss, or disclosure of individually identifiable patient information or violations of VA information security requirements. As applicable, promptly notify FDA, OHRP and notify DoD if following DoD requirements within 30 days. Follow up reports detailing any additional findings and appropriate remedial actions must be provided to ORO at intervals.

- **Local Research Deaths.** VA personnel, including WOC and IPA appointees, must ensure oral notification of the Institutional Review Board (IRB) **immediately** upon becoming aware of any local research death that is both **unanticipated** and **related** to the research. The IRB must alert ORO by e-mail or telephone **within 2 business days** after receiving such notification and provide relevant information as requested. The Facility Director and the ACOS/R&D must receive concurrent notification. VA personnel, including WOC and IPA appointees, must ensure written notification of the IRB **within 5 business days** of becoming aware of the death. **Within 5 business days** after receiving written notification of the death, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects. The IRB must review the death and the determination of the IRB Chair or qualified IRB member-reviewer at its next convened meeting and must determine and document that: (a) The death was both unanticipated and related to the research; or (b) There is insufficient information to determine whether the death was both unanticipated and related to the research; or (c) The death was not unanticipated and/or the death was not related to the research. Regardless of the determination, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented. The IRB must notify the Facility Director and the ACOS/R&D of its determinations **within 5 business days** of the determinations. The Facility Director must report the determinations to ORO **within 5 business days** after receiving the IRB's notification.
- **Problems involving, or involving risks to subjects or others in VA research.**

Investigators, RCOs, and other members of the VA research community must report all problems involving risks to subjects or others in VA research to the IRB **within 5 business days** after becoming aware of any serious unanticipated problem involving risks to subjects or others. Members of the VA research community are required to ensure that the problem has been reported in writing to the IRB. Where applicable, employees are required to report Information Security and Privacy Incidents, including the loss of confidential or Privacy Act protected data to the Information Security Officer (ISO), Privacy Officer (PO) their Supervisor, ACOS/R and/or relevant oversight committees within 1 hour. Subject notification about compromised information will be coordinated with PO and ISO in accordance with VA Handbook 6500.2, "Management of Breaches Involving Sensitive Personal Information." (July 28, 2016)

Investigators/study staff use the **5 Day Reporting Form** to notify the IRB. Such events may include:

1. Events that occur any time during or after the research study, which in the opinion of the principal investigator: (a) Involve harm to one or more participants or others, or placed one or more participants or others at increased risk of harm; (b) Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the informed consent document.); (c) Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures or if it is more likely than not that the event affects the rights and welfare of current participants).
2. Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example: (a) An interim analysis indicates that participants have a lower rate of response to treatment than initially expected; (b) safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected; (c) A paper is published from another study that shows that an arm of the research study is of no therapeutic value.
3. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
4. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
5. Incarceration of a participant or unexpected pregnancy of a participant.
6. Event that requires prompt reporting to the sponsor.
7. Complaint of a participant when the complaint indicates unexpected risks or may not be resolved by the research team.
8. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that placed one or more participants at increased risk, or has the potential to occur again.
9. Unanticipated adverse device effect (Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).
10. Unanticipated Serious Adverse Event (death, a life-threatening experience, hospitalization (for a research participant not already hospitalized), persistent or significant disability or incapacity, congenital anomaly or birth defect, the need for medical surgical, behavioral, social, or other intervention to prevent any of the above).

Examples of IRB Review Considerations - Unanticipated Problems Involving Risks to Subjects Others

- Is the nature of the problem unanticipated, unexpected, out of the norm?
- Was anyone injured?
- Was research data compromised?
- Were laws, regulations or policies violated?
- What caused the problem?
- Was the research protocol followed?

- Was this an isolated event or has it happened before?
- Is corrective action required to protect subjects or others or to validate data?
- Would information about this problem affect a subject's willingness to participate in research and should the subject be notified?
- Should the research be modified, suspended or terminated?

Examples of IRB Action Considerations - Unanticipated Problems Involving Risks to Subjects or Others

- Unanticipated problems are always unanticipated by definition. (1) Determine if the nature of the problem is unanticipated. (2) If yes, does it involve risks to research subjects and/or others beyond that originally approved by the IRB? (3) If both answers are yes then the event should be processed as an unanticipated problem involving risks to subjects and/or others and reports should be sent to appropriate institutional officials, and regulatory agencies.
- The IRB conducts a risk-benefit assessment for all problems involving risk to subjects and/or others regardless of whether they are determined to be "unanticipated" or "anticipated" in order to (1) determine if the research should continue, (2) if modifications are needed prior to continuation of the research or (3) if the research should be discontinued. The IRB assures that appropriate plans are in place to maximize subject safety (e.g. continuation of research participation, subject withdrawal or transition to standard of care).
- Require additional training.
- Revise policies and procedures.
- Modify the research project.
- Revise the frequency of Continuing Review, if the project requires continuing review
- Add continuing review if project currently does not require continuing review
- Require additional monitoring of the research.
- Coordinate corrective action with other services in the medical center (lab, pharmacy, nursing service, medical service, surgical service etc.) to resolve the problem.
- Inform subjects (current and past if warranted) and identify who should inform them. Interventions with subjects are based upon what the IRB judges to be in the subject's best interest. The IRB understands that the information and the manner in which it is conveyed (should the IRB decide to inform subjects) to subjects could influence a subject's decision to continue participation in the research.
- Suspend or terminate research. Project suspensions and terminations trigger reporting procedures to institutional officials, regulatory officials and sponsors if applicable.
- Determine if any injuries occurred and the seriousness of such injuries. Serious injuries will be reported to appropriate officials and regulatory agencies.
- For studies that are terminated, the IRB assures that subject withdrawal plans and/or transition to standard of care are in place and do not compromise subject safety.

IRB Determination – First, the IRB must make a determination whether a reported event meets the definition of an unanticipated problem involving risks to subjects or others. If it does not, no action is required. Within 5 business days after a report of a serious unanticipated problem involving risk to subjects or others, or a unanticipated local SAE is received, a qualified IRB member-reviewer (or alternatively, the convened IRB) must determine and document whether or not the problem is serious, and unanticipated and related to the research. The 5 Day Reporting Form includes a “For IRB Only Section” to document findings.

IRB Review of SAEs and Serious Problems

Within 5 business days after receiving written notification of an SAE or serious problem, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.

- (1) The IRB must review the incident and the determination of the IRB Chair or qualified IRB member reviewer at its next convened meeting and must determine and document that:
- A. the incident was serious, unanticipated and related to the research,
 - B. there is insufficient information to determine whether the incident was serious and unanticipated and related to the research
 - C. the incident was not serious, and/or the incident was not related to the research
 - (a) The report must be made in writing, with a simultaneous copy to the ACOS for Research and the R&D Committee.
 - (b) The Facility Director must report the problem or event to ORO within 5 business days after receiving such notification.

(2) Regardless of the determination, the convened IRB must also determine and document whether any protocol or consent form modifications are warranted. If modifications are warranted, the convened IRB must also determine and document 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.

- (3) The IRB must notify the Facility Director and the ACOS/R&D in writing within 5 business days after it's convened meeting if:
- A. actions were taken to eliminate apparent immediate hazards to subjects; or
 - B. the IRB determined that the incident was serious and unanticipated and related to the research, or there was insufficient information to make the determination; or
 - C. Protocol or informed consent modifications were warranted.

(4) The Facility Director must report the situation to ORO within 5 business days after receiving the IRB's notification.

Examples of actions the IRB may take as appropriate:

- Monitoring of research
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to current participants (This must be done whenever the information may relate to the participant's willingness to continue participation)
- Providing additional information to past participants
- Requiring current participants to re-consent to participation
- Alteration of the frequency of continuing review
- Addition of continuing review
- Observation of the research or the consent process

- Requiring additional training of the investigator and study staff
- Notification of investigators at other sites
- Suspension or termination of the research according to IRB SOP "Suspension or Termination of IRB Approval" policy
- Obtaining additional information
- Reporting to other hospital divisions/officers (Information Security Officer (ISO) Privacy Officer (PO), Research Compliance Officer, Facility Director)
- Taking no action

B. Non-compliance (Serious or Continuing)

Definition (Handbook 1058.01) version 6/15/15)

Noncompliance – any failure to adhere to the requirements for conducting VA research covered by VHA Handbook 1058.01.

Serious noncompliance is any failure to adhere to requirements for conducting human research that may reasonably be regarded as;

- Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human subjects, research staff, or others including their rights to privacy and confidentiality of identifiable private information; or
- Substantively compromising human research protection

Non-serious non-compliance does not affect the rights and welfare of research subjects and is determined by the IRB not to be a flagrant violation of regulations, or the requirements or determinations of the IRB. Non-serious non-compliance may be relatively minor such as reporting an event to the IRB a few days after the due date or it may be a one-time event.

Continuing noncompliance is a persistent failure to adhere to the laws, regulations, or the policies governing human research.

Allegations of apparent non-compliance - HRPP officials may learn of allegations of apparent non-compliance that may or may not be true. HRPP officials, as applicable, will review and investigate the allegation to determine if it has some possibility of truth. If the allegation has no basis in fact, no further action is required. If it is determined the allegation is true, the non-compliance will be referred to the IRB/R&D for review and determination. The IRB may determine a Corrective Action Plan, as appropriate, commensurate with the level of non-compliance. The Committee determination along with any required corrective actions will be recorded in the IRB/R&D minutes. Determinations of continuing or serious non-compliance are reportable to appropriate institutional officials and regulatory agencies as required by VHA Handbook 1058.01.

Examples of materials provided to and reviewed by IRB – Apparent Serious or Continuing Non-compliance

- A copy of written allegations or a summary of verbal allegations.
- A copy of an accused individual's response to allegations or a summary of his/her verbal response.
- A copy of relevant internal or external audits or reports and the protocol and consent form when applicable.

- A summary, if any, of relevant previous HRPP findings of serious or continuing non-compliance.
- As warranted, an electronic IRB Protocol History documenting in chronological order, all IRB minutes and correspondence for relevant protocols.
- As warranted, any relevant IRB documents. Note: IRB records are filed in the same room in which the IRB meets and are available for review during all convened meetings.
- As warranted, parties involved may be requested to attend an IRB meeting to address allegations of non-compliance.
- As warranted, any other information felt to be relevant to the review of the allegation by any of the parties involved.

Examples of IRB Review Considerations - Is Non-compliance Serious or Continuing?

- Did it or could it result in serious harm to subjects?
- Did it or could it significantly impact subject safety?
- Did it or could it significantly impact the research record or data integrity?
- Was it an isolated event, first occurrence or part of a pattern?
- Was it reported by the investigator or by a third party?
- Was it intentional?
- Was it reckless?
- Were laws, regulations or policies violated?
- What caused the problem?
- What needs to be done to prevent re-occurrence?
- What type of corrective action plan is needed?
- Should the project be suspended or terminated?

Examples of IRB Action Considerations for Non-Serious and Non-Continuing Non-Compliance

- Evaluate the seriousness of the problems and determine if actions are required to protect subjects, staff and others and to validate data integrity.
- Require a corrective action plan.
- Require additional training (e.g. GCP, ACRP training, or individual training by the Research Compliance Officer and/or IRB Coordinator).
- Require the investigator attend an IRB/R&D meeting to discuss non-compliance and plans for improvement.
- Require additional monitoring.
- Place restrictions on this or other studies. (e.g. stop enrollment, not allow initiation of new studies, HRPP official observe informed consent process or study procedures)
- Increase the frequency of Continuing Review.
- Add continuing review for studies not currently undergoing continuing review
- Require additional research staff and or research resources.

Examples of IRB Action Considerations for Serious or Continuing Non-Compliance

- The IRB evaluates the seriousness of the problems and determines if the rights and welfare of subjects are adversely affected. The IRB takes actions in order to protect subjects, staff and others and to validate data integrity.

- The IRB conducts a risk-benefit assessment in order to (a) determine if the research should continue, (b) if modifications are needed prior to continuation of the research or (c) if the research should be discontinued. The IRB assures that appropriate plans are in place that maximize subject safety (e.g. continuation of research participation, subject withdrawal or transition to standard of care).
- Require a corrective action plan. If a problem persists (i.e. there has not been compliance with the corrective action) after the HRPP has identified it as a problem, completed an analysis and provided written notification of corrective action, then the non-compliance will be considered to be continuing non-compliance and will be reported to institutional officials, regulatory agencies and sponsors if applicable.
- Suspend or terminate the study in question (or other studies, if applicable) and notify institutional, regulatory and sponsor officials.
- Place restrictions on this or other studies. (e.g. stop enrollment, not allow initiation of new studies, HRPP official observe informed consent process, monitor other aspects of the research).
- Determine if modification of the research and/or re-training of study staff is a condition of re-approval. Determine if the research data can be used.
- If the IRB determines that additional training will not resolve the problem and the problem cannot be resolved privileges to conduct research at NWHCS may be revoked.
- Determine if subjects (current and past if warranted) should be notified, when subjects should be notified, how subjects should be notified, what information should be provided to the subjects, and who should provide subjects with such information. The IRB makes these determinations based upon what it judges to be in the subject's best interest and understands that the information and the manner in which it is conveyed to subjects could influence a subject's decision to continue participation in the research.
- Determine if a new investigator needs to assume responsibility for the study and determine if other research staff changes are necessary.
- Determine if the consent form needs revision, if subjects should be re-consented or if the consent process should be changed.
- Assign an outside monitor to supervise the continuation and/or withdrawal process.
- Determine an appropriate Continuing Review timetable or add continuing review if study does not require continuing review
- As warranted, coordinate actions with other services in the medical center (lab, pharmacy, nursing service, medical service, surgical service etc.).
- For studies that are terminated assure that subject withdrawal plans and/or transition to standard of care are in place and do not compromise subject safety.

Reports of Apparent Serious or Continuing Non-compliance – VA personnel including WOCs and IPA appointees, must ensure the IRB is notified in writing, within 5 business days of becoming aware of any apparent serious or continuing noncompliance with IRB or other human research protection requirements.

1. The convened IRB must review any such notification at the earliest practicable opportunity, not to exceed 30 business days after the notification. The IRB chair may take interim actions as needed to eliminate apparent immediate hazards to subjects.
2. The convened IRB must determine and document whether or not serious or continuing noncompliance actually occurred.
3. If the IRB determines that serious or continuing noncompliance occurred:
 1. A documented IRB determination is also required as to whether remedial actions are needed to ensure present and/or future noncompliance.
 2. IRB must notify the Facility Director and the ACOS/R&D within 5 business days after making its determinations.
 3. The Facility Director must report a determination to ORO within 5 business days after receiving the IRB's notifications.
 4. If the apparent serious or continuing noncompliance was identified by an RCO audit the IRB must notify the RCO within 5 business days of its determination, regardless of outcome.
 5. The IRB must track the determinations required under paragraph 6.f.(2) and 6.f.(3) of VHA Handbook 1058.01 for use in the Facility Director Certification.

IRB Review of Apparent Serious or Continuing Noncompliance - The IRB must review any report of apparent serious or continuing noncompliance, according to VHA Handbook 1058.01 Version June 15, 2015, at its next convened meeting. **NOTE:** *The IRB Chair, or designee, needs to consult ORO if the significance of a reported event is not clear.*

- (1) Should the IRB determine that the reported incident constitutes serious noncompliance or continuing noncompliance (as defined in VHA Handbook 1058.01 Version June 15, 2015), the IRB Chair, or designee must report the determination directly (without intermediaries) to the Facility Director within 5 business days after the determination.
- (2) The IRB Chair's report must be made in writing, with a simultaneous copy to the ACOS for Research, the R&D Committee, and any other relevant research review committee.
- (3) The Facility Director must report the determination to ORO, with a simultaneous copy to the VISN Facility Director and the ORD, within 5 business days after receiving such notification, unless the noncompliance has already been reported in accordance with subparagraph 7h (2).
- (4) An initial report of an IRB determination that serious noncompliance or continuing noncompliance occurred is required, even where the determination is preliminary or disposition of the matter has not been resolved at the time of the report.

Examples of Apparent Serious Noncompliance. Examples of apparent serious noncompliance that must be reported to the IRB within 5 business days include, but are not limited to:

- (1) Initiation of VA human subject research, regardless of level of risk or number of subjects, without written notification from the ACOS for Research that the project may begin.
- (2) Initiation of VA human subject research, regardless of level of risk or number of subjects, without approval by the IRB.

- (3) Initiation of research interactions or interventions with one or more subjects prior to obtaining required informed consent.
- (4) Use of an informed consent document, for one or more subjects, whose content was not approved by the IRB.
- (5) Failure to report one or more known unanticipated SAEs or unanticipated serious problems involving risks to subjects or others as required by this Handbook.
- (6) Participation by one or more members of the research team in the conduct of an active protocol without the required credentialing, privileging, or scope of practice, or engaging in activities outside the approved scope of practice.
- (7) Continuation of interventions with human subjects beyond the specified IRB approval period.
- (8) Implementation of substantive protocol changes without IRB approval, except where necessary to prevent immediate hazard to a subject.
- (9) Involvement of prisoners in VA research, or conduct of international VA research, without the required approval by the VHA Chief Research and Development Officer (CRADO).
- (10) Any noncompliance that substantively compromises the effectiveness of the facility's human research protection or human research oversight programs.
- (11) Serious programmatic noncompliance. Examples include, but are not limited to:
 - (a) Conduct of IRB business by an improperly constituted committee or with less than a quorum of voting members present.
 - (b) Improper designation of research as exempt under 38 CFR 16.104(d).
 - (c) IRB approval of a waiver of informed consent, a waiver of documentation of informed consent, or a waiver of HIPAA Privacy Rule Authorization when the respective approval criteria at 38 CFR 16.116(ee)(3) or 16.116(ff)(3), 38 CFR 16.117(c), or 45 CFR 164.512(i)(1)(i) are not met or are not documented.
 - (d) Programmatic failure to provide for and document Privacy Officer (PO) and Information Security Officer (ISO) review of proposed human subject research.
 - (e) Any programmatic noncompliance involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;
 - (f) Any programmatic noncompliance that substantively compromises the effectiveness of the facility's human research protection or human research oversight programs.

Examples of Apparent Continuing Noncompliance. Examples of apparent continuing noncompliance that must be reported to the IRB within 5 business days include, but are not limited to:

- (1) Failure to implement IRB-required changes to an on-going protocol within the time period specified by the IRB.
- (2) Failure to implement remedial actions within the periods specified at VHA Handbook 1058.01 Version June 15, 2015.

Other apparent noncompliance -- The IRB must be notified of, and review, other apparent noncompliance in accordance with local SOPs.

Institutional Reporting Requirements – The Facility Director must report to ORO within 5 business days (except as otherwise specified) after receiving notification of any situation that is reportable to ORO under VHA Handbook 1058.01 Version June 15, 2015.

(1) The Facility Director's written report is required regardless of whether or not the situation has been resolved at the time of the report. Reports of ORO should be directed to the appropriate ORO regional office or subject matter group(s) as specified on the ORO SharePoint/websites at

<http://www.vha.vaco.portal.va.gov/sites/ORO/RCO/default.aspx> and <http://www.va.gov/oro/>.

(2) The Facility Director must ensure that ORO is notified by email or telephone as soon as possible but no longer than 2 business days after becoming aware of:

- a) any research-related citation or determination of regulatory noncompliance issued by a state or federal agency; or
- b) any situation covered by VHA Handbook 1058.01 that has generated media attention or congressional interest

Where there are sponsors beyond VA, reports must be sent in accordance with MOUs or other similar agreements. Where the FDA regulations apply to a study, reporting must also be made to FDA. Where an ORD program office is the sponsor, reporting is also required to the program office.

Implementation of Remedial Actions:

The Facility Director must ensure timely implementation of remedial actions in response to identified noncompliance or as otherwise found warranted by ORO.

(1) Except where remediation requires substantial renovation or fiscal expenditure, hiring, legal negotiations, or other extenuating circumstances, remedial actions must be completed within 120 calendar days after any determination of noncompliance.

(2) Where remedial actions cannot be completed in 120- days must provide ORO with a written justification for the delay and an acceptable timeline for completion.

Secure Transmission to ORO:

Reports to ORO are likely to include VA sensitive information as defined in VA Directive 6500. Electronic transmissions of such reports must be encrypted, and hard copies of such reports must be sent by secure carrier in accordance with VA requirements in VA Directive and Handbook 6500 and VA Directive 6609.

D. Suspension or Termination of IRB Approval [21 CFR 56.113]

VA facility officials and research review committees must notify the Facility Director, the ACOS/R&D and the RCO within 5 business days of suspending or termination any VA human research study. The Facility Director must report to ORO, and all other responsible sponsoring agencies and organizations the suspension or termination within 5 business days after receiving the notification.

- **Termination** – refers to a permanent halt in all research activities due to concerns about the safety, rights, or welfare of human subjects, research personnel or others regardless of whether the action to terminate was taken by an investigator, facility official, research review committee or external entity. Termination does not refer to interruptions for other reasons, including the expiration of project approval periods.
- **Suspension**- refers to a temporary interruption in selected research activity (e.g., new enrollments or specific interventions) due to concerns about the safety, rights, or welfare of human subjects, research personnel, or others regardless of whether the action to suspend was taken by an investigator, facility official, research review committee or external entity. Suspension does not refer to interruptions for other reasons, including

the expiration of project approval periods.

- The IRB promptly notifies the principal investigator of the suspension.
- Once notified of the suspension, the principal investigator must immediately submit to the IRB Chairperson, a list of research participants for whom suspension of the research would cause harm. The IRB Chairperson, with appropriate consultation with the Chief of Staff, determines if the participants may continue in the research.
- If study approval is terminated the IRB must determine if enrolled participants should be notified. The IRB considers their rights and welfare when determining procedures for withdrawal. When follow-up of participants for safety reasons is deemed necessary, participants are informed and any subsequent adverse events that may occur will be reported to the IRB and sponsor.
- The sponsoring agency, private sponsor, ORD, OHRP, FDA, NIH, DoD and other Federal agencies must be informed, as required.
- Once suspended or terminated the IRB review and re-approval must occur prior to re-initiation of the research.
- Suspensions and terminations do not include interruptions in research resulting solely from the expiration of a protocol approval period or administrative holds by an appropriate VA facility official, researcher or sponsor when the issues involved are not related to concerns about the safety, rights, or welfare of human research participants.
- Administrative hold:
 - An administrative hold is a voluntary interruption of research enrollments and ongoing research activities by an appropriate VA facility official, researcher, or Sponsor (including the 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 that otherwise require reporting by federal agencies.

C. Research Misconduct

Definition

- Fabrication is making up data or results and recording or reporting them.
- Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
- Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit and can occur in proposing, performing, or reviewing research, or in reporting research results.
- Research misconduct does not include honest error or differences of opinion.
- VHA Handbook 1058.2 (issued on May 4, 2005) adopts the Federal wide definition of research misconduct and sets out a precise process for responding to misconduct allegations involving VA research. The potential consequences

and severity of research misconduct necessitate a procedurally detailed mechanism for handling such allegations.

- The standard response to a research misconduct allegation involves a threshold determination, an initial Inquiry, and a formal Investigation conducted by the facility where the research in question is located. Based on the Investigation's findings and conclusions, the appropriate VISN Facility Director adjudicates (determines the outcome of) each case of research misconduct. Respondents found guilty of research misconduct have an opportunity to appeal the findings and recommended corrective actions to the Under Secretary for Health.
- The Facility Director has appointed a Research Integrity Officer (RIO) who is responsible for overseeing the fact-finding process at NWHCS.

D. ORO Decision Charts

The following ORO Decision Charts are available for reference on the ORO website (http://www.va.gov/ORO/ORO_Policy_Docum.asp)

1. ORO Decision Chart – Reporting Serious Adverse Events (SAEs) and Problems Involving Risk to Subjects or Others in VA Research
2. ORO Decision Chart – Reporting of Noncompliance in VA Human Research V December 1, 2011
3. ORO Decision Chart – Reporting SAEs

XV. INVESTIGATIONAL DEVICE STUDIES AND INVESTIGATIONAL DRUG STUDIES

A. Significant or Non-Significant Risk Determination

[IDE Regulations 21CFR 812 and 21 CFR Parts 50 and 56]

The IRB must determine if an investigational device is a Significant Risk Device (SRD) or a Non-Significant Risk Device (NSRD) and document that determination in IRB minutes. The IRB determines what documentation is necessary to verify that an approved FDA issued IND exists (for example, an IND/IDE on an Investigational Brochure is not adequate documentation). As appropriate, IRB review and documentation includes the rationale for the risk determination. For SRD studies investigators must receive an Investigational Device Exemption (IDE) approval from the FDA and submit it to the IRB for review. The IDE must be reviewed by the IRB prior to approval and study initiation in accordance with FDA regulations and VA requirements. NSR device studies as determined by the IRB do not require submission of an IDE application to the FDA prior to starting the study. The FDA considers an NSR device study to have an approved IDE application after and maintaining IRB approval. *(Note: an NSR study may represent greater than minimal risk depending on the research)* No research involving an investigational device can be approved by the IRB if it is unclear whether the device requires an IDE, or if the IDE status for an investigational device is unknown. If the investigator feels a device is an NSR device and the IRB determines it is a SRD, then the investigator must obtain an IDE from the FDA prior to study approval. *(Note: although certain clinical investigations of devices are exempt from IDE regulations (21 CFR 812.2 (c)), exemption from IDE regulations does not necessarily mean the study is exempt from IRB review and approval and informed consent,)*

B. Procedures for Risk Determination – When an IDE is required

IRB procedures for determining whether an investigational device study is a Significant Risk device (SRD) study or a Non-Significant Risk Device (NSRD) study are:

1. Members review the risk assessments and rationale used by a sponsor and/or an investigator reports of prior investigations, subject selection criteria, and monitoring procedures. Risk determination is based on proposed use of a device and not on the device alone. The IRB may consider a sponsor's justification for an NSRD determination. The IRB may consider a device to be a SRD even if the sponsor considers the device to be a NSRD.
2. Members reference examples of Significant Risk Devices and Non-Significant Risk Devices listed in FDA Information Sheets incorporated in the IRB Standards of Procedures.
3. The IRB determines what documentation is necessary to verify that an approved FDA issued IDE exists and/or whether an investigational device is SRD or NSRD. The IRB may request such information from the investigator, sponsor and/or FDA. If SRD, the investigator must provide FDA documentation to the IRB. If an NSR determination is made, the IRB follows procedures in accordance with the criteria the IRB would use in considering approval of any research involving an FDA-regulated product, including all applicable local, VA and other Federal requirements including 38 CFR 16.111 and 21 CFR 56.111. (i.e. conditions of approval)
4. The IRB will provide written notification to the investigator and when appropriate to the sponsor regarding SR or NSR risk determination and the determination will be documented in IRB minutes. If an SRD determination is made by the IRB and no sponsor IDE exists, IRB review and approval can occur only after the sponsor obtains an IDE from the FDA.
5. Humanitarian Use Device – A Humanitarian Use Device (HUD) is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the US per year (21 CFR 814.3(n)) (*Note: If a physician uses a HUD as defined and described in FDA regulations, the physician must follow FDA regulations.*)

C. Storage, Security and Dispensing Investigational Devices

The investigator is responsible for storage, security and dispensing of investigational devices. NWHCS does not conduct many investigational device studies and does not have a centralized investigational device repository and dispensing facility and in some cases the sponsor brings in the device the day it is to be used. The investigator is required to describe procedures for storage, security, and dispensing of investigational devices in the Initial Review Submission Form. The IRB assesses the plan and determines if procedures are appropriate to human subject protections. The IRB Administrator reviews/monitors security and dispensing of investigational devices, as appropriate.

D. Investigational Drug Studies

An investigational drug for clinical research is one for which the principal investigator or the sponsor has filed an IND application for (FDA Form 1571). Research involving an investigational drug may not begin until a valid IND is in place. An IND is required when a drug or other article including a biological product (e.g. food supplement, fish oil, herb etc.) is used in clinical investigations involving human subjects or their specimens. The IRB determines what documentation is necessary to verify that an approved FDA issued IND exists (for example, an IND/IDE on an Investigational Brochure is not adequate documentation). The IRB may request such information from the investigator, sponsor and/or FDA as warranted and may require an investigator to submit an IND application to the FDA. An investigational drug is also an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial. Use of investigational drugs must be conducted according to FDA IND regulations and other applicable FDA and VA regulations. Pursuant to these regulations an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or an earlier notification by FDA that the clinical investigation may begin. Members review the risk assessments and rationale used by a sponsor and/or an investigator reports of prior investigations, subject selection criteria, and monitoring procedures. Risk determination is based on proposed use of a drug and not solely on the drug alone.

E. Expanded Access

When a patient has a serious or life-threatening condition that is not addressed by current approved treatments, options may exist to use an investigational medical drug, device, or biologic (i.e., one that has not been approved or cleared by FDA) to treat the patient. A variety of FDA mechanisms exist to grant this expanded access, including:

- Treatment Use.
- Compassionate Use.
- Intermediate-Size Patient Population Expanded Access
- Single patient Expanded Access
- Open Label Protocol/IND
- Humanitarian Use Devices

This policy only addresses these pathways which still require FDA approval prior to expanded access. If a physician needs to treat a patient in an emergency capacity in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB or FDA approval, please see  IRB SOP on Emergency Use of Investigational Drugs, Devices or Biologics.

DEFINITIONS:

Expanded Access: The use outside of a clinical trial of an investigational medical product (i.e., one that has not been approved by FDA). This term is used broadly by the FDA. It can cover treatment use and emergency use. It is often used by the device arm of the FDA synonymously with compassionate use. It is often used by the drug arm of the FDA to address intermediate-size patient population expanded access and single patient expanded access.

Clinical Trial: A research project in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health related outcomes.

Treatment Use: The use of an unapproved drug, biologic or device when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain information in support of a clinical trial.

Treatment IND/IDE: There are four requirements that must be met before the FDA will issue a treatment IND/IDE:

1. The product is intended to treat a serious or immediately life-threatening disease;
2. There is no satisfactory alternative treatment available;
3. The product is already under investigation, or trials have been completed; and
4. The trial sponsor is actively pursuing market approval.

Compassionate Use: This term is used primarily by the device arm of the FDA. Compassionate use can be for devices that are being studied in a clinical trial under an IDE for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. It can also be used for devices that are not being studied in a clinical investigation (i.e., an IDE for the device does not exist). This provision is typically approved for individual patients but may be approved to treat a small group.

Immediately Life-Threatening Disease: A stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Open Label Protocol or Open Protocol IND: These are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective Institutional Review Board (IRB) review and informed consent.

Humanitarian Use Device (HUD): A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

PROCEDURE:

1. When an Investigator wishes to utilize an investigational drug, device or biologic to treat a patient; the Investigator must complete and submit an initial submission for IRB review. The IRB is responsible to conduct initial reviews, and maintain ongoing monitoring of all drugs, devices or biologics used in human subjects under its jurisdiction. This includes the following FDA expanded access pathways:

- Treatment Use
- Compassionate Use
- Intermediate-Size Patient Population Expanded Access
- Single Patient Expanded Access requests
- Open Label Protocols
- Humanitarian Use Devices – see HUD section of this document*

2. The Investigator must include the following information in the submission:

- A. IND or IDE number and;
- B. Approval Letter from the FDA; and
- C. A consent form for the patient based on the VA research intervention
- D. consent template; and
- E. Approval from the Sponsor for the treatment use of the device or the single patient use of the drug or biologic.

3. Unlike an emergency use of an investigational drug, device or biologic, FDA approval is required before the treatment use occurs. To obtain FDA approval to use an

Investigational Drug, Device or Biologic for a single patient, the Investigator or Sponsor must:

I. For Devices:

- a. investigational Submit an IDE supplement requesting approval for a deviation from the IDE plan to treat the patient.
- b. For approval to treat a few patients, the Investigator must request access to the Investigational Device through the IDE Sponsor, who must submit an IDE supplement indicating the total number of patients to be treated.
- a. A follow-up report must be submitted to the IRB and the FDA in the form of an IDE supplement in which summary information regarding the patient outcome is presented. The IRB requires follow-up reports to be submitted at 30 days and 90 days post use.
- b. If any problems occur as a result of using the investigational device these should be discussed in the supplement.

II. For Drugs or Biologics:

- a. The Investigator should contact the Sponsor to submit or file for a
 - i. Treatment Use IND with the FDA. *Treatment IND or Treatment Protocol*: Expanded access to an investigational product for treatment use by a large (widespread) population, submitted under a new IND or as a protocol to an existing IND.
 - ii. *Intermediate-Size Patient Population Expanded Access*: Expanded access to an investigational drug for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted under a new IND/IDE or as a protocol to an existing IND.
 - iii. *Individual patient expanded access IND*: Expanded access to an investigational product for treatment use by a single patient submitted under a new IND or as a protocol to an existing IND.

4. Following the treatment use of an investigational drug, device, or biologic the patient should be monitored to detect any possible problems arising from the use of the investigational drug or biologic. The IRB requires follow-up reports to be submitted at the end of the treatment period or no later than 12 months after the initial approval was granted. The follow up must be submitted to the IRB.

5. If any problems occur as a result of using the investigational drug or biologic these should be reported promptly to the IRB, the Sponsor and/or FDA.

Humanitarian Use Devices (HUD)

1. To be considered for HUD status, an investigator or the device sponsor must submit a request for HUD designation to the FDA. The FDA will determine if it should grant a Humanitarian Device Exemption (HDE) for use of the device.

2. The FDA requires IRB review and approval for local use of an HUD, including convened Committee review and, at a minimum, annual continuing review, which may be expedited. This is the only situation where federal regulations require IRB approval and monitoring of an activity that is clearly not research. However, if the HUD is being used in research or in a clinical investigation, the IRB must comply with all FDA regulations related to IRB review of research.

3. FDA regulations require that the investigator and/or sponsor clearly state that the device is an HUD and that the effectiveness of the device has not been demonstrated.

4. When an Investigator wishes to utilize a HUD to treat a patient population; the Investigator must complete and submit an initial submission for IRB review. The IRB is responsible to conduct initial reviews, grant approvals and maintain ongoing monitoring of all HUD devices, used in human subjects under its jurisdiction.

5. The Investigator must include the following information in the submission:

- generic and trade name of the device
- FDA HDE #
- date of HUD designation
- indications for the use of the device
- description of the device
- contraindications, warnings, and precautions for use of the device
- adverse effects on health
- alternative practices and procedures
- marketing history
- summary of projects using the device
- clinical consent form for the patient that includes a clear statement that the device has not been proven safe or effective in the way most devices are approved.

6. The IRB will review the submission and issue an approval letter if the criteria for the use of HUD have been met.

7. Investigators are required to submit continued progress reports to the IRB to continue the use of an HUD once approval has been obtained.

REFERENCES:

21 CFR 312 subpart I

21 CFR 812.36

FDA website and guidance documents

XVI. THE INFORMED CONSENT PROCESS

(In order to approve research, the IRB ensures that the consent process meets the riteria for approval)

1. No human being can participate as a research subject unless legally effective informed consent of the subject or the subject's LAR has been obtained. Obtaining written informed consent is required unless waived by the IRB (*e.g. exempt 101b (pre-2018 Requirements) or 104d (2018 Requirements), waive informed consent 116d, waive documentation of informed consent 117c*) and participation is research must be voluntary. Documented informed consent is required (unless specifically waived by the IRB) from research participants prior to initiating any research activities including recruitment and screening procedures. The informed consent process begins prior to the conduct of any research procedures (including screening procedures) and must be conducted in a language that subjects and legally authorized representatives (LAR) can understand. The investigator or an approved study staff designee who has knowledge about the study, appropriate training and scope of practice must obtain informed consent using the NWHCS IRB currently approved and date stamped consent form. The research subject or (LAR)and witness, if required by the IRB, must carefully review the consent document, and sign and date the most current IRB approved consent form version. Authorized study staff who are obtaining consent are available to answer questions throughout the consent process. Subjects and LARs must not be coerced and

must be given ample opportunity to consider whether to participate – **no subject or LAR should be forced, coerced, or unduly influenced to participate.** Subjects and LARs must be kept informed throughout the research study and after, as appropriate, of significant new information that might impact subject safety. 45 CFR 46.102(C) defines Legally Authorized Representative as, “an individual or judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subjects participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject’s participation in the procedures involved in the research..” Copies of ICF are given to subject or LAR.

2. The IRB ensures that the informed consent form includes required elements and that it is consistent with the protocol and HIPAA authorization. The consent form is written at an eighth grade level and does not include language that inappropriately minimizes risks or exaggerates potential benefits in a seductive or coercive manner. The IRB considers risks and benefits that may result from the research and distinguishes risks of research activities (including screening tests) from the risk of therapeutic activities (i.e. usual care). Identification of probable individual and societal benefits are assessed.
3. The IRB has the authority to observe and monitor the consent process and the research. Investigators are required to allow internal and external auditors to review their study files and to observe study procedures as appropriate to verify compliance with federal regulations.
4. The IRB has the authority to require independent monitoring of the health status of incapacitated participants by an appropriate individual and to authorize that individual to withdraw a participant from the research if necessary to protect his/her welfare.
5. Surrogate informed consent must be obtained from the Legally Authorized Representative (LAR) of each participant determined to be an individual with impaired decision making capacity unless the IRB has waived or modified the informed consent requirement. In addition, even if an LAR gives consent, the subject should assent if able to do so **and dissent must be respected.** Under no circumstances should a subject be forced or coerced to participate in research against his/her will. **NWIHCS Veterans Affairs Medical Center follows federal law regarding who can serve as a legally authorized representative.**

Order of Priority

- (a) Health care agent appointed by the person in a Durable Power of Attorney for Health Care or similar document
- (a) Legal guardian or special guardian
- (c) Next of kin 19 years or older in the following order:
 - i. Spouse
 - ii. Child
 - iii. Parent
 - iv. Siblings
 - v. Grandparent
 - vi. Adult grandchild

A HIPAA authorization or waiver is required if the study involves use of Protected Health Information. Surrogate HIPAA Authorization may be obtained by a personal representative (i.e. a legal guardian or individual who has power of attorney). NOTE: a “LAR” for the purposes of research informed consent is not synonymous with HIPAA’s

“personal representative.”

The written HIPAA authorization may either be a standalone document or combined with the research informed consent approved by the IRB. If a standalone document is used as the written HIPAA authorization, VA Form 10-0493: Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research located at <http://vaww.va.gov/vaforms/medical/pdf/10-0493-fill.pdf> must be used.

Surrogate consent will be requested and accepted only when the prospective research subject has an impaired decision making capacity, as determined and documented in the person’s medical record in a signed and dated progress note.

Responsibilities of LARs acting on behalf of the potential subjects:

- (1) Must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision.
- (2) If the potential subject’s wishes cannot be determined, the LARs must be told they are responsible for determining what is in the subjects’ best interests.
- (3) LARs generally assume the same rights and responsibilities as the individuals who lack decision-making capacity in the informed consent process.

6. Federal regulations do not specify who is eligible to inform the prospective subject about all aspects of the trial and conduct the informed consent process however the person who conducts the consent interview should be knowledgeable about the study and able to answer questions. The NWHCS IRB requires investigators to identify persons authorized to obtain informed consent and requires those individuals to have received appropriate training.
7. The process for obtaining informed consent is systematically evaluated during Initial Review and includes review of the investigator plan for: (a) Assessing capacity to consent, (b) Ensuring information is given to the subject or their designated LAR in a language that is understandable to the subject or representative, (c) Providing the prospective subject or the designated LAR sufficient opportunity to consider whether or not to participate and be given an opportunity to ask questions or voice complaints - contact numbers for study staff and an individual unaffiliated with the study must be included in the consent form, and (d) Ensuring that subjects give consent without coercion or undue influence and that study participation is voluntary.
9. An IRB approved Research Consent Form must be used as the consent document. The only exception is that a Department of Defense (DoD) consent document may be employed for active duty military personnel participating in VA research at DoD sites when VA-specific language is not necessary.
 - When appropriate, VA requires one or more of the following elements of information be provided to each participant. Also, when any of these additional elements are appropriate, the VA requires them to be documented in the IRB-approved consent document, unless documentation of consent is waived.
 - Commercial product. If applicable, that the researcher believes that the human biologic specimens obtained could be part of, or lead to the development of, a commercially valuable product.

- 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. Organizations, VA, and other federal requirements must be met for handling, use and storage of biologic specimens and data.
- 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. Organizations, VA, and other federal requirements must be met for use and storage of data.
- Re-contact. If the participant will be re-contacted for future research whether within a VA facility or outside a VA facility.
- Payment for participating in the study. If appropriate, a statement regarding any payment the participant is to receive for participating in the study and how the payment is to be made.
- Disclosure of results. If the participant will receive a report of the aggregate results or any results specific to the participant.

A witness, if required by the sponsor or **IRB (e.g.,** the IRB may require a witness if the study involves an invasive intervention or an investigational drug or device).

- The witness is required to observe only the participant's or participant legally authorized representative's signature, not the consent process, unless the Sponsor or **IRB** requires the witness to observe the consent process.
- The witness cannot be the person who obtained consent from the participant, but may be another member of the study team or may be a family member.

If someone other than the researcher conducts the interview and obtains consent, the researcher must formally and prospectively designate in writing in the protocol or the IRB application, the individual who will have this responsibility must be specified. The person so delegated must have received appropriate training to perform this activity. This person must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study. This designee must be a member of the research team.

XVII. CRITERIA FOR IRB APPROVAL CONTAIN ALL REQUIREMENTS OF [21 CFR 56.111 45 CFR 46.111]

In order to approve a research study, the IRB determines that the regulatory criteria for approval are met:

1. Risks to subjects are minimized: (1) by using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive, even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research, and the setting in which the research will be conducted, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, lack of decision making capability, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
6. When appropriate, the research plan makes adequate provision for monitoring the data collected, to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects, and to maintain the confidentiality of data.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, those who lack decision making capability, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

XVIII. FURTHER REVIEW/APPROVAL OF IRB ACTIONS BY OTHERS WITHIN INSTITUTION
(Override of IRB disapprovals is prohibited)

Research cannot be initiated at Omaha VA Medical Center until the local investigator has obtained written notification that the research can be initiated from the Omaha VA Medical Center ACOS/Research. This notification occurs only after the research project has been approved by all applicable R&D Committee sub-committees, and after the R&D subcommittees' notification of approvals have been approved by the R&D Committee. The ACOS/Research is also responsible for notifying the investigator of approval after Continuing Review (as applicable) by the Research and Development Committee and sub-committees. The IRB reports to the R&D Committee however the R&D Committee or other institutional officials, including the Facility Director, cannot overrule IRB disapprovals. R&D Committee minutes with appended IRB minutes are forwarded through the Chief of Staff to the Facility Director for review and approval.

XIX. COMMUNICATION FROM THE IRB

IRB determinations will be communicated in writing to the investigator. Official IRB correspondence is maintained in a computer database and hard copy file.

A. To the Investigator for Additional Information

The IRB may request additional information from the Principal Investigator or sponsor to enable appropriate review. Investigator responses should be received within 90 days unless an earlier response is required due to a subject safety issue.

B. To the Investigator Conveying IRB Decision

IRB determinations are conveyed to the Principal Investigator in writing within one week of the IRB meeting and include actions required if applicable.

C. To the Institution Administration Conveying IRB Decision

The IRB submits minutes to the Research and Development Committee. Research and Development Committee minutes with IRB minutes attached are reviewed and approved through the Chief of Staff by the Facility Director.

D. To Sponsor of Research Conveying IRB Decision

The IRB normally does not notify sponsors of IRB determinations. The Principal Investigator serves as the communications link between the IRB and the sponsor. There may be circumstances where the IRB feels it is necessary to directly notify the sponsor (e.g. suspension, termination).

XX. COMPLAINT PROCESS

A.

D. Complaint Process for Subjects and Others including Current, Prospective, Past Subjects, and Designated Legally Authorized Representatives

1. Ensuring a response to each question, concern or complaint. Every IRB approved consent form provided to subjects includes the telephone number to call for questions, concerns, complaints and an issue concerning an individual's rights as a research participant. The number (xxxxxx-xxx-xxxx) is the direct telephone line to the IRB Administrator (unaffiliated contact person). Research staff (including the investigator) contact numbers are also included in the approved consent form. The ACOS/Research, the Administrative Officer for Research and Research Compliance Officer are individuals to whom complaints can be reported. Complaints shall be referred to the Institutional Review Board/Research and Development Committee for evaluation at a convened meeting. A timely resolution and response is expected.
2. Investigating complaints and allegations of wrongdoing and noncompliance not involving noncompliance. The IRB Administrator, Research Compliance Officer, Associate Chief of Staff for Research, Administrative Officer for Research, or other IRB/R&D member assigned on behalf of the Committees is responsible for investigating complaints or allegations and reporting findings to the Committees,

as appropriate. The investigation process will consist of review of written allegations, responses to those allegations, personal interviews, review of research records and monitoring the informed consent process as appropriate. The complainant shall be notified in writing that his/her allegation has been received and is being investigated. As appropriate the Committees will inform the complainant of the results of the investigation. The Committees will review the findings and take remedial actions as necessary. The procedures in Section XIV.C will be followed if a complaint or allegation suggests the possibility of noncompliance.

3. Identifying individuals who have responsibility for responding to questions, concerns or complaints regarding an individual's rights as a research subject.

Responsible individuals are:

- (a) Associate Chief of Staff for Research and Development
 - (b) Administrative Officer for Research
 - (c) IRB Administrator
 - (d) Chairperson IRB
 - (e) Chairperson R&D
4. The IRB and/or R&D Committee monitor responsiveness to ensure a timely response to questions, concerns and complaints is made as appropriate.

XXI. INVESTIGATOR RESPONSIBILITIES

(see VHA Directive [1200.05 Paragraph 9g](#)):

A. Professional Qualifications and Responsibilities

In addition to meeting the NWHCS standards for professional qualifications based upon their role and research activities, investigators are responsible for oversight and management of all aspects of the research as outlined in the IRB approved protocol and as conducted by the research staff. Investigators must effectively communicate with the IRB and respond to requests from the IRB in a timely manner. They, or a representative are requested to be available to the IRB during meetings and/or reviews.

NWHCS and the Research Service requires that all independent license holders participating in research be credentialed and privileged and hold a valid license.. The IRB requires the submission of curriculum vitae for all study staff and requires that mandatory training be completed. Additional research training may be required prior to conducting research activities. If the IRB determines that the Principal Investigator and/or key research staff do not have the professional qualifications or resources necessary to conduct research in accordance with regulations this can be the basis for disapproval or a stipulation to involve individuals with appropriate expertise in the study. The IRB may consider investigator collaborations with other professionals who have the required expertise and who agree to serve as sub-investigators, preceptors, mentors, or medical monitors.

Investigator Responsibilities - Maintenance of Research Records

It is the investigator's responsibility to maintain research records. This means

maintaining written documentation on file that the protocol is being implemented as approved by the IRB and in accordance with other required approvals.

B. Study Protocol

The IRB addresses many complex, overlapping and intermingled issues dealing with the basic question, “is there any possible benefit from this study and does the potential gain outweigh the potential risk?” In order to judge if criteria are met the Committee needs detailed information. If a protocol is submitted for review and Committee members believe that there is insufficient information to enable an appropriate review, a written request for additional information will be sent to the Principal Investigator. The investigator is responsible for the research protocol and for ensuring research compliance.

Initial and Continuing Review Submission Forms require investigators to provide detailed information about their proposed research (Pertinent information described in IRB submission forms include:

1. Complete protocol (including questionnaires, surveys and data collection tools).
2. Consent form and details about the process (e.g. capacity to consent).
3. HIPAA authorization form or waiver of HIPAA authorization request
4. Title of the study.
5. Purpose of the study.
6. Sponsor of the study including addresses.
7. Sponsor obligations regarding safety information notification.
8. FDA Form 1572 (drug), Investigator Agreement (device) FDA IND#, IDE#, HDE#, 510k#, Off-label use justifications. Register FDA regulated studies on <http://www.ClinicalTrials.gov>.
9. Complete federal grant applications and contract proposals (e.g. VA Merit Reviews, NIH, CDC, DoD).
10. Results of previous related research.
11. Study design, scientific rationale, and study purpose.
12. Description of subject inclusion/exclusion criteria, enrollment and recruitment plans.
13. Description of the informed consent process, to include informed consent forms
14. Requests to waive informed consent and documentation of informed consent when applicable
15. [For studies subject to the 2018 requirements, approval requests for access to prospective subject’s identifiable information or identifiable biospecimens without informed consent or waiver of informed consent under specific conditions.](#)
16. Investigator risk-benefit assessment and risk designation. Consider potential risks and potential benefits including physical, psychological, economic, social/legal and privacy risks. Consideration of benefits to subjects and importance of knowledge to be reasonably expected.
17. Description of plans to minimize risk.
18. Presence of a DSMB and/or other data safety monitoring for prospective and retrospective studies
19. Plans to protect privacy and confidentiality of data.
20. Investigational Brochures and package inserts.
21. Justification for use of any special/vulnerable subject populations and surrogate consent procedures if applicable. [See 1200.05 para 19, 20, 21.](#)

22. Distinguish research risks from therapeutic activities (i.e. usual care), describe study related procedures to be performed. When a study involves usual care, the investigator must differentiate the personnel/entity responsible for relevant aspects of both the research and the usual care.
23. Use of placebo, washouts, withholding of approved treatment, deception studies.
24. Randomization plans.
25. Tissue banking provisions.
26. Investigational device status (SRD, NRD) and plans for storage, security and dispensing.
27. Provisions to identify, monitor and report serious adverse events.
28. The circumstances surrounding consent procedures (e.g. setting, subject autonomy concerns, use of surrogate consent, language difficulties, cultural differences, educational capabilities, vulnerable populations, use of witnesses if applicable, documentation). **(VA requirements must be met.)**
29. Subject selection.
30. Non-Veteran subjects.
31. Payments to subjects for their participation and payment terms.
32. Medical treatment and compensation for injured research subjects.
33. HIPAA Authorization Form; HIPAA waiver of authorization (including Partial HIPAA and Common Rule Waiver for Recruitment purposes), when applicable
34. How and where research data will be collected & stored.
35. Extra costs to subjects for their participation in the study.
36. Extra costs to NWHCS or to third party payers because of subject's participation.
37. Disclosure of conflicts of interest.
38. VA Form 9012 (Investigational Drug Information Record).
39. Radiation and biohazard safety plans.
40. Adequacy of research resources to conduct the proposed project.
41. For study research staff description of the role in study and scope of duties.
42. Completion of training requirements.
43. Impact of research on other hospital services (financial and access).
41. When medical records need to be flagged. The patient health record MUST be flagged if the subject's participation in the study involves:
 - a. Any invasive procedure (e.g. muscle biopsy or bronchoscopy)
 - b. Interventions that will be used in the medical care of the subject, or that could interfere with other care the subject is receiving or may receive (e.g. administration of a medication, treatment, or use of an investigational device.
 - c. Clinical services that will be used in the medical care of the subject (e.g. orders for laboratory tests of x-rays ordered as a part of the study), or that could interfere with other care the subject is receiving or may receive
 - d. The use of a survey or questionnaire that may provoke undue stress or anxiety unless the IRB determines that mandatory flagging is not in the best interests of the subject (e.g. an interview study or victims of sexual assault.
 - e. In circumstances other than above the IRB determines if flagging is necessary.

Certain types of studies may require special safeguards including:

1. Placebo.
2. Challenge studies.
3. Wash-out periods.
4. Deviations from standard of care.
5. Withholding approved treatment.
6. Deception studies.

7. Other – e.g. risks when there appears to be no potential clinical benefit to the subject. (e.g. Phase I studies).

C. Subject Recruitment

In order to approve research, the IRB must determine that selection of subjects is equitable. The NWHCS IRB requires investigators to submit for review the final copy of all advertisements and recruitment incentives associated with the research that they oversee. The IRB understands that recruitment is the beginning of the informed consent process and must be consistent with prohibitions on coercion and undue influence. The initial contact must provide a telephone number or other means that the potential subject can use to verify the study constitutes VA research.

NWHCS IRB recruitment procedures are designed to assure that informed consent is given freely and to avoid coercion or undue influence. To evaluate this the IRB needs to obtain appropriate information in order to know from what population the subjects will be drawn, what incentives are being offered, and the conditions under which the offer will be made.

For studies requiring continuing review, at the time of

The IRB may approve payments to research participants, in the following circumstances:

- **No Direct Benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation.
- **Others Being Paid.** In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.
- **Comparable Situations.** In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate.
- **Transportation Expenses.** When transportation expenses are incurred by the subject that would not be normally incurred in the normal course of receiving treatment and which are not reimbursed by any other institution or other mechanism. Most VA patients travel by car to clinic visits - the price of gasoline is considered by the IRB when determining if the amount of reimbursement is appropriate.

Compensation (i.e. “finders fees” or “recruitment incentives” or “bonus payments” to accelerate recruitment) to investigators, physicians and other health care providers for identifying and/or enrolling subjects are prohibited. This applies to the sponsor, VA, researcher and those referring potential participants.

Examples of acceptable recruitment practices - referrals from other health care providers, review of DHCP/CPRS data by authorized individuals, patient-provider interviews, and IRB approved recruitment letters, flyers, posters, internet ads, radio ads, newspaper ads, and video ads. During the recruitment process, ensuring the research team makes initial contact with the 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 the 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. (Note: one source of information about clinical trials is the ClinicalTrials.gov database (<http://www.clinicaltrials.gov>) where VA clinical trials are listed.) Note: research team members are prohibited from requesting Social Security Numbers by telephone.

Example of unacceptable recruitment practice - cold calls are often determined to be unacceptable because telephoning is intrusive and has significant potential to violate privacy and to be coercive. After recruitment and during follow-up phase, calls to subjects may be appropriate (e.g. appointment change). Researchers verify the identity of subjects (i.e. make sure they are talking to the enrolled subject) and identify themselves to subjects by referring to previous contacts). Pertinent study information (e.g. information described in the approved consent form) may be discussed.

During the recruitment process researchers make initial contacts with potential subjects in person and/or by an approved recruitment letter. Cold telephone calls to potential subjects are not allowed. After recruitment and during follow-up phase, calls to subjects may be appropriate (e.g. appointment changes). Researchers verify the identity of subjects (i.e. make sure they are talking to the enrolled subject) and identify themselves to subjects by referring to previous contacts). Pertinent study information (e.g. information described in the approved consent form) may be discussed.

D. Equitable Selection of Subjects

To approve research, the IRB must determine that the selection of subjects is equitable. In making this determination, the IRB should evaluate the purposes of the research, the research setting, and the inclusion/exclusion criteria.

(1) Purposes of research.

The purposes of the research are evaluated by the IRB during Initial Review. The IRB documents if the purpose is appropriate and if it should yield useful information.

(2) Setting in which research occurs.

Investigators are required to specify the study site in their Initial Review submission. If a site other than or in addition to NWHCS is to be used, the IRB requires additional information. The role of participating institutions, IRBs, and off-site research personnel including how they communicate with each other must be provided to the IRB for review. The IRB evaluates if adequate plans are in place to minimize potential risks due to lack of communication or misunderstanding of responsibilities between research sites. As part of its review the IRB evaluates the standard NWHCS informed consent process to determine if modifications are required in order to minimize risks. The IRB may require as appropriate a formal inter-institutional agreement. Details of the IRB review and approval for off-site research are documented in IRB minutes and investigator correspondence.

(3) Scientific and ethical justification for including vulnerable populations.

The IRB is especially cognizant of problems involving vulnerable subject populations and has expanded the FDA list to include special consideration of additional populations. Investigators incorporate scientific and ethical justifications for use of vulnerable populations and include a plan for providing additional safeguards in their Initial Review Submission. The IRB documents if vulnerable subjects are appropriately identified and if additional protections are adequate. Generally, a

population that stands no chance of benefiting from the research should not be selected to assume the risk.

(4) Scientific and ethical justification for excluding classes of persons who might benefit from the research.

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 subjects or the groups to which they belong. Non-English speaking participants are not systematically excluded because of inconvenience in translating informed consent documents. The IRB ensures that subjects are not taken from one group of people because it is convenient. The IRB is mindful of the desirability of including both women and men as research subjects 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. Children under the age of 18 cannot be included in VA approved research unless a Waiver has been granted by the Chief Research and Development Officer (VA Directive 2001-028 dated April 27, 2001).

(5) Non-Veterans in VA Research.

VA Policy allows participation of non-Veterans as research subjects when the investigator can present a compelling reason (e.g. insufficient number of Veterans; survey of VA employees; study of active duty military; study involving Veterans' family members; the research is relevant to the care of Veterans or active duty personnel etc.) Investigators should show evidence of attempts to recruit Veterans, if applicable. (e.g. notify other VA providers about the study and request patient referral, distribute IRB approved flyers in VA clinic areas, use of IRB approved recruitment letters, etc.) The IRB reviews the justification to enroll non-Veterans and recruitment plans and determines if recruitment of non-Veterans is justified. R&D Committee approval of the enrollment of non veterans is required by VHA Directive 1200.01.

Outpatient Care for Research Purposes – any person who is a bona fide volunteer may be furnished outpatient treatment when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study. (38 CFR 17.92)

Hospital Care for Research Purposes – any person who is a bona fide volunteer may be admitted to a VA hospital when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study. (38 CFR 17.45)

If non-Veteran subjects are enrolled, an electronic VAMC medical record will be created for subjects receiving clinical services (e.g. using the lab, radiology, audiology, etc.) as part of the study. They will be given a VA Notice of Privacy Practices (IB10-163), this will be documented on VA Form 10-0483, and scanned into the medical record.

E. Subject Selection Criteria

Includes consideration that risks, burdens and benefits of research are distributed fairly.
Includes consideration of:

1. Purposes of research.
2. The burdens and risks of the research.
3. Potential benefits of the research.
4. Inclusion criteria.
5. Exclusion criteria.
6. Vulnerable populations.
7. Use of non-Veterans.
8. Projected enrollment.
9. Methods to identify and recruit subjects.
10. Nature of the information sought.
11. Subject payment.

F. Subject Enrollment

Includes evaluation of the following:

1. Projected enrollment and number of subjects entered into the study.
2. Gender of subjects entered into the study.
3. Number of women entered into the study.
4. Minority status of subjects entered into the study.
5. Names of subjects entered into the study.
6. Enrollment of vulnerable subjects.
7. Use of surrogate consent.

G. Privacy, Confidentiality and VA Sensitive Information

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” *CFR 164.501*. A covered entity may always use or disclose for research purposes health information, which has been de-identified (in accordance with 45 CFR 164.502(d), and 164.514 (a)-(c) of the Rule) with regard to the provisions below. The Privacy Rule also defines the means by which individuals will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them held by the covered entities. Where research is concerned, the Privacy Rule protects the privacy of individually identifiable health information necessary to conduct vital research.

Definition of VA Sensitive Information

VA Handbook 1200.12 (March 9, 2009) - “VA sensitive information or data means 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. This term includes information whose improper use or disclosure could adversely affect the ability of an agency to accomplish its mission, proprietary information, records about individuals requiring protection under various confidentiality provisions, such as the Privacy Act, HIPAA, Privacy Rule, and information that can be withheld under the Freedom of Information Act.”

Examples of VA sensitive information:

- Individually-identifiable medical, benefits, and personnel information.
- Financial, budgetary, research, quality assurance, confidential commercial, critical infrastructure, investigatory, and law enforcement information.
- Information that is confidential and privileged in litigation such as (a) information protected by the deliberative process privilege; (b) attorney work-product privilege; (c) attorney-client privilege.
- Other information, which released could (a) result in violation of law or harm, or unfairness to any individual or group; or, (b) adversely affect the national interest or the conduct of Federal programs.

Use of VA Records for Research and Development:

VA personnel are bound by all legal and ethical requirements to protect the rights of human subjects, including the confidentiality of information that can be identified with a person.

- Obtaining and using medical, technical, and administrative records from other VA facilities or VA databases (national, regional, or subject specific) for R&D purposes must be in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information (45 CFR Parts 160 and 164). Obtaining and disclosing individually-identifiable patient records must be in compliance with all applicable and confidential statutes and regulations including: Privacy and Confidentiality – Adequate provisions must be taken to protect the privacy of subjects and to maintain the confidentiality of individually-identified data. Such provisions must consider the requirements of Standards for Privacy of Individually-Identified 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.
- Research data repositories must be under an approved research protocol including provisions for initial and continuing review (when applicable) and other applicable reporting requirements. The Principal Investigator responsible for the creation of the research database will ensure that each use of the database for a new research protocol has been reviewed and approved by the R&D Committee and appropriate sub-committees. (Reference - VHA Handbook 1200.12 entitled, Use of Data and Data Repositories in VHA Research).
- The VAMC Research Data Security for Principal Investigators (PI) is reviewed at Initial and Continuing Review (when applicable). This document serves as a review tool to obtain information from investigators about how research data (i.e. VA sensitive information) will be transported, used and stored both inside and outside the VA protected environment. If the VA sensitive information will be stored outside the VA protected environment the investigator must complete a formal request and obtain appropriate authorizations. The VAMC form used to

obtain authorizations is entitled, “Request for Issuance of USB Flash Drive and/or Authorization to Transport and Utilize VA Sensitive Information Outside Protected Environments.”.

REPORTING REQUIREMENTS RELATED TO RESEARCH INFORMATION PROTECTION

a. **Research Information Protection Incidents – Immediate Reporting.** Within 1 hour of becoming aware of any situation described in VHA Handbook 1058.01 Version November 15, 2015 subparagraph 10a members of the VA research community are required to ensure that the situation has been reported to the ACOS for Research, the facility ISO, and the facility PO.

(1) **Reportable Incidents** - Any unauthorized use, disclosure, transmission, removal, theft, loss, or destruction of VA research-related PHI, or confidential information, as defined by the HIPAA Privacy Rule, the Common rule, the Privacy Act, or 38 USS 5701, 5705, and 7332.

(2) **Notification** - The ACOS/R must immediately notify the Facility Director, the R&D Committee, and any relevant research review committee upon discovering, receiving, or otherwise becoming aware of a credible report of a reportable incident as described above and must ensure that the facility ISO and PO have also been notified.

(3) **Written Report** - Any oral report or notification by the ACOS/R as described in 11a (1) and listed above must be followed by a written report.

b. **Research Information Protection Incidents – Regular Reporting.** Independent of the reporting requirements described in VHA Handbook 1058.01 Version November 15, 2011 subparagraph 11a and described above, within 5 business days of discovering, receiving a credible report of, or otherwise becoming aware of any situation described in 11b and described below, the ACOS/R must report the situation directly (without intermediaries) to the Facility Director, the R&D committee, and any relevant research review committees, and must ensure that the facility ISO and PO have also been notified.

(1) **Findings of Noncompliance** - Any findings of noncompliance related to research information security or privacy by any VA office (other than ORO) or any other Federal or state entity. Reports to ORO based on findings made by entities external to the facility must include a copy of the official findings.

(2) **Other Deficiencies** - Other deficiencies are any other deficiency that substantively compromises the effectiveness of the facility’s research information protection program.

(3) **Suspensions or Terminations** - Suspensions or Terminations are any suspension or termination of research (e.g., by the ACOS for Research or other authorized facility official or committee) related to concerns about research information protection.

c. **Reports to ORO** - Within 5 business days of being notified of them, the Facility Director must report the research information protections incidents listed in VHA Handbook 1058.01 Version November 15, 2011 subparagraphs 11a and 11b to ORO (as specified below) and must ensure that the facility ISO and facility PO have also been notified.

(1)  Uses and disclosures of PHI under an invalid (or nonexistent) HIPAA authorization or waiver of HIPAA authorization, and deficient (or nonexistent) ISO or PO protocol review practices that substantively compromise the effectiveness of the facility’s research information protection program, must be reported to ORO.

(2) All other research information protection incidents described in paragraph 11 and listed above (for example, unauthorized transmission, removal, theft, loss, or destruction of VA PHI related to research) must be reported to ORO.

The IRB ensures that there are adequate provisions to protect the privacy of subjects and the confidentiality of data. Privacy refers to people and confidentiality refers to data.

Privacy refers to a person's desire to control the access of others to themselves (Example: a patient may not want to be seen entering a place that might stigmatize them such as an erectile dysfunction clinic or a Hepatitis C clinic or an AIDS clinic that is clearly identified as such by signs on the front of the clinic; similarly, the IRB would be particularly careful to assure appropriate safeguards were in place when reviewing recruitment plans for stigmatized populations. Confidentiality refers to the researcher's agreement with the participant about how the participant's identifiable private information will be handled, managed and disseminated. (e.g. HIPAA Privacy Rule). Investigators are required to describe their plans to protect subject privacy and confidentiality of data during the study and after study completion (Initial Review Submission Form) and the IRB reviews and approves their plans. The IRB considers the following:

(1) Methods used to obtain information about subjects - Investigators are required to specify at Initial Review the methods used to obtain information about subjects and provisions to protect the privacy of subjects and confidentiality of data. Examples of common methods used to obtain information about subjects are use of: (a) personally identifiable records, (b) subject questionnaires, (c) medical records, (d) DHCP data, (e) third party requests for information, (f) provider-patient interviews, and (g) DNA or other bodily fluids or substances including storage of DNA or other bodily fluids for future use.

(2) Methods used to obtain information about individuals who may be recruited to participate in studies - Investigators are required to specify at Initial Review the methods used to recruit subjects. Examples of common recruitment practices are: (a) referrals from other health care providers, (b) patient-provider interviews, (c) recruitment letters, (d) flyers, (e) posters, (f) internet ads, (g) radio ads, (h) newspaper ads, and (i) video ads.

(3) Nature of information that may be sought - The IRB reviews the nature, probability and magnitude of harm that would likely result from the disclosure of collected information outside research or from a breach of privacy that might stigmatize or embarrass subjects. For example, (a) use of a subject's blood or urine sample to test for "recreational" drug use would trigger a legal jeopardy concern or (b) use of a questionnaire with a consented subject that collects information about an un-consented third party (e.g. relatives) would trigger concerns that the informed consent process was being circumvented and undermined.

(4) Use of personally identifiable records - Investigators are required to specify at Initial Review if they plan to use identifiable records and if yes, to describe measures to protect privacy and confidentiality of data.

(5) Methods to protect the confidentiality of research data that may include such measures as coding, removal of identifying information, limiting access to data, or other effective methods - Investigators are required to specify at Initial Review measures taken to protect confidentiality of research data. Proposed measures may include use of: (a) coding systems, (b) encryption methods, (c) anonymizing techniques, (d) VA approved tissue storage facilities, (e) access limitations, and (f) other relevant factors in determining the adequacy of confidentiality protections.

(6) The investigator's disclosures to participants about confidentiality - Investigators are required to specify at Initial Review disclosures to participants about confidentiality. The IRB

Consent Form Template Section 10, "Are my records safe from the public? (Confidentiality of Records) provides guidelines.

(7) Determination of whether a Federal Certificate of Confidentiality should be obtained - When research involves the collection of identifiable, sensitive information about research subjects the IRB may determine that an investigator should apply for a Certificate of Confidentiality from the NIH (<https://humansubjects.nih.gov/coc/index>) or FDA to demonstrate the added protection to subjects from the risks of investigative or judicial processes.

(8) VA personnel may obtain and use medical, technical, and administrative records from this or other VA facilities for approved research purposes. Requests for records from other VA facilities must be approved by the IRB, R&D Committee and the Facility Director before being submitted to the appropriate Service Facility Director in VA Central Office.

(9) The IRB requires that the research team obtain either a valid **HIPAA authorization** from each research subject or an IRB approved waiver of HIPAA authorization for use and disclosure of protected health information for research purposes. The requirements of a HIPAA authorization are provided in VHA Handbook 1605.01 (Par 14(b) Page 31 – see below). The HIPAA authorization form includes required criteria/statements and prompts the investigator to provide specific and meaningful study specific descriptions. The IRB may review but does not have authority to approve a HIPAA authorization. The Privacy Officer reviews the HIPAA authorization to verify it meets requirements. The IRB working with the Privacy Officer, ensures that the protocol, consent form and HIPAA authorization are consistent. HIPAA authorizations or waiver of HIPAA authorization are required for certain exempt research categories and when a study involves the collection of PHI for the purposes of screening, recruitment or determining eligibility, even without informed consent.

HIPAA Authorization:

- a. **If Protected Health Information (PHI) is being used and/or disclosed in a research study, the investigator must obtain formal and prospective authorization in writing. or,**
- b. **Has obtained an IRB approved Waiver of HIPAA authorization (Note: IRB Waiver of HIPAA Authorization Submission Form contains waiver criteria and met/not met box and /Chair signature for IRB to make a determination for each criteria).**

A written HIPAA authorization signed by the individual to whom the information or record pertains is required when VA health care facilities need to utilize individually-identifiable health information for a purpose other than treatment, payment, or health care operations (e.g., research) (VHA Handbook 1605.01).

- (1) In accordance with 45 CFR 164.508(b)(3)(ii), an authorization for a use or disclosure of psychotherapy notes may not be combined with any other authorization for a use or disclosure unless the other authorization is also for a use or disclosure of psychotherapy notes.
- (2) For the use of PHI containing information regarding drug or alcohol use or treatment, sickle cell anemia or HIV, special protections must be considered under 38 CFR 7332.

(2) The written HIPAA authorization for the use or disclosure of individually-identifiable health information for a VA research study is VA Form 10-0493: Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research located at <http://vaww.va.gov/vaforms/medical/pdf/10-0493-fill.pdf> must be used

(3) . Surrogate HIPAA authorization may be obtained by a personal representative (i.e. a legal guardian or individual who has power of attorney). NOTE: a “LAR” for the purposes of research informed consent is not always synonymous with HIPAA’s “personal representative.”

(4) Investigators can obtain and use real Social Security Numbers (SSNs) only when real SSNs are required to meet the specific aims of the research protocol or to enter information into the subject’s health record. (See Appendix J)

Privacy Officer and Information Security Officer Responsibilities:

(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. The Privacy Officer and Information Security Officer are non-voting consultants of the R&D Committee.

(2) Reviewing the proposed study protocol and any other relevant materials submitted with the IRB application. They are given a complete packet of IRB review materials and R&D review materials prior to each IRB/R&D meeting and they conduct project specific reviews, document those reviews and provide them to the IRB for inclusion in the protocol file. Also, they have been given access to the IRB /R&D electronic data management system.

(NOTE: It is not sufficient for the Privacy Officer 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 Privacy Officer and the ISO, the investigator may dedicate specific sections of the protocol to privacy and information security. In addition the investigator must complete the VAMC Research Data Security for Principal Investigators (PI) t and privacy and information security sections in the Initial and Continuing Review Submission Forms. These additional documents become part of the IRB protocol file. In addition the PO and ISO conduct project specific reviews and these reviews are submitted to the IRB and become part of the IRB protocol file)

(3) Completing their respective reviews of the proposed research and informing IRB of all their findings related to privacy and confidentiality, and to information security, respectively.

(NOTE: They 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 written, signed and dated summary reports of their review and assessment of each study according to the requirements of this paragraph. 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 R&D approval. For exempt studies, they must submit their summary reports to the 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 (whether VA or affiliate IRB) in a timely manner.



Waiver of HIPAA Authorization

(1) The Investigator must submit a request to the IRB for approval of a **Waiver of HIPAA Authorization** to allow use of protected health information for research purposes. The HIPAA Waiver of Authorization requirements are incorporated in the NWHCS IRB HIPAA Waiver of Authorization Template. Investigators are instructed to provide study-specific justifications for, i) use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, ii) the research could not be practicably be conducted without the waiver of alteration, and iii) the research could not practicably be conducted without access to and use of the protected health information. **See Form “HIPAA Waiver of Authorization.”** The Waiver of HIPAA Authorization Template includes required criteria/statements and prompts the investigator to provide specific and meaningful study specific descriptions. The IRB has the authority and is required to approve Waiver (full or partial) of HIPAA Authorization and must document in writing the basis for its determinations.

See Appendix I

(2) The Investigator must submit a request to the IRB for a **HIPAA Waiver of Authorization for Recruitment Purposes and either (1) a Waiver of Informed Consent for Recruitment Purposes or (2) include information in the protocol request that the IRB allow the investigator to obtain information or biospecimens without the subject’s informed consent for the purpose of screening, recruiting, or determining eligibility of prospective subjects** if the investigator plans to access medical records or other protected health information without having first obtained written informed consent and HIPAA authorization from each research subject. The investigator should use the **“Request for HIPAA Waiver of Authorization Form”** and **“the Request for Waiver of Informed Consent”** for these requests..

Health Insurance Portability and Accountability Act of 1996 (HIPAA) 18 Identifiers

1. Name
2. Geographic subdivisions smaller than a state (includes street address, city, county, precinct, zip code and equivalent geo codes – except the first three digits of zip codes unless the population density is under 20,000)
3. All date elements other than year related to an individual (includes birth date, admission date, discharge date, date of death)
4. Telephone numbers
5. Fax numbers
6. E-mail addresses
7. Social security numbers

8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers (includes license plate numbers)
13. Device identifiers and serial numbers
14. Web universal resource locators (i.e., URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers (includes finger and voice prints)
17. Full face photographs
18. Any other unique identifying number, characteristic or code and the covered entity does not have knowledge that information could be used alone or in combination to identify an individual.

H. Investigational Brochure

The Investigational Brochure and/or package inserts will be reproduced and provided to members prior to the convened meeting when the relevant protocol is to be reviewed.

I. Case Report Forms

The case report form that is provided by the sponsor will not be reviewed by the IRB unless requested by the sponsor.

J. Proposed Informed Consent Document – Documentation

1. Components, documentation, legally authorized representatives - The IRB reviews all components of the informed consent document and ensures the following are included as appropriate: basic and additional elements, oral scripts, advertisements, future use of specimens and data, re-contact, payments, subject injury (*Note: for DoD research disclosure for research-related injury must follow DoD requirements*), disclosure of results and study information sheets. When the IRB or sponsor requires a witness to the consent process in addition to the witness to the participant's signature and when the same person needs to serve in both capacities a note that describes what they are witnessing (e.g. are you witnessing the process, presentation, or signature only) is placed under the witness's signature line. A court appointed guardian and the following may serve as a legally authorized representative (LAR) for subjects determined to be incapable of making an autonomous decision. **NWIHCS follows Federal law regarding who can serve as a legally authorized representative.**

Order of Priority:

- (a) Health care agent appointed by the person in a Durable Power of Attorney for Health Care or similar document
- (b) Legal guardian or special guardian
- (c) Next of kin 19years or older in the following order:
 - i. Spouse
 - vii. Child
 - viii. Parent
 - ix. Siblings
 - x. Grandparent
 - xi. Adult grandchild

NOTE: a "LAR" for the purposes of research informed consent is not always synonymous with HIPAA's "personal representative." **The Consent Form Template provided to researchers includes required elements and other guidance regarding**

what to include in the consent document.

2. Consent Form Process and Documentation – The investigator or a designee who has knowledge about the study, appropriate training and scope of practice may obtain informed consent. A copy of the consent document must be given to the participant or the participant’s legally authorized representative (38 CFR 16.117a). The investigator shall keep the original and the process shall be documented in the subject’s medical record. The consent form includes telephone contact numbers for the IRB. Informed consent must be obtained prior to entering a subject into a study or on the Master List of subjects - this includes screening tests prior to study enrollment. Informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research **unless the IRB has specifically approved access to prospective subject’s information or identifiable biospecimens for recruitment and screening purposes or a waiver of informed consent for recruitment purposes has been approved.** The investigator is required to identify research staff authorized to conduct informed consent. Such individuals must be knowledgeable about the study and must complete formal Human Research Training prior to study approval. Any exceptions to informed consent requirements require IRB approval of a waiver in accordance with federal regulations and state law.

The Department of Veterans Affairs requirement to utilize a consent form to document informed consent applies to all VA-approved research. The informed consent form must be the most recent IRB-approved informed consent form that includes all the required elements and, as appropriate, additional elements. *(Note: The only exception is that a DoD informed consent form may be employed for active duty military personnel participating in VA research at DoD sites when VA-specific language is not necessary (e.g., when language for treatment of research related-injury is not needed because active duty military personnel are covered by DoD).*

Documentation - Signature and Dates: The IRB approved and stamped consent form must be documented prospectively by the use of a written consent form approved by the IRB (38 CFR 16.117a unless documentation of informed consent has been explicitly waived by the IRB (38 CFR 16.117c). Informed consent forms must be signed and dated by:

- (1) The subject or the subject's LAR (38 CFR 16.117(a)),
- (2) A witness, if required by IRB (e.g., the IRB may require a witness if the study involves an invasive intervention or an investigational drug or device) or sponsor. A witness is always required when a short form consent is employed.
 - (a) The witness is required to witness only the subject’s or subject’s LAR’s signature, not the informed consent process (e.g., if the subject does not want the witness to know the nature of the research study), unless the sponsor or IRB requires the witness to witness the informed consent process.
 - (b) The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member.
- (3) If use of facsimile or scanned and emailed document is approved by IRB, the subject may submit the signed and dated informed consent form to the investigator or designee by facsimile/email. If facsimile/email is used for the informed consent document, measures must be employed to ensure the confidentiality of the information, and the privacy of the subject.

3. Consent Form Date Stamp - The IRB affixes an approval date to the informed consent document. This mechanism decreases the likelihood that an expired or unapproved consent document would be used. The IRB requires that the IRB date stamped consent form be used to document consent. When the consent document

is amended during the protocol approval period the consent form date stamp must bear the approval date of the amendment rather than the date of the approved protocol. The IRB maintains copies of approved consent forms in IRB files. The original signed and dated informed consent form must be filed in the investigator's research file for that subject so that it is readily accessible for auditing.

4. Exculpatory Language - No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. --- 45 CFR 46.116. The IRB Consent Form Template does not include such language however the IRB must be vigilant in its review of sponsored research because sponsor template language that is exculpatory may creep in.

Examples of Exculpatory Language:

- By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances.
- I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.
- By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
- I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.

Examples of Acceptable Language:

- Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.
 - By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.
5. Short Form Consent – In order to approve research covered by this policy the IRB shall approve a written summary and a short form written consent and shall determine that informed consent will be appropriately documented, in accordance with and to the extent required by the regulations (46.111(a)(5) and 56.111(a)(5)). A written consent form (i.e. written summary) that embodies the elements of informed consent may be read to the participant or the participant's legally authorized representative. A short form written consent stating that the elements of informed consent required by 46.111(a)(5) and 56.111(a)(5) have been presented orally to the participant or the participant's legally authorized representative is signed by the participant. When this method is used:
 - (1) there must be a witness to the oral presentation of the written summary;
 - (2) the witness must sign and date both the short form written consent and a copy of the written summary;

- (3) the person obtaining consent would also sign and date a copy of the written summary;
 - (4) a copy of the signed and dated written summary is given to the participant or the representative;
 - (5) only the short form written consent must be signed and dated by the participant or the representative;
 - (6) a copy of the signed and dated written summary and short form written consent must be given to the participant or the representative.
6. Basic and additional elements - Federal law [21 CFR 50.25(a)(b)] requires that in seeking informed consent basic criteria must be met. The NWHCS IRB requires that basic and additional elements be included in a consent form. IRB submissions must be in the proscribed format and must include the following basic and additional elements:

Basic Elements of Informed Consent

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others that may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and 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;
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
- (8) A statement that participation is voluntary, refusal to participate will involve 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; and
- (9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
 - (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the

information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

- (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional elements of informed consent disclosed when appropriate

(1) 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 may become pregnant) that are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;

- If the study doctor believes, for any reason, that it is within your best interest.
- If you develop side effects that are considered dangerous.
- If you refuse to take [study article] or fail to return for follow-up as recommended by your study doctor or fail to follow the study doctor's instructions.
- If you refuse to have tests that are needed to determine whether [study article] is safe and effective.
- If you require treatment with drugs that are not allowed in this study.
- If you become pregnant.
- If other causes prevent continuation of the clinical research study.
- [Sponsor's name], FDA, NCI, IRB may also end the study at any time.

- (3) Any additional costs to the subject that may result from participation in the research;
- Veteran participants are not required to pay for care received as a participant in a VA research project except in accordance with Title 38 United States Code (U.S.C.) 1710(f) and 1710(g) (i.e. certain Veterans are required to pay co-payments for medical care and services provided by VA that are not part of the study).

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

- When withdrawal from a research study may have deleterious effects on the subject's health or welfare, the informed consent should explain any withdrawal procedures (e.g. tests, treatment changes) that are necessary for the subject's safety and specifically state why they are important to the subject's welfare.

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;

(6) The approximate number of subjects involved in the study;

(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen). 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 may become pregnant) which are currently unforeseeable. The IRB requires that this element be included in all consent forms that are not minimal risk.

Other required, if applicable, additional elements:

1. The amount and schedules of payments.
2. For applicable clinical trials, the mandates clinicaltrials.gov disclosure
3. For studies involving genetic tests, the prescribed GINA language
4. If payments to subjects are made the informed consent form will include either:
 - (a) If you receive payments from the Dept. of Veterans Affairs they will be reported to the IRS along with your SS#, or
 - (b) If you receive payments from NWHCS which are greater than \$600 in a calendar year they will be reported to the IRS along with your SS#.

The Committee review process evaluates the informed consent document, reviews inclusion of basic and additional elements, understandability (i.e. written at an eighth grade level) and evaluates risk-benefit. Translation of the document is not generally necessary for the NWHCS study population however, if translation is required translation services will be provided. The NWHCS IRB requires inclusion of basic elements and additional elements as appropriate of informed consent - a consent form template that includes all elements of informed consent is provided to investigators. Written and oral consents cannot include any exculpatory language or waiver of the participant's legal rights or release of liability for negligence of the investigator, sponsor, NWHCS or their agents.

When Participants Withdraw From a Clinical Trial IRB Determines:

- When a participant withdraws from a study, the data collected on participant to the point of withdrawal remains part of the study database and may not be removed. It is advised that the consent document should not give the participant the option of having data removed to maintain the integrity of the science. Exceptions can be made.
- A researcher may ask a participant who is withdrawing whether the participant 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 participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-

invasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

- The researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). 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.

For studies subject to the 2018 Common Rule, clinical trials conducted or supported by a Federal department or agency, must post an IRB-approved informed consent form used to enroll subjects on a publicly available Federal Web site after the study is closed to recruitment and no later than 60 days after the last study visit by any subjects, as required by the protocol (See section on Clinical Trials above).

RESEARCH INVOLVING COLLECTION OF DATA FROM VOICE, VIDEO, OR PHOTOGRAPHS MADE FOR RESEARCH PURPOSES

a. **Informed Consent for Research**

(1) 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.

(2) Unless IRB grants a waiver of documentation of informed consent for research, the informed consent form for research 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.

(3). The IRB approved consent (separate consent for picture and voice no longer required) form documents permission for pictures, video, and voice recordings to be made or taken. In the conduct of research. When the research subject is a patient (either an inpatient or outpatient), the subject must sign the consent form to permit photographs or video and voice recordings that will be used for research purposes. Photography or recordings cannot occur prior to the patient's granting such permission.

b. **VA Form 10-0493, Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research.** VA Form 10-0493 documents permission for the disclosure of medical records or health information, including pictures, video, and voice recordings to another individual. In the conduct of research, VA Form 10-0493 must be used in accordance with applicable VA and VHA policy.

K. **Modifications To Approved Research Submission Form**

Requests for changes in study after initiation (i.e. amendments).

Changes in IRB approved research during the period for which IRB approval has already been given may not be initiated without IRB approval except where necessary to

eliminate apparent immediate hazard to human subjects. Examples include, protocol modifications, consent form changes, advertisements, DSMB/Interim Safety Reports and Updates Summaries, Investigator Changes, Investigational Brochure Updates, etc. Reports are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator. Reports are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator. The IRB ensures the amended protocol, informed consent, and HIPAA authorization are consistent.

L. Five (5) Day Reporting Form

Reports of local SAEs and unanticipated problems involving risk to subjects or others are reported to IRB no later than 5 business days after becoming aware of the problem.

VA Policy – Within 5 business days local unanticipated SAE's, unanticipated problems involving risks to subjects or others, and unanticipated plus related deaths must be reported to the IRB. Deaths that are unanticipated problem and related to the research must also be reported to the IRB within 5 business days.

Local Policy – In addition to VA policy the NWHCS IRB requires the reporting of all local serious adverse events. The IRB recognizes that subjects enrolled in non-interventional minimal risk studies have common life time events such as hospitalization and early mortality that are unlikely to be unanticipated and are unlikely to be related to the research. In these cases, the requirement for IRB notification may be waived.

Initial Review – The IRB reviews the protocol and submission documents for reporting of serious adverse events and unanticipated problems involving risks to subjects or others. As with all studies the investigator must follow reporting procedures described in the IRB approved protocol.

Determinations – Reports are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator.

IRB Reporting to ORO regarding review of serious unanticipated problems and unanticipated SAEs:

If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related to the research, the IRB Chair or designee must notify 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. The report must be made in writing, with a simultaneous copy to the ACOS/R and the R&D Committee. The Facility Director must report the problem or event to ORO within 5 business days after receiving such notification. A simultaneous determination is required regarding the need for any action necessary to prevent an immediate hazard to subjects including whether or not a protocol or informed consent modification is warranted and if previously enrolled subjects need to be notified.

M. Non-Five (5) Day Reporting Form

Reports of sponsor SAEs, protocol deviations or other issues that do not significantly affect the rights, safety or welfare of subjects, or the integrity of the research data, in the investigator's judgment. Reports are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator.

N. Progress Reports (e.g. Continuing Reviews)

Investigators are required to submit Continuing Review reports as required by the IRB. The IRB schedules Continuing Reviews based upon level of risk and for studies subject to continuing review requirements, at least annually according to federal regulations. Continuing Review dates are conveyed to investigators in writing. The IRB staff provides a written reminder to the Principal Investigator and study coordinator prior to the scheduled Continuing Review. The Continuing Review Submission Form solicits detailed information from investigators. The IRB reviews this information in order to determine if the criteria for IRB approval of research described in 45 CFR 46.111 remain satisfied.

Research Status Updates

Investigators are required to provide annual updates on the status of research studies that do not require continuing review by the IRB. The research office will send out a data call on an annual basis requesting a status update on all open studies that do not undergo continuing review. The research status update form will be sent out to all PIs at the start of the new fiscal year. Responses that indicate that the study should be closed will prompt a request for the PI to submit a study closure report. Investigators failing to respond will be re-contacted once the suspense date has passed for an update. [See HRPP Appendix 2.](#)

O. Final Report

Investigators are required to notify the IRB when their studies are completed. The Continuing Review Submission Form provides the framework for final reporting. Submission forms provide instructions and require investigators to certify they will follow VA records storage requirements.

P. Dissemination of Completed Study Research Results to Study Subjects and the IRB

Investigators verify that they will disseminate study results as they become available to study subjects and to the IRB as appropriate. The Initial and Continuing Review Submission Forms notify investigators of their responsibilities. The IRB Conditions of Approval also notifies investigators of their responsibilities. The IRB has full authority to require reports of interim findings as warranted. Investigators publish study results in professional journals. VA hyperlink to submit presentations/publications listed in submission forms.

<https://vaww.ord.portal.va.gov/sites/comm/PubTracker/Pages/default.aspx>

Q. Incarcerated or Pregnant Enrolled Subjects

If during the course of this research any enrolled subject becomes pregnant or incarcerated the investigator must immediately notify the IRB. Additional regulatory requirements apply. (See Initial Review Submission Form and Conditions of Approval).

R. Institutional Forms

1. Informed Consent Form
2. VA Form 10-9012 (Investigational Drug Information Record)
3. Research Financial Conflict of Interest Statement (investigators and oversight committee members)
4. IRB Submission Forms (Initial Review, Minimal Risk Review, Continuing Review, Modifications To Approved Research, 5-Day Submission Form, Non-5 Day Submission Form, HIPAA Authorization, HIPAA and Common rule Waiver of Authorization, Data Management Plan, VAMC Privacy and Data Security Plan, Waiver of Informed Consent (116d), Waiver of Documentation of Informed Consent (117c))
6. Electronic medical record flag/alert (CWAD) identifies research subject
7. Research and Development Information Sheet Project Data Sheet (VA Form 10-1436)
8. Request for Issuance of USB Flash Drive and/or Authorization to Transport & Utilize VA Sensitive Information Outside Protected Environment
9. VA Form 10-5345, request for and authorization to release medical records or health information documents permission for disclosure to another individual. (Privacy Officer consulted).

XXII. EMERGENCY USE OF INVESTIGATIONAL PRODUCTS IN LIFE THREATENING SITUATIONS

(Note: persons receiving a test article in an emergency use regulated by FDA is not considered to be involved with research and is not a research participant)

The IRB will determine that:

- The participant is (was) confronted by a disease or condition that is (was) life threatening meaning either:
 - The likelihood of death is high unless the course of the disease is interrupted.
 - A disease or condition with a potentially fatal outcome, where the end-point of clinical trial analysis is survival.
 - The disease or condition causes major irreversible morbidity.
- The situation necessitates (necessitated) the use of the investigational article:
- No standard acceptable treatment is (was) available.
- There is (was) NOT sufficient time to obtain IRB approval.

- **The emergency use will be (was) reported to the IRB within five working days.**
- Any subsequent use of the investigational product at the institution will have prospective IRB review and approval.
- If the research involves (involved) an investigational drug, and the FDA has (had) issued an IND.
- The research is (was) NOT subject to VA regulation (It is not a systematic investigation designed to develop or contribute to generalizable knowledge in which the investigator is collecting data about the individual being given the investigational article.)
- **One of the following is (was) true:**
 - Informed consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with and to the extent required by 21 CFR 50 and informed consent will be appropriately documented, in accordance with and to the extent required by 21 CFR 50.27.
 - Informed consent is not required because all of the following are true:
 - Before the use of the test article both the investigator and a physician who is (was) not otherwise participating in the clinical investigation certified in writing that:
 - The participant is (was) confronted by a life-threatening situation necessitating the use of the test article.
 - Informed consent cannot (could not) be obtained from the participant because of an inability to communicate with, or obtain legally effective consent from, the participant.
 - Time is (was) not sufficient to obtain consent from the participant's legal representative.
 - There is (was) available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant.
 - The above written certification will be (was) submitted to the IRB within five working days after the use of the test article
 - Informed consent is not required because all of the following are true:
 - Immediate use of the test article is (was), in the investigator's opinion, required to preserve the life of the participant.
 - Time is (was) not sufficient to obtain the independent determination a physician who is (was) not otherwise participating in the clinical investigation.
- Before the use of the test article the investigator will certify (has certified) in writing all of the following:**
 - The participant is (was) confronted by a life-threatening situation necessitating the use of the test article.
 - Informed consent cannot (could not) be obtained from the participant because of an inability to communicate with, or obtain legally effective consent from, the participant.
 - Time is (was) not sufficient to obtain consent from the participant's legal representative.
 - There is (was) available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant.
- After the use of the test article a physician who is (was) not otherwise participating in the clinical investigation will certify**

(has certified) in writing within five working days after the use of the article all of the following:

- The participant is (was) confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot (could not) be obtained from the participant because of an inability to communicate with, or obtain legally effective consent from, the participant.
- Time is (was) not sufficient to obtain consent from the participant's legal representative.
- There is (was) available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant.

-The above written certification will be (was) submitted to the IRB within five working days after the use of the test article.

When investigators provide prior notifications of their intent to use a test article in an emergency or their intent to invoke the exception to the requirement to obtain consent, the IRB Chairperson and Research Compliance Officer review the notification to determine whether the circumstances would follow FDA regulations.

The IRB Chairperson and Research Compliance Officer review five-day reports of the emergency use of a test article and the exception to the requirement to obtain consent to determine whether the circumstances met FDA regulations.

INVESTIGATIONAL PHARMACY POLICY – EMERGENCY USE PROCEDURES (Telephone. After hours)

The investigator is responsible for reporting Emergency Use of a test article to the IRB. NWHCS policy requires that investigational drugs be stored and dispensed by the Investigational Pharmacy. The Investigational Pharmacist may not dispense drugs unless a copy of a signed consent form is submitted and a medical chart entry (CWAD) is made. Emergency use of an investigational drug, device, or biological product may be exempt from VAMC, IRB and FDA requirements. If authorized prescribers listed on the VA Form 9012 - Investigational Drug Information Form declare an emergency use need, the Investigational Pharmacist may dispense the article to them without having received a copy of a signed consent form. The Investigational Pharmacist is also required (in addition to the investigator) to report emergency use to the IRB and to the Pharmacy and Therapeutics Committee. Specific documentation requirements are described below. The Investigational Pharmacy serves as a gatekeeper to ensure that physicians follow appropriate procedures for providing emergency medical care.

INVESTIGATIONAL PHARMACY PLAN FOR EMERGENCY UNBLINDING

The decision to un-blind any study drug is made by the principal investigator or sub investigator. The procedures for emergency un-blinding are specific to the protocol and may include calling an Interactive Voice Response System, opening a sealed envelope or unmasking portions of the drug label located in the Case Report Form. Each Investigator should be familiar with the un-blinding procedures and know where to find the information. Typically, the un-blinding information is available to the PI via the Interactive Voice Response System. Additionally, provisions are made for the PI or his designee to be available 24 hours a day, 7 days a week, 365 days per year. The contact information for the person designated as the individual to be contacted in the event of an emergency is included on the 9012 and the CWAD note. If the investigational pharmacist is the only un-

blinded individual in the study it would be appropriate to contact him/her for the information after the PI has granted permission to un-blind the drug.

DOCUMENTATION REQUIRED FOR REPORTING EMERGENCY USE TO THE PHARMACY AND THERAPEUTICS COMMITTEE AND TO THE IRB

Emergency use must be reported to the Pharmacy and Therapeutics Committee and the IRB within 5 days. (Note: (1) one-time use only is permitted, (2) additional use will require submission of a protocol to IRB, and (3) data collected in this type of event is not usable for research purposes). The following information must be included in the report:

a. Description of use

- Identification of patient (i.e., Initials, medical record number)
- Name of drug/device
- Provider of drug/device
- IND/IDE number
- Date of administration
- Nature of ailment/disease
- Expected duration of use
- How did the patient respond to the use of the test article?

b. Rationale/justification for use in this subject

c. Physician verification that these conditions were met for use of the article without prior IRB review:

- A life-threatening situation
- In which no standard acceptable treatment was available, and
- In which there was not sufficient time to obtain IRB approval.

d. Was informed consent obtained? If yes, attach a copy of the consent form used. If not, verification by independent physician that these conditions were met for use of a test article without consent as required by regulation.

e. Name and signature of treating physician and date.

“COMPASSIONATE” OR “HUMANITARIAN” USE OF A TEST ARTICLE

Questions frequently arise regarding “compassionate” or “humanitarian” use of a test article. “Compassionate use” and “humanitarian use” are not terms that appear in the FDA or DHHS regulations or the Common Rule however they do appear in the VA Manual. “Compassionate use” and “humanitarian use” are usually meant to refer to the emergency use situations discussed above.

XXIII. PLANNED EMERGENCY RESEARCH IN LIFE-THREATENING SITUATIONS WHERE INFORMED CONSENT IS WAIVED

(Emergency Research Consent Waiver)

The VA does not review or conduct planned emergency research.

XXIV. WAIVER OR ALTERATION OF INFORMED CONSENT (46.116d) AND WAIVER OF DOCUMENTATION OF INFORMED CONSENT (47.117c)

Waiver or alteration of informed consent is allowed if the following criteria are met:

- An IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by, or subject to the approval of state or local government officials, and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs, (ii) procedures for obtaining benefits or services under those programs, (iii) possible changes in or alternatives to those programs or procedures, or (iv) possible changes in methods or levels of payment for benefits or services under those programs, and
2. The research could not practicably be carried out without the waiver or alteration.

- An IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
5. For research subject to the 2018 Requirements, if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format

An IRB may not waive or alter any of the elements required for Broad Consent (36 CFR 16.1116(f)(2)). If a subject has refused to agree to Broad Consent, an IRB cannot waive consent for the storage, maintenance, or secondary use of the subject's identifiable information or identifiable specimens.

An IRB cannot approve a consent procedure that omits or alters any of the general requirements of informed consent found in 38 CFR 16.116(a), to include:

- Legally effective informed consent is obtained under circumstances that
 - provide the subject/LAR sufficient opportunity to decide whether to participate;
 - minimize coercion/undue influence and
 - does not include any exculpatory language through which the subject/LAR is made to waive/appear to waive and of their rights or releases/appears to release the investigator, sponsor, institution or its agents from liability for negligence
- Information is provided to subjects/LARs in a language they can understand
- Sufficient information is provided to allow them to make an informed decision
- With the exception of Broad Consent, a short summary of key information related to participation in the study is provided upfront as part of the consent process

Waiver of documentation of informed consent is allowed if the following criteria are met:

46.117(c) - An IRB may waive the requirement for the investigator to obtain documentation of informed consent form for some or all subjects, if it finds either:

1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (Note: FDA-regulated research is not eligible for this waiver)

2. That the research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

3. For research subject to the 2018 Requirements, **If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.**

In cases, in which the documentation of informed consent is waived, the IRB may require the investigator to provide prospective subjects with a written statement describing the research and participation; the IRB reviews the written description of the information that would be provided to participants.

IRB records document all informed consent waivers and include the rationale for granting such waivers (e.g. documentation of the specific CFR reference). Written documentation of basis upon which waivers are approved is required.

XXV. EXEMPT RESEARCH

A. HHS, FDA, and VA Exemption Regulations

1. For research subject to the pre-2018 Common Rule:
 - a. HHS - Studies falling in the specific exempt categories listed in Sub-part **A** 45 CFR 46 Section 101(b)(1) through (6) can be considered for possible exemption.
 - b. HHS - Exemptions at **Sub-part C** 45 CFR 46 Section 101(b)(1) through (6), for research involving prisoners **are not** applicable for this subpart.
 - c. HHS - Exemptions at **Sub-part B** 45 CFR 46 Section 101(b)(1) through (6), for research involving pregnant women, human fetuses and neonates **are** applicable for this subpart.
 - d. HHS - Exemptions at **Sub-part D** 45 CFR 46 Section 101(b)(1) and (b)(3) through (6), for research involving children **are** applicable for this subpart. The exemption at 46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed. The exceptions, additions, and

provisions for waiver as they appear in paragraphs (c) through (i) of Subpart A of 45 CFR 46 are applicable to this subpart.

2. For research subject to the pre-2018 Common Rule:
 - a. Each of the exemptions may be applied to research involving pregnant women if the conditions of the exemption are met.
 - b. The exemptions do not apply to research involving prisoners, except for research aimed at involving a broader subject population that only incidentally includes prisoners.
 - c. The exemptions for Categories 1, 4, 5, 6, 7, and 8 may be applied to research subjects who are children if the conditions of the exemption are met. Exempt category 2(a) and (b) of this section may only apply to research subject to 45 CFR 46, Subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph 2.b.(3) of this section may not be applied to research subject to 45 CFR 46, Subpart D.
3. FDA - Studies involving the use of FDA regulated articles may **not** be considered for an exemption from the Basic HHS Policy for Protection of Human Research Subjects Subpart A of 45 CFR 46 unless the sponsor or sponsor-investigator receives a written waiver from the FDA [21 CFR 56.105].
4. Department of Veterans Affairs policy requires that research involving children is approved by the medical Facility Director and research involving prisoners must receive a **waiver** from the Chief Research and Development Officer (VHA Handbook 1200.5 June 29, 2017).

5. Actions taken where expedited and exempt categories are in conflict

a. The current expedited review as published in the federal register (<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html>) now overlap with newly created exempt categories as defined in the 2018 38 CFR 16. The references to exempt research categories currently listed in the federal register for expedited categories 5 and 7 are now incorrect. The correct references for expedited category 5 regarding overlap is 38 CFR 16 104(d)(4) and for category 7 it is 38 CFR 16 104(d)(2) and (3). Where these classifications are in conflict, it is the position of this institution and the VA that the lesser regulatory category will be implemented. This is in keeping with the spirit of the 2018 38 CFR 16 requirements.

b. Specific expedited and exempt categories that overlap:

(1) Expedited category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). This overlaps with exempt category:

.104(d)(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be

ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501et seq.

(2) Expedited Category 7: Research 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 research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. This now overlaps with 2 categories of exempt research:

(2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 16.111(a)(7).

(3)

(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 16.111(a)(7).

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

XXVI. VA, DHHS and FDA DEFINITIONS - IS ACTIVITY SUBJECT TO THE HRPP?

Activities considered research involving human subjects must meet the definitions of research and human subject as defined in VA, DHHS or FDA regulations.

Considered when determining whether an activity is subject to the organization's HRPP. "If there is any element of research in any activity involving human subjects, the activity (including screening procedures and subject recruitment) must undergo IRB review before it can start" (HRPP page 3)

38.102(a-i)

- a. Department or agency head means the head of any federal department or agency, and any other officer or employee of any department or agency, to whom authority has been delegated.
- b. Institution means any public or private entity or agency (including federal, state, and other agencies).
- c. Legally authorized representative means 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.
- d. 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.
- e. Research subject to regulation, and similar terms are intended to encompass those research activities, for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities, which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities, whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).
- f. Human subject means a living individual, about whom an investigator (whether professional or student) conducting research obtains:
 1. Data through intervention or interaction with the individual, or
 2. Identifiable private information.

Intervention includes both physical procedures, by which data are gathered (for
IRB SOP 132 of 158

- example, venipuncture), and manipulations of the subject or the subjects' environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.
- Private information includes information about behavior that occurs in a context, in which an individual can reasonably expect that no observation or recording is taking place, and information, which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (*i.e.*, the identity of the subject is or may readily be ascertained by the investigator or associated with the information), in order for obtaining the information to constitute research involving human subjects.
- g. IRB means an institutional review board, established in accord with and for the purposes expressed in this policy.
- h. IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB, and by other institutional and federal requirements.
- i. 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 and psychological examinations or tests.
- j. Certification means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

21 CFR – FDA Definitions – summary list

Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulations under the act.

- 21 CFR 56.102(e) - Institutional Review Boards. **Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.
- 21 CFR 56.102(c) - Institutional Review Boards. **Clinical investigation** means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory studies. **The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.**
- 21 CFR 812.3(p) - Investigational Device Exemptions - IDE. **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(h) - Investigational Device Exemptions – IDE. **Investigation** means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

- 21 CFR 50.3(g) - Protection of Human Subjects. **Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.
- 21 CFR 50.3(c) - Protection of Human Subjects. **Clinical investigation** means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory studies.
- 21 CFR 312.3(b) - Investigational New Drug Application - IND. **Clinical investigation** means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.
- **DoD definition of research involving a human being as an experimental subject:** *an activity that includes both a systematic investigation designed to develop or contribute to generalizable knowledge where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction.*

APPENDICIES

Appendix: A

APPENDIX A: REFERENCE MATERIALS

A. Materials

1. FDA Information Sheets and FDA website
2. 21 CFR Part 50 (Code of Federal Regulations)
3. 21 CFR Part 56 (Code of Federal Regulations)
4. Investigations which May Be Reviewed Through Expedited Review Procedures Set Forth In FDA Regulations
5. Significant Differences in FDA and DHHS Regulations for Protection of Human Subjects
6. The Belmont Report (Ethical Principles)
7. NWHCS VAMC Standard Operating Procedures
8. NWHCS VAMC Human Research Protection Plan
9. 45 CFR Part 46 (HHS) Revised November 13, 2001 Effective December 13, 2001
 - Sub-Part B (Additional Protections for Pregnant Women, Human Fetuses and Neonates in Research)
 - Sub-Part C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects)
 - Sub-Part D (Additional Protections for Children Involved as Subjects in Research)
10. OHRP Website including OHRP Guidance
11. Department of Veterans Affairs:
 - a. 38 CFR Part 16, 17 (Code of Federal Regulations)
 - b. Federal Wide Assurance (FWA)
 - c. Consent form template that includes federally required elements
 - d. VA Form 10-9012 (Investigational Drug Information Record)
 - e. VHA Handbook 1200.05 June 29, 2017 (Protection of Human Subjects)
 - f. VHA Handbook 1108.04 Feb 29, 2012 (Investigational Drugs)
 - g. VHA Handbook 1058.01 June 15, 2015(ORO – reporting)
 - h. VHA Handbook 6500, August 4, 2006 (Information Security)
 - i. VHA Handbook 1605.01 August 31, 2016 (Privacy and Release of Information) and 1605.04 Notice of Privacy Practices Oct 14, 2010
 - j. VHA Handbook 1200.12 March 9, 2009 (Use of Data and Data Repositories)
 - k. VHA Directive 2007-040 November 30, 2007 (ISO and PO on R&D)
 - l. ORD Web Site
 - m. ORO Web Site
 - n. VHA Handbook1200.01 June 16, 2009 (R&DC)
12. Human Research Reports – provided to IRB members
13. [Insert facility name] VAMC Research Information Protection Program SOP

Material Provided and/or Available for Research Staff

1. Human Subject Protection Plan (HRPP)

2. IRB Standard Operating Procedures (SOP)
3. Submission forms, templates and materials required for IRB review
4. The Belmont Report
5. Dunn and Chadwick, "Protecting Study Volunteers in Research" which includes human subject protection regulations



Appendix B

APPENDIX B: CONTACT INFORMATION FOR OVERSIGHT

For Drug Products:

Please report suspension or termination of IRB approval; unanticipated problems involving risks to human subjects; or serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB to:

Ms. Dana Walters
Dana.Walters@fda.hhs.gov
Division of Scientific Investigations (HFD-45)
Office of Compliance
Center for Drug Evaluation and Research
White Oak Campus
10903 New Hampshire Ave.
BLDG 51, Rm. 5341
Silver Spring, MD 20993
Phone: (301) 796-3150
Fax: (301) 847-8748

For Biologic Products:

Please report suspension or termination of IRB approval; unanticipated problems involving risks to human subjects; or serious or continuing noncompliance with the regulations or the requirements or determination of the IRB to:

Ms. Patricia Holobaugh
Patricia.Holobaugh@fda.hhs.gov
Bioresearch Monitoring Branch (HFM-664)
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research/FDA
1401 Rockville Pike, Room 400S
Rockville, MD 20852-1448
Phone: (301) 827-6347
Fax: (301) 827-6748

For Medical Devices:

Please report suspension or termination of IRB approval; unanticipated problems involving risks to human subjects; or serious or continuing noncompliance with the regulations or the requirements or determination of the IRB to:

Ms. Sheila Brown
Sheila.Brown@fda.hhs.gov

Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire
WO66 RM 1651
Silver Spring, MD 20993
Phone (301) 796-6563
Fax: (301) 847-8120

Office for Human Research Protections (OHRP/DHHS)
Facility Director, Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
www.ohrp.osophs.dhhs.gov
Tel: 301-496-7005 or 866-447-4777

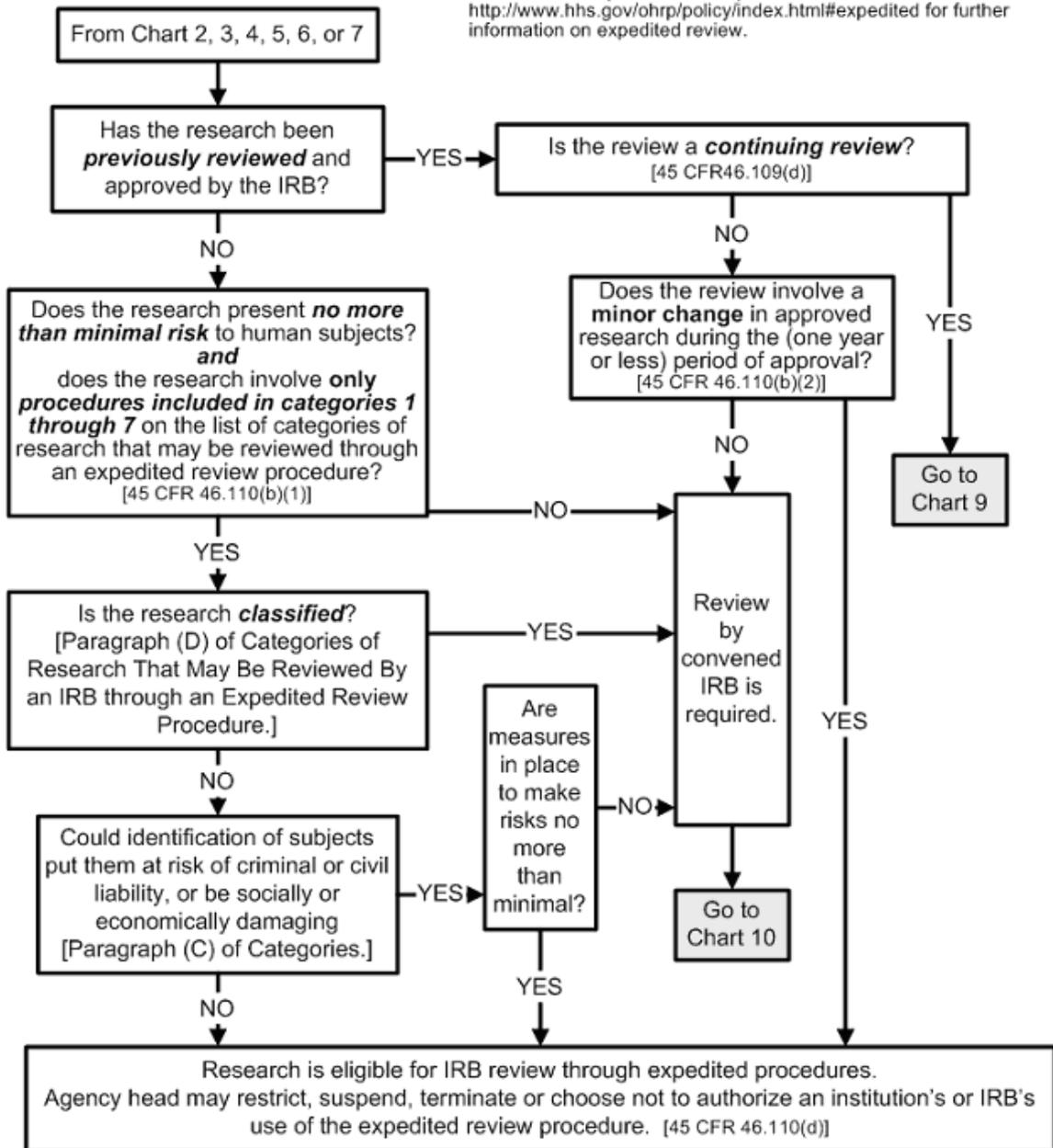
Office of Research Oversight (ORO)
3700 Crestwood Pkwy, NW, Suite 210 (10R)
Duluth, GA 30096
Email: OROHRPCROW@va.gov
Phone: 678-924-5762
Fax: 678-924-5708
Cell: 443-538-7850

ORO Website: <https://www1.va.gov/oro>

APPENDIX E: Human Subject Decision Charts

Chart 8: May the IRB Review Be Done by Expedited Procedures Under 45 CFR 46.110?*

* Note: See expedited review categories and OHRP guidance on the use of expedited review procedures at <http://www.hhs.gov/ohrp/policy/index.html#expedited> for further information on expedited review.



September 24, 2004

Chart 9: Can Continuing Review be Done by Expedited Procedures Under 45 CFR 46.110?

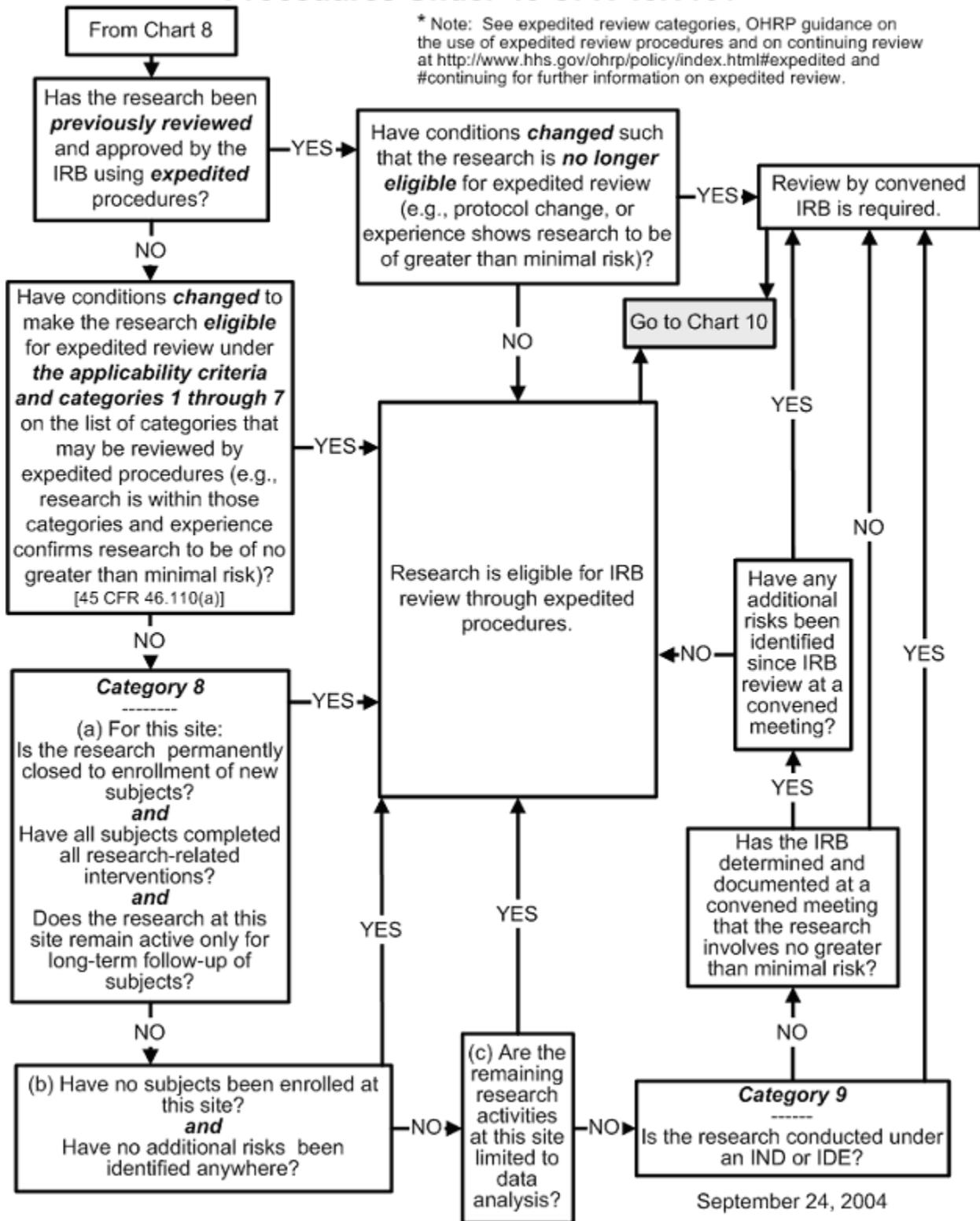
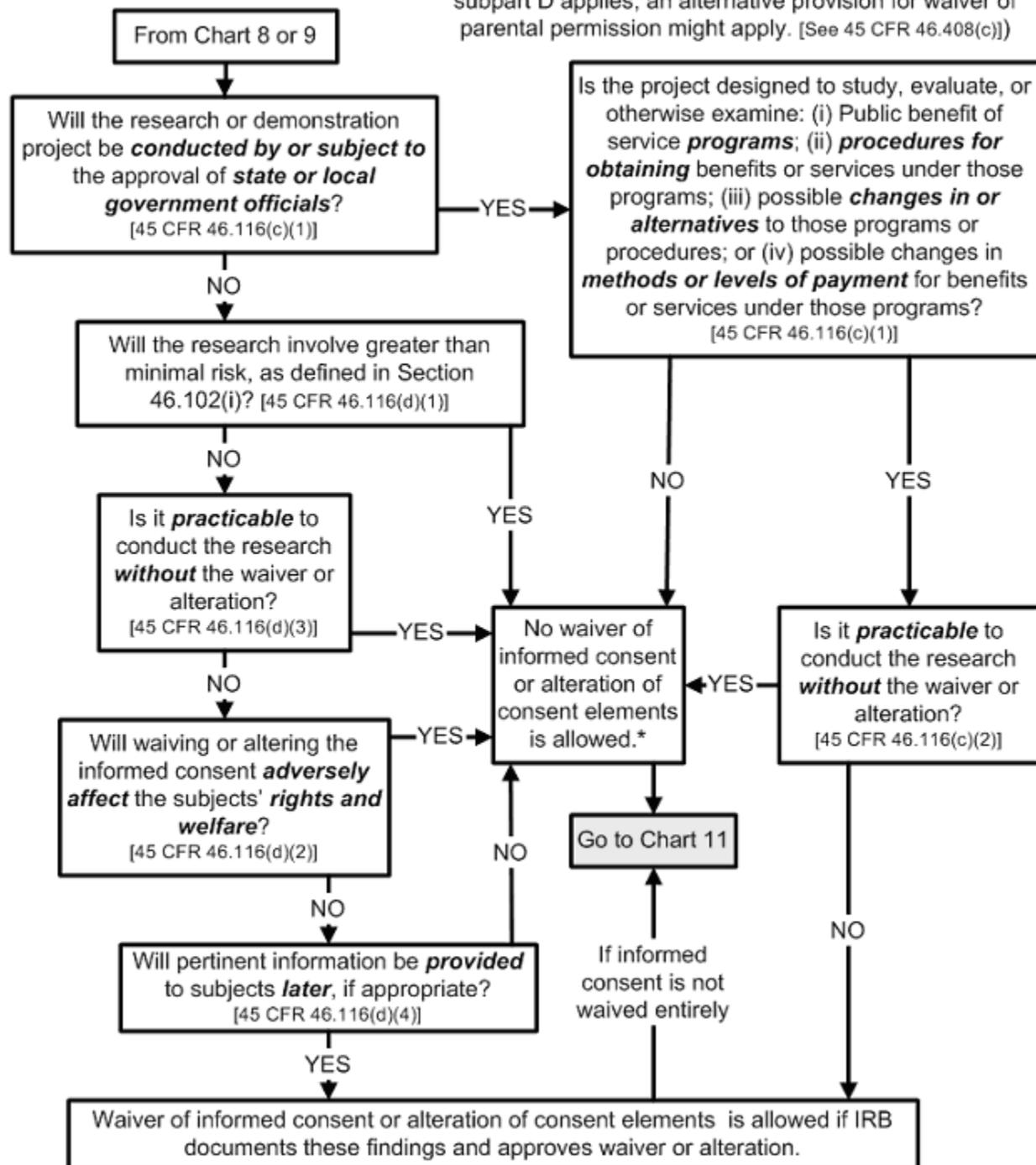


Chart 10: Can Informed Consent Be Waived or Consent Elements Be Altered Under 45 CFR 46.116(c) or (d)?**

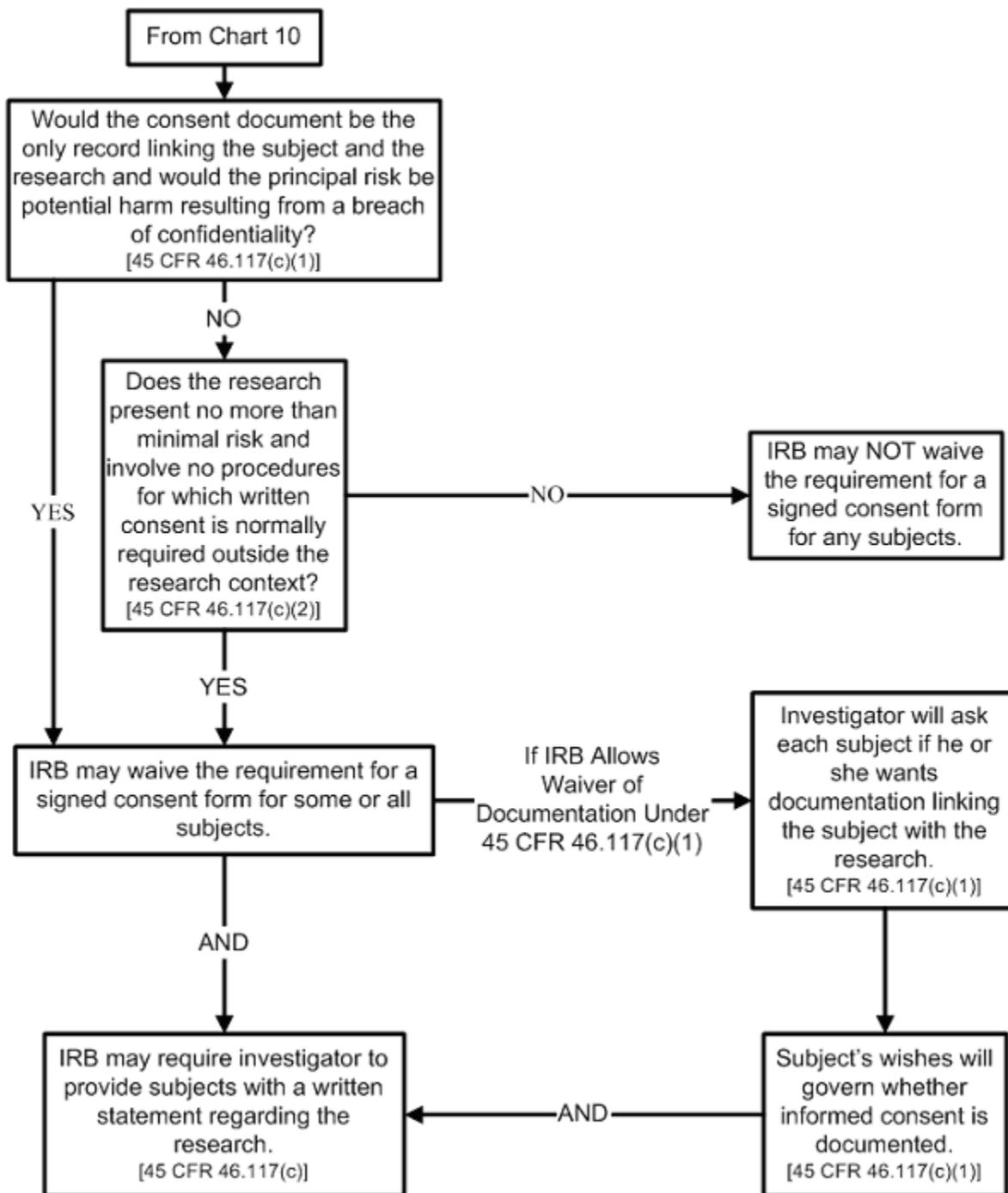
** (Note: If subjects include children to whom 45 CFR part 46, subpart D applies, an alternative provision for waiver of parental permission might apply. [See 45 CFR 46.408(c)])



* Note: See OHRP guidance on informed consent requirements in emergency research at <http://www.hhs.gov/ohrp/policy/index.html#emergency> for further information on emergency research informed consent waiver.

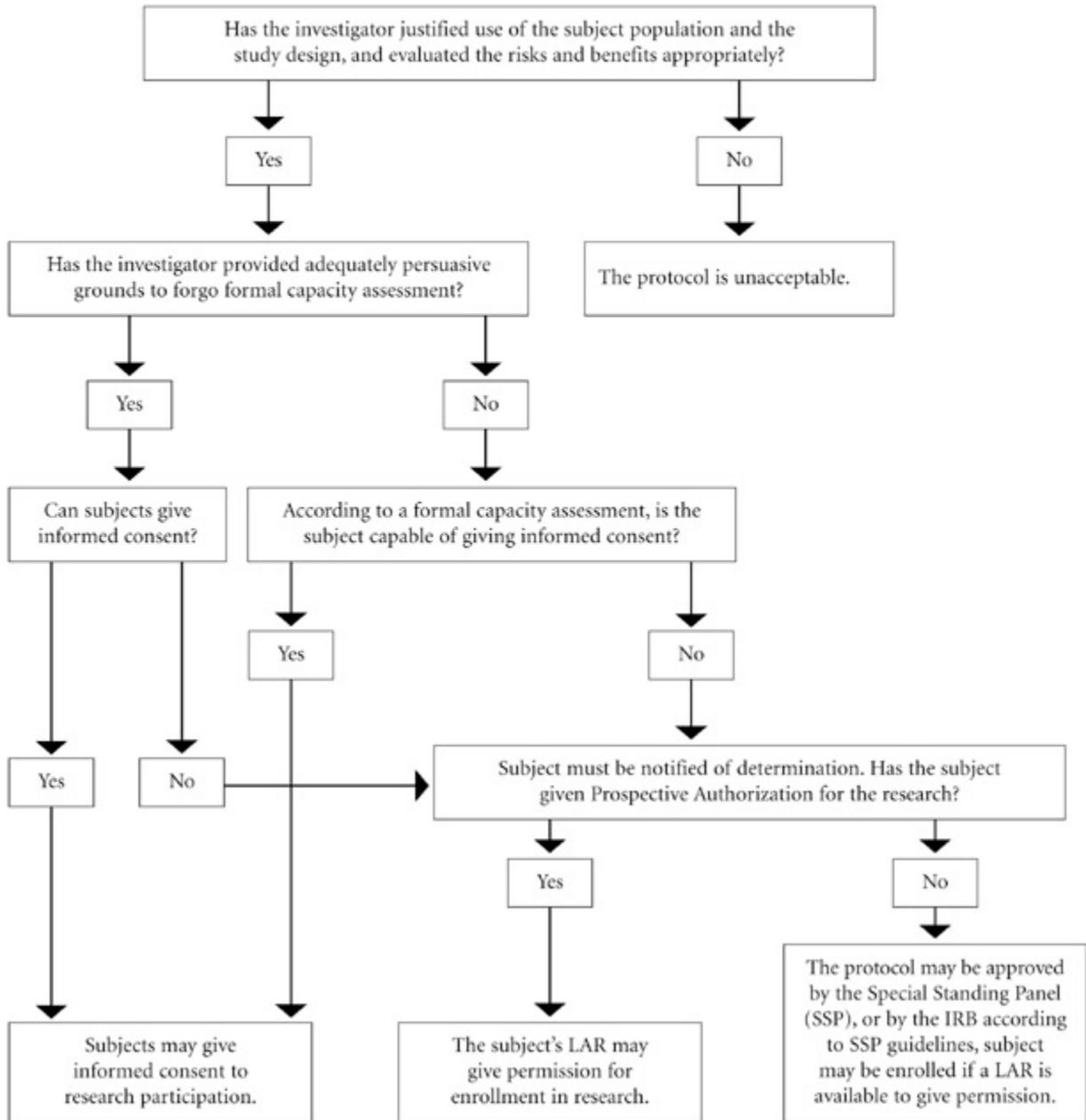
September 24, 2004

Chart 11: Can Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?



September 24, 2004

Guidance for IRBs Reviewing Research Protocols Involving Greater than Minimal Risk that Do Not Offer the Prospect of Direct Medical Benefit to the Subjects



Appendix F: External Expert Reviewer

Appendix G: Expedited Review Categories

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure¹

Applicability

- A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 38 CFR 16.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- B. The categories in this list apply regardless of the age of subjects, except as noted.
- C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- D. The expedited review procedure may not be used for classified research involving human subjects.
- E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

- 1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/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 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
 - b. From other adults and children², 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 kg in an 8-week period and collection may not occur more frequently than 2 times per week.
- 3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring 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) uncannulated saliva collected either in an unstimulated 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 sub-gingival 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. Collection of data 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/approved for marketing. (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: (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 or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or 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 Department of Health and Human Services (HHS) regulations for the protection of human subjects. 45 CFR 46.101(b)(4) located at the HHS website. This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research 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 research employing 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 HHS regulations for the protection of human subjects. Pre-2018 Requirements: 38 CFR 16.101(b)(2) and (b)(3). 2018 Requirements 38 CFR 16.104(d) (2)(iii), (d)(3)(i)(C), (d)(7), and (d)(8) located at the HHS website. This listing refers only to research that is not exempt.)
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. Where 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 investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.
-

¹ An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set for in 38 CFR 16.110.

² Children are defined in the HHS regulations as “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).

Source is Office for Human Research Protections (OHRP), November 9, 1998.

Appendix I: Elements of Documentation Required for HIPAA Waiver

ELEMENTS OF DOCUMENTATION REQUIRED FOR WAIVER OF AUTHORIZATION

*(Title 45 Code of Federal Regulations (CFR) 164.512(i)(2))
(VHA Handbook 1200.05 May 12, 2012 Paragraph 37)*

*1. The Health Insurance portability and Accountability Act (HIPAA) Privacy Rule requires that, if an **IRB** grants a waiver or alteration of the HIPAA Authorization, the Institutional Review Board (IRB) document the findings on which it based its decision. A request from an investigator to waive or alter the HIPAA authorization needs to be accompanied by information sufficient to make the required findings listed in the following:*

2. The documentation must include all of the following:

a. Identification of the IRB

b. Date of IRB approval of waiver of authorization

c. Statement that alteration/waiver of authorization satisfies the following criteria:

(1) The use or disclosure of the requested information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:

(a) An adequate plan to protect the identifiers from improper use and disclosure

(b) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and

(c) Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;

(3) The research could not practicably be conducted without the waiver or alteration; and

(4) The research could not practicably be conducted without access to and use of the requested information.

(5) A brief description of the Protected Health Information (PHI) for which the IRB has determined use or disclosure to be necessary

(6) The specific findings on which the IRB based its decision to grant the waiver of HIPAA authorization.

(7) Identification of the review procedure used to approve the waiver of authorization (either convened review procedures (38 CFR 16.108(b) or expedited review procedures (38 CFR 16.110)).

(8) Signature of Chair of the IRB, or qualified voting member designated by the Chair, on the HIPAA authorization waiver document

Note: The documentation of the IRB's findings may be in the IRB minutes or the IRB protocol file. If IRB does not document the waiver of authorization as required, the waiver is not valid.

Appendix J

Requirements of an Authorization to Release Information (VHA Handbook 1605.01)

When an authorization of the individual is required to release individually-identifiable information, the authorization must be in writing and include the following information:

- (a) The identity, e.g., name and social security number, of the individual to whom the information pertains. If the full name (first, middle, last) is on the authorization, the entire social security number is not required. The last four of the SSN will be required for purposes of filing the document into the Veteran's health record.
- (b) A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion. If HIV, sickle cell anemia, drug or alcohol abuse treatment information is to be disclosed, this information must be specifically identified in the description.
- (c) The name, or other specific identification, of the person(s), class of persons, or office designation(s) authorized to make the requested use or disclosure.
- (d) The name or other specific identification of the person(s), class of persons, or office designation(s) to whom the agency may make the requested use or disclosure.
- (e) A description of each purpose of the requested use or disclosure. A statement "at the request of the individual" is sufficient when an individual initiates the authorization and does not, or elects not to, provide a statement of the purpose.
- (f) An expiration date or event that relates to the individual or the purpose of the use or disclosure. VA Form 10-5345, Request for and Authorization to Release Medical Records, supplies three possible expiration options: 1) upon satisfaction of the need for the disclosure; 2) on a specified date provided by the patient; or 3) under conditions specified by the individual. "Upon satisfaction of the need for the disclosure" is only sufficient if the "purpose" section of the authorization is clearly articulated, such as insurance claim or payment of claim, to allow the facility to determine when the need has been satisfied. Examples of appropriate expiration date language are as follows:
 1. The statement "end of the research study" or similar language may be defined by the investigator or study sponsor for use or disclosure of individually-identifiable health information for research.
 2. The statement "none" or similar language is sufficient if the authorization is for the agency to use or disclose individually-identifiable health information for a research database or research repository. When the information is used in a new research study, the investigator must obtain either a new authorization for the new study or a waiver of authorization from an IRB or Privacy Board.
 3. For purposes of billing where an authorization is needed for 38 U.S.C. 7332-protected conditions, an expiration date of 5 years is acceptable.
 4. For purposes of enrolling Veterans in the Veterans Lifetime Electronic Record (VLER) Health Exchange and VA Form 10-0485, Request for and Authorization to Release Protected Health Information to eHealth Exchange is needed for 38 U.S.C. 7332-protected conditions, an expiration date of 10 years is acceptable.NOTE: Each VHA facility must have a process in place to monitor authorization expiration dates.
- (g) The handwritten or electronically created and authenticated signature of the individual, or the individual's personal representative. If a competent individual is unable to physically sign due to a physical limitation of disability, the authorization will require two adult witnesses to authenticate the symbol or mark executed or adopted by the individual to indicate the individual's present intention to authenticate the authorization. If no symbol or mark can be made by the individual, the authorization form must briefly document the circumstances of the signature and two adult witnesses to authenticate the individual's intent to provide authorization.
- (h) The date signed by the individual or his personal representative. The authorization should not be predated by VHA employees as the individual or the individual's personal representative should enter the date of signature. If a competent individual is unable to enter the date, the VHA employee may enter the date and initial the entry.
- (i) A statement that the individual has the right to revoke the authorization in writing except to the extent that the entity has already acted in reliance on it.
- (j) A description of how the individual may revoke the authorization (i.e., to whom the revocation is provided and any requirements).
- (k) A statement that treatment, payment, enrollment, or eligibility for benefits cannot be conditioned on the individual completing an authorization. Participation in a research study as well as receipt of research-related treatment may be conditioned on the individual signing the authorization (see 45 CFR 164.508(b)(4)(i)). This statement is required on all VHA authorizations and on authorizations from other HIPAA covered entities requesting VHA records.
- (l) A statement that individually-identifiable health information disclosed pursuant to the authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.
 - (2) Authorization may be given on VA Form 10-5345, Request for and Authorization to Release Medical Records or Health Information, or any HIPAA Privacy Rule-compliant authorization form or any correspondence, provided it meets all the requirements noted above in paragraph 14b. to be considered a valid authorization.
 - (3) If the authorization is for research purposes, VA Form 10-0493 Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research should be used. NOTE: Photocopies, scanned documents, or faxes of authorizations forms are acceptable after the validity of the form has been verified by the Release of Information Department. The validation of the authorization form can be accomplished by reviewing previous wet signatures

Appendix K: IRB Exemption Policies and Procedures

B. IRB Exemption Policies and Procedures

2. The IRB Chair, an experienced IRB member, or qualified administrative staff with expertise in applying human research exempt regulations determines if a project is exempt from the requirement for IRB review (not the investigator, other individuals or other entities) and the R&D Committee reviews studies determined to be exempt annually. NOTE: If the exempt activity involves PHI, a waiver of HIPAA authorization must be approved by the appropriate authority (IRB or Privacy Board or designated member of the IRB or Privacy Board), a written HIPAA authorization must be obtained from the subject or subject's LAR or a DUA for use or disclosure of a limited data set must be obtained.

3. The investigator is required to submit a protocol and completed Exemption Submission Form providing adequate information that for the IRB to determine if exemption meets required criteria at 45 CFR Part 46 Part 101 listed below. If a study meets regulatory criteria for exemption but the IRB has ethical concerns the IRB has full authority not to approve exemption and/or the study. In determining whether to approve **EXEMPTION** the IRB may consider issues such as the following:

- Is the study ethical?
- Does the study have sound research design?
- Does it serve the VA mission?
- Are risks minimal?
- Is there coercion to participate (e.g. high payment to complete simple survey)
- Are risks minimized?
- Are privacy and confidentiality protected?
- Are additional protections needed?
- Does it involve children, pregnant women or fetuses?
- Were data in existence before the project begins and was it collected for non-research purposes?
- Are sensitive issues involved?
- Is there a need for informed consent?
- Are personal identifiers used and recorded in unidentified manner that subjects cannot be identified directly or through identifiers linked back to the subjects?
- If applicable, are there procedures for handling participant problems or complaints?

4. For exempt research activities involving the Investigator interacting with human subjects or obtaining information by educational tests, survey or interview procedures, or behavioral interventions, the following information must be given to the prospective human subject as applicable in writing or orally:

- The activity is research;
- Participation is voluntary;
- Permission to participate can be withdrawn;
- Permission for use of data can be withdrawn for exempt research activities involving the collection and use of identifiable data; and
- Contact information for the VA Investigator.

5. IRB actions are documented in meeting minutes, the CFR reference/rationale are documented in meeting minutes and conveyed to the investigator in writing.

6. **Amendments** or other modifications to research determined exempt must be re-submitted to the IRB for re-review. This policy is included in the MIRB “Conditions of Approval” issued with IRB Approval Letters.
4. Protocols determined to be exempt from IRB review are reviewed by the Research and Development Committee for appropriateness and compliance with federal and organizational guidelines and missions.
5. **Projects that the IRB previously determined were Exempt are reviewed at least annually by the Research and Development Committee (R&D). If any significant changes in the research are noted the project is referred to the IRB for re-review. The R&D Committee is authorized to disapprove research that meets regulatory criteria for exemption but that is felt not to be ethical or appropriate to the VA mission.** The R&D Committee considers the following at Continuing Review:

- Objective
- Research plan
- Methodology
- Findings
- Is the exempt research ethical
- Have you initiated any unapproved changes without IRB review and approval except where necessary to eliminate an apparent immediate hazard to human subjects?
- Have you initiated any modifications of research determined to be EXEMPT by the IRB without IRB re-review?
- Have there been any patient complaints? If yes, describe complaint and resolution.
- Report changes in your credentialing and privileging. Report names, roles, scope of duties and certification status for all new employees brought on during the course of the study.

5. Limited IRB Review

The revised Common Rule includes a new process termed “limited IRB review.” Limited IRB review is required for 4 exemptions:

- 2(iii): Educational Tests, Surveys, Interviews, Observations of Public Behavior when information obtained is recorded in an identifiable manner and disclosure of subjects responses could put them at risk.
- 3(i)(C): Benign behavioral interventions where information obtained is recorded in an identifiable manner and disclosure of subjects responses could put them at risk.
- 7: Storage or maintenance of identifiable private information or identifiable biospecimens for which broad consent is required.
- 8: Secondary research use of identifiable private information or identifiable biospecimens for which broad consent is required.

In Limited IRB review the IRB does not have to ensure that all of the 111 approval criteria are met.

If an exempt activity requires a limited IRB review, the limited IRB review must be completed prior to approval by the R&D Committee. When a limited IRB review is conducted, the IRB is not required to evaluate whether all of the IRB approval criteria in section 12 of VHA Directive 1200.05 are satisfied.

When a limited IRB review is required for an exempt activity as described in VHA Directive 1200.05, the IRB must review the research to ascertain whether specific IRB approval criteria are met as described in VHA Directive 1200.05.

For exemptions 2(iii), 3(i)(C), and 8, limited IRB review involves determining that the research plan makes adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. [§_.111(a)(7)]

For exemption 7, limited IRB review involves the IRB determining that:

- Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of §16.116(a)(1)-(4), (a)(6), and (d);
- Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §16.117; and
- If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

§__.109 of the 2018 Rules clarifies that IRBs have the authority needed to conduct limited IRB review and that continuing review is not required for research reviewed in accordance with the limited IRB review procedure. § --.110(b)(1)(iii) clarifies that an IRB may use the expedited review process when conducting limited IRB review.

How is limited IRB review conducted?

The IRB (either the convened IRB, or the IRB chair or designee from among the experienced members of the IRB) will conduct limited IRB review during the initial review of the submitted project. In addition, Investigators are required to submit changes to the IRB when the context or conditions of the original limited IRB review change. (e.g. if the location for the storage and protection of the data change). Continuing review of research is not required for research that had limited IRB review.

When assessing the adequacy of the provisions to protect the privacy of subjects and to maintain the confidentiality of data, the limited IRB review will consider, among other things:

- The use of the information;
- The extent to which the information will be shared or transferred to a third party or otherwise disclosed or released;
- The likely retention period or life of the information;
- The security controls that are in place to protect the confidentiality and integrity of the information; and
- The potential risk of harm to individuals should the information be lost, stolen, compromised, or otherwise used in a way contrary to the contours of the research under the exemption.

For research subject to the pre-2018 Common Rule:

Protection of Human Subjects

Pre-2018 Common Rule: 38 CFR Part 116 Part 101 – To what does this policy apply?

Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian

employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

1. Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in 46.102(e), must comply with all sections of this policy.
2. Research that is neither conducted nor supported by a federal department or agency, but is subject to regulation as defined in 46.102(e) must be reviewed and approved, in compliance with 46.101, 46.102, and 46.107 through 46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Specific EXEMPTION of IRB review categories listed in [38 CFR 16.101(b)(1-6)]

16.101(b)(1) - Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

16.101(b)(2) - Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, or reputation.

VHA Handbook 1200.05: The Department of Veterans Affairs (VA) also includes loss of insurability as a potential risk in this category.

16.101(b)(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 paragraph (2) of this section if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

16.101(b)(4) - Research, involving the collection or study of existing data documents, records, pathological specimens or diagnostic specimens, if these specimens are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

IRB clarification of **“existing”** - In order to qualify for this EXEMPTION from IRB review, documents, records, or specimens (tissue, blood, urine etc.) **must be in existence before the project begins and must have been collected for purposes other than the research, and the information is recorded by the investigator in such a manner that subjects cannot be identified.** For example, if an investigator proposes to use specimens that will be drawn after the start date of the project even for reasons unrelated to his/her research, the protocol is not exempt from IRB review, even though the specimens will be

drawn regardless of the research project. The protocol may however be eligible for Waiver of Documentation of Informed Consent.

16.101(b)(5) - Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

VHA Handbook 1200.05: The determination of exempt status for these research and demonstration projects must be made by the Under Secretary for Health on behalf of the Secretary of Veterans Affairs, after consultation with Office of Research and Development, the Office of Research Oversight, the Office of General Counsel, and other experts, as appropriate.

- There is no statutory requirement for IRB review of such projects.
- Such projects will not involve significant physical invasions or intrusions upon the privacy interests of participants.
- Such projects will have authorization or concurrence by the funding agency.

16.101(b)(6) - Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or

(ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or, below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized. In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

16.101(i) - Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks Department of Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.

For research subject to the 2018 Common Rule:
Protection of Human Subjects

2018 Common Rule: 38 CFR Part 16 Part 104:

- (d) Except as described in paragraph (a) of this section, the following categories of human subjects research are exempt from this policy:
- (1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
 - (2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
 - (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §16.111(a)(7).
 - (3)(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
 - (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §16.111(a)(7).
 - (ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having

them decide how to allocate a nominal amount of received cash between themselves and someone else.

- (iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
- (4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
 - (i) The identifiable private information or identifiable biospecimens are publicly available;
 - (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
 - (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
 - (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
- (5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.
 - (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or

supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(ii) [Reserved]

(6) Taste and food quality evaluation and consumer acceptance studies:

(i) If wholesome foods without additives are consumed, or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §16.111(a)(8).

(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §16.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §16.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by §16.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

Appendix L: Definitions

VHA Handbook 1200.05 Definitions

k. **Human Subject.** A human subject is a living individual about whom an investigator (whether professional or student) conducts research(i) , and:

(1) Obtains information or biospecimens through intervention or interaction with the individual, and, uses, studies, or analyzes the information or biospecimens; or (ii)

(2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens).

NOTE: *Individuals who receive test articles or who serve as controls in clinical investigations, including clinical investigations as defined under FDA regulations in 21 CFR 50.3, 312.3(b), and 812.3(h), are also considered human subjects for the purposes of this directive.*

Research. Research is defined as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question. The Common Rule (38 CFR 16) defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:
(1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Note: The FDA definition of research differs according to the applicable regulations. See above (21 CFR 812.3(h), 21 CFR 50.3(c), 312.3(b) and 56.102(c)).

Clinical trial. A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.