

**Standard Operating Procedures for Research
Involving Human Subjects**

**Research Service
Providence VA Medical Center
Providence, Rhode Island**

October 19, 2011

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Section 1: Role and Function

October 19, 2011

IRB ROLE AND FUNCTION

1. INTRODUCTION

This manual specifies the standard operating procedures (SOPs) required for the conduct of research involving human subjects in which the Providence VA Medical Center or its staff or patients play a role. It applies to all research involving human subjects that is conducted completely or partially in VA facilities, conducted in approved off-site locations/facilities and/or conducted by VA researchers while on VA official duty time. This also includes recruitment of VA patients to research protocols conducted elsewhere by VA investigators while on duty at VA facilities or approved off-site locations. The research may be VA funded, funded from extra-VA sources, or conducted without direct funding. The PVAMC requires that all research projects involving humans as subjects or human material be reviewed and approved by the PVAMC IRB prior to initiation of any research related activities, including recruitment and screening activities.

The Human Research Protection Program (HRPP) of the Providence VA Medical Center is implemented through an Institutional Review Board (IRB). IRB activities are monitored through its parent committee, the Research and Development Committee (R&D), the facility Research Office, the Quality Management Committee and the Medical Center Director's Office.

2. INSTITUTIONAL AUTHORITY UNDER WHICH THE IRB IS ESTABLISHED AND EMPOWERED (38 CFR 16.109; 21 CFR 56.109(a); FWA)

The Department Of Veterans Affairs is one of 17 departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects (Common Rule), effective June 18, 1991 (56 Federal Register (FR) 28001), known as "The Common Rule". This policy is incorporated in [38 CFR 16]. Each VA Medical Center that conducts human research is required to have an Institutional Review Board (IRB) [VHA Handbook 1200.05]. The Providence VA Medical Center possesses a Human Research Protection Program (HRPP) that describes the structure and policies for conducting human research ethically, in compliance with regulations and according to the PVAMC FWA at the Medical Center. The HRPP designates the Research and Development (R&D) Committee as responsible for all research activities conducted under the auspices of

Providence VA Medical Center. The R&D Committee reports to the Medical Center Director. The Institutional Review Board (IRB) is a subcommittee of the R&D and is empowered to protect the rights and welfare of human research subjects participating in biomedical and behavioral research conducted at the PVAMC. The IRB has the responsibility delegated from the R&D Committee to consider, both at initial review and at continuing review, the scientific quality and appropriateness of all research involving human subjects. These considerations are included by the IRB in its considerations of the balance of risks and benefits.

A. Assurance

The Providence VA Medical Center and Ocean State Research Institute each possess a current Federal Wide Assurance (FWA) with OHRP, approved by the VA Office of Research Oversight (ORO) and have been authorized to conduct human studies. In addition, the IRB is registered with OHRP. The Medical Center Director is the Institutional Official responsible for maintaining the PVAMC FWA and HRPP.

The R&D Committee is responsible for monitoring the HRPP policies and procedures through quality assurance reports, monthly review of minutes, and budget review. In addition, the R&D Committee may require the implementation of required improvements or procedural changes. This Committee is also responsible for reviewing the changes in a timely manner to ensure the imposed procedural changes have been met. The follow-up may be in the form of reports, memos, or other forms of documentation deemed necessary. The R&D Committee also evaluates the performance of the IRB members, IRB Chair, and IRB Staff at least annually. The review is conducted through a performance based peer/self review survey, training validation, membership composition evaluation, quality assurance reports, budget reviews, review of minutes, workload reports, and other reports as deemed necessary. The R&D Committee findings may include but are not limited to accepting the reports, requiring program changes and requests for additional information and/or monitoring activities. The findings are reported through the IRB Coordinator, in writing, to the IRB Chair, Research Administration and the IRB Members. The findings are also documented in the R&D minutes which are also reviewed by the Institutional Official.

The Associate Chief of Staff for Research and Administrative Officer for Research assist the Medical Center Director and the IRB Chair in developing operating procedures, ensuring compliance with rules and regulations, monitoring changes in VA and Federal regulations relating to human research protection, and ensuring that adequate resources exist for the IRB to conduct its business.

3. DEFINITION OF THE PURPOSE OF THE IRB [38 CFR 16.101; 21 CFR 56.101(a)]

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 ensure that the rights and welfare of individuals involved as subjects of research under Federal auspices are being protected in accordance with federal regulations, and other pertinent regulations, guidance, state and local laws. VA [38 CFR Part 16,17], FDA [21 CFR Part 50,56] and DHHS [45 CFR Part 46]. At VA medical centers, the IRB is a subcommittee of the Research and Development (R&D) Committee.

4. PRINCIPLES WHICH GOVERN THE IRB IN ENSURING THAT THE RIGHTS AND WELFARE OF SUBJECTS ARE PROTECTED

Widely accepted ethical principles and guidelines for the protection of human subjects of research are contained in the April 18, 1979 report of the National Commission for the Protections of Human Subjects of Biomedical and Behavioral Research, entitled: Ethical Principles and Guidelines for the Protections of Human Subjects of Research (the "Belmont Report" at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>). Three basic principles contained in The Belmont Report are central to the ethics of research involving human research and govern the IRB in ensuring that the rights and welfare of subjects are protected:

A. Respect for persons

Individuals should be treated as autonomous agents, and persons with diminished autonomy are entitled to protection (e.g., consent, privacy, and confidentiality).

B. Beneficence

Research should always be conducted so as to maximize possible benefits and minimize possible risks to the persons involved.

C. Justice

Equals should be treated equally in bearing the burdens of research and in receiving its benefits (equitable selection of subjects).

5. AUTHORITY OF THE IRB (38 CFR 16.103 & 109; 21 CFR 56.109(a); FWA)

A. Scope of Authority Defined

The PVAMC IRB is named in the FWA and is registered with OHRP. Its members are appointed by the PVAMC Medical Center Director and it reports to the Director through the Chief of Staff and R&D Committee. The

IRB prospectively reviews and makes a decision concerning all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the policy applicable to such research. [38 CFR 16,17]. This authority covers all human research conducted at the PVAMC, or by PVAMC employees or agents, or otherwise under the auspices of the PVAMC. The IRB has the authority:

- (1) To approve, require modifications in (to secure approval), or disapprove, all research activities covered by VHA Handbook 1200.05, regardless of whether the research is funded by VA, funded from other sources, or unfunded (see 38 CFR 16.109(a) and 38 CFR 16.102(h)). An IRB-approved research activity may be disapproved by the VA facility Director, the R&D Committee, or ORD. If a research activity is disapproved by the IRB, the disapproval cannot be overruled by any other authority (e.g., the facility Director or R&D Committee). Any VA research reviewed by the PVAMC IRB will have at least one VA investigator who serves as PI.
- (2) To observe the consent process or to have a third party observe the consent process and the conduct of the research (38 CFR 16.109(e)).
- (3) To suspend or terminate approval of a study not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, IO, and the department or agency head, according to applicable local, VA, and other Federal requirements (see section 4.10 of this SOP, 38 CFR 16.113, and VHA Handbook 1058.01).

B. Statutory Basis for Authority

The statutory bases for these authorities are as follows:

- (1) Statutory provisions for protection of VA patient rights. *U.S.C. (United States Code) Sections 501, 7331 through 7334*
- (2) VA (Department of Veterans Affairs) regulations pertaining to protection of patient rights. [38 CFR 16.116, 38 CFR 17.32, and 17.33a]
- (3) 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*]
- (4) VA (Department of Veterans Affairs) requirements for the protection of human subjects in research. [*VHA Handbook 1200.05*]
- (5) VA (Department of Veterans Affairs) regulations pertaining to research related injuries. [38 CFR 17.85]

- (6) VA (Department of Veterans Affairs) regulations pertaining to hospital care for research purposes and outpatient care for research purposes. [38 CFR 17.45, 17.85 and 17.92]
- (7) VA (Department of Veterans Affairs) regulations pertaining to confidentiality of medical quality assurance records statute. [38 U.S.C. 5705]
- (8) FDA (Food and Drug Administration) regulations pertaining to rights and welfare of patients participating in research involving investigational drugs and devices. [21 CFR Parts 11, 50, 54, 56, 312, 314, 812, and 814]
- (9) DHHS (Department of Health and Human Services) regulations pertaining to rights and welfare of patients participating in research supported by DHHS. [45 CFR 46]
- (10) Statutes and regulations pertaining to the release of patient information. [5 U.S.C. § 552.a; 38 U.S.C. §§ 5701a, 7332; 45 C.F.R. Parts 160-164]
- (11) Nuclear Regulatory Commission (NRC) regulations pertaining to medical use of byproduct material and protection of human subjects. [10 CFR Parts 20 (Standards for Protection Against Radiation) and 35 (Medical Use of Byproduct Material)]
- (12) Department of Defense (DoD) regulations pertaining to the protection of human subjects . U.S.C. Sections 980

6. Independence of the IRB

The Providence VA Medical Center upholds the authority of the IRB to assure the ethical conduct of research, adherence to regulations and protection of human subjects (as described in the VA version of the Common Rule, Title 38 CFR 16 and FDA Title 21 CFR 50 and 56). No one may approve research that has not been approved by the IRB. The IRB reports to the R&D Committee however the R&D Committee cannot overrule IRB disapprovals. If circumstances warrant it, the IRB is authorized to contact the Chief of Staff and or the Director without going through the R&D Committee or through the Associate Chief of Staff (ACOS) /R&D. This and other research standard operating procedures and policies involving the IRB are not only approved by the IRB, but also are approved by the R&D Committee and the minutes of which are approved by the Director.

The IRB must be and must be perceived to be fair and impartial, immune from pressure either by the institution's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources. The PVAMC will take action to assure that the IRB remains immune from pressure.

If IRB members experience coercion or undue influence concerning their roles as IRB members they are to report this to the ACOS/R&D (or the Acting ACOS/R&D in the absence of the ACOS/R&D).

The ACOS/R&D is encouraged to resolve the issue through informal means if possible, however, if the matter is not amenable to an informal solution, the ACOS/R&D will take all appropriate means to resolve the matter. These means may include the full range of actions and resources available to the institution. The IRB member should feel satisfied that the coercion or undue influence has been removed.

If the IRB member's concerns are not alleviated by the efforts of the ACOS/R&D or if the ACOS/R&D is the source of the coercion or undue influence, then the IRB member is to report to the Chief of Staff (COS) for resolution of the matter. Every effort will be made to resolve such issues at the local level. PVAMC top officials, in consultation with legal counsel, will determine if said issues warrant further corrective action.

If the IRB member feels that the coercion or undue influence exists after referral to the ACOS/R&D or the COS or if the institution is the source of the undue influence, there are offices outside the PVAMC for reporting complaints, concerns, or breaches of ethics, laws, or regulations including: VA Office of the Inspector General (OIG) and VA Office of Research Oversight (ORO).

7. EXTERNALLY FUNDED RESEARCH

If the study is part of an application to a sponsoring agency, the human protocol must be reviewed by the IRB before, or when the grant or contract application is processed, and/or prior to expenditure of any grant funds.

8. THE IRB'S RELATIONSHIP TO:

A. The Senior Administration of the Institution

The Providence VA Medical Center Research and Development Committee reports to the Medical Center Director, through the Chief of Staff and is responsible for all research activities conducted under medical center auspices. The Director is the responsible official for the institution's Federal Wide Assurance (FWA). He/she reviews and approves the minutes of the Research and Development Committee meetings and the minutes of IRB meetings.

B. The Other Committees and Department Chairpersons within the Institution

Review of research by officials and other committees: Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials or other committees. However, those officials or committees may not approve research if it has been disapproved by the IRB. No one may approve human research that has not been approved by the IRB.

The Providence IRB is a Sub-Committee of the Research and Development Committee. The R&D Committee is responsible for the scientific quality and appropriateness of all research conducted, including human research. The

PVAMC R&D has delegated this function to the IRB. The IRB Committee possesses sufficient expertise (supplemented by advisors or consultants, if necessary) to review the scientific quality of all projects and the R&D will conduct audits at least annually to assure protection of human subjects. The results of this audit will be reported to both the R&D and IRB and will be reflected in their respective minutes. Additionally, the IRB may require projects to be reviewed and approved by the Radiation Safety Committee, Research Safety Sub-Committee or by ad hoc reviewers.

The Research Safety Sub-Committee: All research projects involving biological, chemical, physical, and radiation hazards must be approved by SRS and then by the R&D Committee prior to commencement of the research. The IRB requires all researchers to submit VA Form 10-0398, Bio-Safety Form, with their new protocols. This form and pertinent protocol elements are reviewed by the Safety Officer and SRS Chair prior to review by the IRB to determine if the protocol is required to be reviewed by the whole board SRS committee. If not (i.e. chart reviews or protocols determined not to involve biological, chemical, physical or radiation hazards), the Safety Officer and SRS Chair will sign the Bio-Safety form allowing the protocol to go to the R&D for approval. If protocols are determined to contain the above listed hazards, they are forwarded to the SRS committee coordinator to place on the SRS agenda for review and approval prior to R&D approval.

Radiation Safety Committee: Research involving exposing humans participants to radiation through x-rays or radionuclide for which the participant would otherwise not have been exposed except for research must receive approval from the Radiation Safety Committee. The Radiation Safety Committee reviews protocols prior to R&D approval to insure that appropriate radiation risks are properly documented in the consent form and that the appropriate level of review is carried out for projects that involve radiological procedures in addition to what would normally be required for standard clinical use. The IRB may grant approval of a study if the project is undergoing Radiation Safety Committee approval. However, the R&D Committee may not grant final approval until approval from the Radiation Safety Committee. Radiation Safety approval will be forwarded to the IRB as information and filed with the IRB minutes.

The Medical Center Compliance Committee and Medical Center Quality Management Committee also review the IRB minutes and quality management reports.

The ACOS for Research assists the R&D Committee with implementation of the HRPP, including: arranging for space and resources, monitoring changes in Federal regulations and policies and reviewing and evaluating compliance and quality improvement activities, and implementing needed improvements. The ACOS for Research and the R&D Chairperson meet annually with the Medical Center Fiscal Service to discuss the HRPP budget, taking into account workload, personnel, materials and supplies, capital equipment and

training and education costs covering all research committees under this umbrella.

C. The Research Investigators (21 CFR 56.108(b); 312.64, and 312.66)

The Providence VA IRB recognizes one Principal Investigator for each project. The PI must be a member of the PVAMC as either compensated by the VA, be appointed to work without compensation, or may be an employee assigned to the VA through the Intergovernmental Personnel Act (IPA) of 1970. The Principal Investigator has ultimate responsibility for his/her research project and all official IRB correspondence is addressed to the Principal Investigator. Co-investigators communicate with the IRB through the Principal Investigator. All investigators involved in a research protocol must submit a curriculum vitae or other statement of qualifications, which are considered by the IRB in its review of research protocols. All investigators must provide evidence of training in human research ethics. Students and non-VA employees cannot serve as Principal Investigators.

D. Other Institutions

The Providence VA IRB is responsible for the protection of the rights and welfare of human research subjects at Providence VAMC. There exists a cooperative agreement with Ocean State Research Institute; the VA non-profit Research Corporation associated with the Providence VA Medical Center. The IRB has authority over and responsibility for research conducted by the Ocean State Research Institute.

- (1) For research conducted at the Providence VAMC and concurrently at another institution (such as another University or another hospital), separate IRB approvals are required if the institution is engaged in research. Please refer to Paragraph G: Cooperative Research and Multi-Center Trials for additional information.
- (2) If the other institution is not engaged in research, a letter of support from the institution may be needed dependent upon the research protocol and/or institutional policies. It is the responsibility of the investigator conducting research at non-engaged institutions to obtain letters of support and/or notify appropriate services or institutional officials if required by institutional policy.

E. Regulatory Agencies

The Providence IRB is subject to regulation and inspection by all governmental regulatory agencies (e.g. FDA, GAO, OIG, OHRP, ORD, and ORO) and accreditation agencies, such as AAHRPP.

F. Ocean State Research Institute

The Providence VAMC IRB serves as the IRB for research studies administered for the Ocean State Research Institute (OSRI), a VA Non-profit, Educational and Research Corporation. A Memorandum of Understanding

(MOU) between OSRI and the VA Medical Center IRB formalizes this relationship. All research studies administered by OSRI involving human subjects are reviewed by the IRB, whether or not they occur on site at the Providence VA Medical Center.

G. Cooperative Research and Multi-Center Trials

For local PIs involved in cooperative research or multi-center trials for which the local PI is not the lead investigator, the PVAMC IRB is the IRB of record for investigators recruiting at this site. The PVAMC does not rely on commercial IRB review or oversight from other IRBs, with the exception of the VA Central IRB (See Section 15). Any necessary communication from other sites, including protocol amendments, reports of serious adverse events, or unanticipated problems involving risks to subjects, is communicated to the PVAMC IRB through the local PI.

If PVAMC is the coordinating site for a multi-site research study (e.g., the principal investigator is the lead investigator), the PVAMC must review and approve the coordinating site protocol and receive documentation of IRB review and approval from each participating site engaged in the research before issuing IRB approval. If participating sites are engaged in the research, the investigator must communicate how important human subject protection issues will be communicated to the participating sites. An institution becomes "engaged" in human research when its employees or agents (i) intervene or interact with living individuals for research purposes; (ii) obtain individually identifiable private information for research purposes; or (iii) if the institution receives a direct HHS award to support such research. The IRB and or IRB Chair, in consultation with the IRB Administrator, determine whether an institution is engaged if the research involves activities conducted outside of the PVAMC. Investigators are strongly encouraged to consult with the IRB Chair or IRB Administrator prior to submitting a protocol involving non-PVAMC sites if there is a question concerning engagement of the non-PVAMC institutions.

(1) The PVAMC principal investigator is responsible for serving as the liaison with outside regulatory agencies, with other participating sites, and for all aspects of review and oversight.

(2) During the initial IRB submission of a multi-site study, the principal investigator must indicate in their protocol and/or accompanying cover letter that PVAMC is the coordinating site.

(3) When PVAMC is the coordinating site, the principal investigator must clarify in the cover letter or protocol whether participating sites are engaged in research. The convened IRB will determine whether participating sites are engaged in research if needed. Investigators are encouraged to consult with the Research Office prior to submitting a

protocol when a PVAMC investigator is serving as the principal investigator and PVAMC is the coordinating site in a multi-site study. The following information must also be included in initial application materials to the IRB:

- i. Name of participating sites;
- ii. Confirmation that each participating site has an FWA;
- iii. Contact person and contact information for each participating site; and
- iv. IRB of record for each participating site.

(4) Communication of critical aspects of the human subject protocol is the responsibility of the principal investigator. When the participating sites are engaged in the research, the principal investigator must also document in a cover letter or protocol:

- i. The method for assuring that all participating sites have the most current version of the protocol;
- ii. The method for confirming that all amendments and modifications to the protocol have been communicated to participating sites;
- iii. The method for communicating serious adverse events and unanticipated problems involving risk to subjects or others to participating sites; and
- iv. The method of communicating regularly with participating sites about study events.

(5) For all participating sites engaged in the research, the principal investigator is responsible for obtaining IRB approval of the protocol (all other participating sites must use their IRB of record), and for ensuring that all sites review, approve and adopt all protocol modifications in a timely fashion.

(6) The principal investigator is responsible for ensuring that each participating site that is engaged in the research has IRB approval and any other appropriate approvals prior to enrollment of participants. This documentation must be maintained by the principal investigator.

- Unanticipated problems involving risks to participants or others.
- Interim results.
- Protocol modifications

(7) For studies following the DoD Addendum, a written agreement shall be established between the collaborators that includes a Statement of Work and specific assignment of responsibilities. This agreement should briefly describe the specific roles and responsibilities of each party, including but

not limited to, responsibility for scientific and IRB review, recruitment of participants, and procedures for informed consent, oversight and data monitoring, reporting requirements and compliance of entire research project. See SECNAVINST 3900.39 for additional information.
http://www.fas.org/irp/doddir/navy/secnavinst/3900_39d.pdf.

H. Community Member Involvement

The PVAMC does not solicit community-based input for study design, conduct, and data analysis as the current protocol portfolio does not support the necessity of this type of involvement. In addition, the PVAMC does not conduct community-based participatory research (CBPR). Research Administration will periodically review the protocol portfolio and proposed grant submissions to assess the future need for this type of involvement.

I. Participant Outreach Activities

The PVAMC Research Service distributes the VA Office of Research & Development “Veterans Participation in Research; Volunteering in Research” brochure throughout the hospital and is presented during New Patient Orientation. These brochures are labeled with the Research Service main phone number. In addition, a slideshow providing information on volunteering in research is displayed on the LCD monitors throughout the hospital as part of general information provided to participants and their families. These methods are evaluated by the IRB Coordinator, Administrative Officer, and/or other appropriate members of Research Administration. The annual assessment, which includes but is not limited to the number of brochures distributed and the number of participant calls, is distributed to the IRB and R&D committees for review and evaluation to determine the effectiveness of the Outreach process.

9. WRITTEN STANDARD OPERATING PROCEDURES AND GUIDELINES

FDA (21 CFR), VA (38 CFR) and DHHS (46 CFR) require that an Institutional Review Board (IRB) operate according to written Standard Operating Procedures to ensure protection of the rights and welfare of individuals involved as subjects of research. There is significant overlap between FDA, DHHS and VA. However, there are some significant differences between FDA, DHHS, and VA regulations. This document constitutes the record of the Standard Operating Procedure. The Standard Operating Procedure document is approved by the Research and Development Committee and updated as necessary.

This organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program to include this SOP. These documents are made available to sponsors, researchers, research staff, participants, and members of the IRB through the research SharePoint, e-mail, and printed manuals. Changes to these documents are made on the SharePoint and sent out to those who do not have access to the

SharePoint by e-mail. These changes are also updated in the hard copy manuals kept in the research office.

10. ACTIVITIES REQUIRING IRB REVIEW

All research involving human subjects (as defined below) and all other activities which, even in part, involve such research, regardless of sponsorship, must be reviewed and approved by the Providence VA Medical Center IRB. No intervention or interaction with human subjects in research, including recruitment, may begin until the IRB has reviewed and approved the research protocol. Specific determinations as to the definition of research or human subject, and their implications for the jurisdiction of the IRB under the Providence VA Medical Center policy are determined by their IRB.

A. Applicable Regulations and Definitions and Definitions

There is one Institutional Review Board at the Providence VA Medical Center. The IRB review and approve research in accordance with:

- Department of Health and Human Services (DHHS) regulations at 45 CFR 46
- Department of Veterans Affairs regulations at 38 CFR 16

For studies involving products regulated by the Food and Drug Administration (FDA), the IRB complies with the requirements set forth in:

- 21 CFR 50 Protection of Human Subjects
- 21 CFR 56 Institutional Review Boards
- 21 CFR 312 Investigational New Drug Application
- 21 CFR 812 Investigational Device Exemptions

In addition, studies regulated by the Department of Defense (DoD), the IRB complies with the regulations set forth in:

- 32 CFR 219 Protection of Human Subjects
- 10 USC 980 United States Code

Food and Drug Administration: The office responsible for implementing regulations governing the use of investigational drugs, biologics, devices and radiological procedures including radioactive drugs in clinical investigations with humans.

VA Research: VA research is research that is approved by the R&D Committee and conducted by VA investigators including PI's, Co-PI's, and site investigators (serving on compensated, work without compensation (WOC), or Intergovernmental Personnel Agreement (IPA) appointments) while on VA time, utilizing VA resources, and/or VA property including space leased to, and used

by, VA. The research may be funded by VA, by other sponsors, or be unfunded. (VHA Handbook 1200.1) *Note: Research conducted by non-VA investigators that does not utilize VA resources and that occurs on space, or with equipment, leased from VA or covered under a use agreement between VA and a non-VA entity is not considered VA research.*

Human Subject: This definition of human subject includes investigators, technicians, and others assisting investigators, when they serve in a “subject” role by being observed, manipulated, or sampled. “Human Subject” as defined by VA and DHHS regulations means a living individual about whom an investigator (whether professional or student) conducting research obtains either (1) data through intervention or interaction with the individual; interaction includes communication or interpersonal contact between the researchers and the subjects, or (2) identifiable private information. [38 CFR 16.102(f) and 45 CFR 46.102(f)]

Intervention as defined by VA and DHHS regulations means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes. [38 CFR 16.102(f)(2) and 45 CFR 46.102(f)] Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured.

Interaction as defined by VA and DHHS regulations means communication or interpersonal contact between investigator and subject. [38 CFR 16.102(f)(2)) and 45 CFR 45.102(f)]

Private information Private information must be individually identifiable in order for the information to constitute research involving human subjects. As defined by VA and DHHS regulations, private information includes (1) information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and (2) 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). [38 CFR 16.102(f) and 45 CFR 46.102(f)]

Identifiable information as defined by DHHS and VA means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

The FDA regulations [21 CFR 50.3(g),21 CFR 66.102(c)] defines **human subject** as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. For research covered by FDA device regulations, subject means a human who participates in an investigation, either

as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease (21 CFR 812.3(p)).

Research: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. [38 CFR 16.102(d), 45 CFR 46.102(d) and 32 CFR 219]

When determining whether an activity is or is not a systematic investigation, the IRB will consider, but not limited to, the following questions related to the activity:

- referred to as a “research” activity?
- designed to address a research intent?
- using an organized method (e.g., methodical, purposeful, carried on by using step-by-step procedures, or characterized by the use of logically and carefully planned succession of steps)?
- designed to answer a question or test a hypothesis that addresses a Research intent even though it is not specifically stated?

When determining whether an activity is or is not designed to develop or contribute to generalizable knowledge, the IRB will consider, but not limited to, the following questions related to the activity

- designed to be used for operational purposes only?
- applied to populations or settings different from the ones from which it was collected?
- going to be published or presented? If so, what kind of publications will the manuscripts be submitted to and/or what is the type of conference?

Research as defined by FDA regulations means any clinical investigation that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

“Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

“Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act” means any activity that evaluates the safety or effectiveness of a medical device. [21 CFR 812.2(a)]

“Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Research involving a human being as an experimental subject is defined by DoD regulations means an activity, for research purposes, where there is an intervention or an interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32 CFR 219.102(f), reference (c)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject’s environment, the withholding of an intervention that would have been undertaken if not for the research purpose. This does not include:

- activities carried out for purposes of diagnosis, treatment, or prevention of injury and disease in members of the Armed Forces and other mission essential personnel under Force Health Protection programs of the DoD
- Authorized health and medical activities as part of the reasonable practice of medicine or other health professions.
- Monitoring of compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units. This includes such activities as drug testing, occupational health and safety monitoring, and security clearance reviews.
- Activities exempt under 32 CFR Part 219 (reference (c)).
- Support

[DoD Directive 3216.02. E2]

Human Subject Research: Any activity that either:

- (1) Meets the VA or DHHS definition of “research” and involves “human subjects” as defined by VA or DHHS (VA or DHHS-regulated “Human Subject Research”); or
- (2) Meets the FDA definition of “research” and involves “human subjects” as defined by FDA (FDA-regulated “Human Subject Research”).

The Institutional Review Board (IRB) is a board established in accordance with and for the purposes expressed in the Common Rule (38 CFR 16.102(g).)

Within VHA, an IRB was formerly known as the Subcommittee on Human Studies. At VA medical centers, the IRB is a subcommittee of the R&D Committee. An IRB is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with VA Policies, the Common Rule and FDA regulations, the IRB has responsibility for approving, requiring modification in (to secure approval), or

disapproving research. The VA IRB also has the authority to suspend or terminate research for continued noncompliance with VA Policies, the Common Rule, FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

IRB approval means the IRB has determined that the research has been reviewed and may be conducted at an institution with the constraints set forth by the IRB and by other institutional and federal requirements.

Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The **risks** to which research subjects may be exposed have been classified as physical, psychological, social, legal, and economic.

Physical Harms. Medical research often involves exposure to minor pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. Some of the adverse effects that result from medical procedures or drugs can be permanent, but most are transient.

Psychological Harms. Participation in research may result in undesired changes in thought processes and emotion (*e.g.*, episodes of depression, confusion, or hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem). These changes may be transitory, recurrent, or permanent.

Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics such as drug use, sexual preferences, selfishness, and violence. These feelings may be aroused when the subject is being interviewed or filling out a questionnaire. Stress may also be induced when the researchers manipulate the subjects' environment - as when "emergencies" or fake "assaults" are staged to observe how passersby respond. Psychological harm may also result from behavioral research that involves an element of deception, particularly if the deception includes false feedback to the subjects about their own performance.

Invasion of privacy is a risk of a somewhat different character. In the research context, it usually involves either covert observation or "participant" observation of behavior that the subjects consider private. Breach of confidentiality is sometimes confused with invasion of privacy, but it is really a different problem. Invasion of privacy concerns access to a person's body or behavior without consent; confidentiality of data concerns safeguarding information that has been given voluntarily by one person to another. A breach of confidentiality may result in psychological

harm to individuals (in the form of embarrassment, guilt, stress, and so forth) or in social harm (see below).

Social and Economic Harms. Some invasions of privacy and breaches of confidentiality may result in embarrassment within the subject's business or social group, loss of employment, or criminal prosecution. Areas of particular sensitivity are information regarding alcohol or drug abuse, mental illness, illegal activities, and sexual behavior. Some social and behavioral research may yield information about individuals that could "label" or "stigmatize" the subjects (e.g., as actual or potential delinquents or schizophrenics).

Participation in research may result in additional actual costs to individuals. Any anticipated costs to research participants should be described to prospective subjects during the consent process.

Legal Harm: harm that could occur which results in legal action as a result of participation in human research activities. Legally Authorized Representative is defined as an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. As per VHA Handbook 1200.05, Requirements For The Protection Of Human Subjects In Research, July 2008, a legally authorized representative includes not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court appointed guardian of the person, but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older). RI State Law on definitions of legal guardian is less restrictive than VHA 1200.05. The IRB will consult with the PVAMC legal counsel for research that occurs outside of Rhode Island to determine appropriate state laws regarding legally authorized representatives.

Test Article: Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation or under §§ 351 and 354-60F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n; 21 CFR 50.3(j)).

Office for Human Research Protections (OHRP): The office under the Department of Health and Human Services responsible for implementing DHHS regulations (45 CFR 46) governing biomedical and behavioral/social science research involving human subjects.

Office of Research and Development (ORD): Within VHA Central Office, ORD is the office responsible for the overall policy, planning, coordination, and direction of VA research activities.

Office of Research Oversight (ORO): The VHA office in advising the Under Secretary for Health on all matters of compliance and assurance regarding human subjects protections, animal welfare, research safety, and research misconduct. **NOTE:** *ORD and ORO are two separate offices within VHA. The CRADO reports to the Principal Deputy Under Secretary for Health. The Chief Officer of ORO reports to the Under Secretary for Health.*

B. Determining if an Activity is Considered Research Involving Humans

To determine if an activity is considered research the IRB follows a two-step approach to defining research involving human participants. This two step approach includes first deciding whether the activity is research regulated by VA, DHHS, or FDA, and if so, whether it involves human subjects as defined by VA, DHHS, or FDA. In order for an activity to be considered research involving humans, it must:

- (1) Meets the VA or DHHS definition of “research” and involves “human subjects” as defined by VA or DHHS (VA or DHHS-regulated “Human Subject Research”); or
- (2) Meets the FDA definition of “research” and involves “human subjects” as defined by FDA (FDA-regulated “Human Subject Research”).

The determination whether the activity is considered research involving human participants will be made by the ACOS for R&D, AO, IRB Coordinator, Chair, or designee using the “Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions Worksheet”. If determined human subjects research, the protocol will be placed on the following month’s IRB Agenda and the protocol materials will be distributed to all members.

Research is considered PVAMC research when any one and/or a combination of the following apply:

1. One of more members of the research team are working on the research while on VA duty time;
2. The Investigator and/or members of the research team are using VA resources.
3. The Investigator and/or members of the research team are using VA space for the research, and/or
4. VA is funding any or a portion of the research, or
5. While on VA time, VA investigators, clinician, or other VA staff
 - (a) release identifiable subject data to the research staff with subjects’ written approval;
 - (b) recruit and obtain informed consent from subjects for the research;

- (c) obtain identifiable private information about living individuals for research purposes, or
- (d) interact or intervene with living individuals for research purposes.

C. Activities Requiring Review

The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research conducted in VA. They may be done at one VAMC or may be conducted as multi-center projects (i.e.: Cooperative Studies Program).

- a. Clinical Research.** Clinical research involves research: (a) to increase scientific understanding about normal or abnormal physiology, disease states, or development and (b) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of clinical research. As defined in the FDA regulations, clinical investigation means any experiment that involves a test article and one or more human subjects. (21 CFR 56.102) The terms research, clinical research, clinical study, and clinical investigation are generally considered to be synonymous.
- b. Behavioral and Social Sciences Research.** The goal of social and behavioral research is similar to that of clinical research — to establish a body of knowledge and to evaluate interventions — but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention. Note: for DoD regulated research, surveys typically require DoD Survey Review and approval. The DoD Survey Approval Manager may require IRB review of the survey instrument prior to granting approval.
- c. Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB should review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of

data. The IRB may then determine the parameters under which the repository may share its data or materials with or without IRB review of individual research protocols. The VA has specific requirements for repository research.

- d. Quality Assurance/Quality Improvement Activities.** Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities may constitute human subject research, and require IRB review, if they are designed or intended to contribute to generalizable knowledge. Quality assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, will probably not require IRB review or will qualify for an exemption. The investigator conducting the QA/QI research may submit the protocol to the IRB for human subject research determination.
- e. Pilot Studies.** Pilot studies involving human subjects are considered human subject research and require IRB review.
- f. Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. OHRP representatives have advised that "third parties," about whom identifiable and private information is collected in the

course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider if informed consent from third parties can be waived in accordance with Section.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

- g. Standard Diagnostic or Therapeutic Procedures:** (1) The collection of data about a series of established and accepted diagnostic, therapeutic procedures, or instructional methods for dissemination or contribution to generalizable knowledge; (2) An alteration in patient care or assignment for research purposes.
- h. Innovative Procedures, Treatment, or Instructional Methods:** A systematic investigation of innovations in diagnostic, therapeutic procedure, or instructional method in multiple participants in order to compare to standard procedure. The investigation is designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge.
- i. Retrospective Data:** (1) Retrospective review of a patient's medical record with the intent to report and/or publish the summary; (2) Retrospective review of a patient's medical records for use in an educational setting. The data will be de-identified.
- j. Internet Research:** Online websites are set up for the purposes of collecting data regarding a particular topic. This may include the completion of questionnaires/survey, personal data, etc.

D. Failure to Submit Project for IRB Review

The implications of engaging in activities that qualifies as research that is subject to IRB review without obtaining such review is significant. Results from such studies may not be published unless IRB approval was obtained prior to collecting data. To do so is in violation of PVAMC policy.

If an Investigator begins a project and later finds that the data gathered could contribute to the existing knowledge base or that he or she may wish to publish the results, the Investigator should submit a proposal to the IRB for review as soon as possible. If the IRB does not approve the research, data collected cannot be published.

RESPONSIBILITY

Institutional Official (IO). The Medical Center Director, who is also the IO, is responsible for the HRPP Program advised and assisted by the Chief of Staff, the Associate Chief of Staff for Research, and the Research and Development Committee. The IO is responsible for maintaining a current Federal Wide

Assurance (FWA) in accordance with VHA Handbook 1058.03. The IO is responsible for implementing the R&D program, policies and procedures, including establishing and appointing members to the R&D Committee and any appropriate subcommittees. The IO, with recommendation from the R&D Committee, is responsible for ensuring that R&D funds are used appropriately and that adequate resources, including funds, space and personnel, are provided for research and its administrative functions as outlined in VHA Directive 1200.

In addition, the Medical Center Director is responsible for:

- Fostering an institutional culture that supports the ethical conduct of all research involving human subjects.
- Serving as signatory authority for the FWA, and thereby making a written commitment to protect human subjects participating in research at the local VA facility and to comply with the requirements of 38 CFR Part 16.
- For completing assurance training required in VHA Handbook 1058.03 prior to signing the FWA initially, and every 3 years after that.
- Ensuring that detailed SOPs are developed and implemented to satisfy all requirements of VHA Handbooks (i.e., 1200.05, 1058.01, etc.), including requirements affecting the facility's academic affiliates.
- Appointing a RCO who reports directly to the Director and is responsible for developing and implementing a research compliance program (VHA Directive 1200 and VHA Handbook 1058.01).
- Delegating authority in writing for all respective roles and responsibilities within the local VA facility's HRPP. This delegation of authority must provide the organizational structure and ensure accountable leadership for compliance oversight activities for all human subjects research conducted at the facility.
- Creating and implementing initial and continuing education programs.
- Ensuring that any IRB designated as an IRB of record for a VA facility is established in accordance with the requirements of this Handbook and 38 CFR 16.103(b)(2); registered with OHRP and, if appropriate, FDA; and listed as an IRB of record on the VA facility's FWA. The IRB(s) of record may include the facility's own IRB(s), VA Central IRB, IRB of another VA facility, or an IRB(s) established by an affiliated medical or dental school. Neither the VA facility nor the investigator may engage the services of another IRB for the purposes of avoiding the rulings of the IRB of record.
- Ensuring that the IRB(s) of record functions independently, and that its Chair, or Co-Chairs, and members have direct access to the IO for appeal if they experience undue influence or if they have concerns about the IRB.
- Ensuring that all persons working in research or performing any research activities have been officially appointed by Human Resource Management and are appropriately knowledgeable to fulfill their respective duties in accordance with ethical standards and all applicable local, VA and other Federal requirements.

- Being the point of contact for correspondence addressing human subjects research with OHRP, FDA, and VHA Central Office.
- Ensuring the VA facility's HRPP is accredited by an organization approved by ORD to perform this function (per par. 64 of VHA Handbook 1200.05).
- Ensuring that recruiting documents, flyers, and advertisements for non-VA research are not posted within or on the premises of a VA facility. Posting of such documents may give the Veteran or visitors to the VA facility the impression that the non-VA study is VA-approved research, the VA supports or endorses the research, or that VA will pay for the research expenses that are incurred. General guidance may be posted within VA indicating that Veterans may speak with their health care providers if they wish to participate in research and that information on clinical trials is available at: <http://clinicaltrials.gov>.
- Ensuring that all RCO informed consent audits, regardless of outcome, are reported to the IRB and the R&D Committee in a timely fashion.
- Ensuring that all RCO regulatory audits, regardless of outcome, are reported to the IRB and R&D Committee in a timely fashion.
- Reporting to the Office of Research Oversight (ORO) in writing within 5 business days after being notified of a research problem or event for which such reporting is required under VHA Handbook 1058.01.
- Completing the annual facility Director's Certification of Research Oversight.
- Providing a copy of any ORO compliance reports regarding the research program to the ACOS for Research, R&D Committee, any relevant research review committee(s), and the RCO in a timely fashion.
- Fulfill all educational requirements mandated by the VA Office of Research and Development and OHRP.
- Approving the request for permission to conduct international research at the VA facility and ensuring CRADO approval of international research is obtained prior to its initiation at the facility per subpar. 56e in VHA Handbook 1200.05.
- Suspending or terminating the IRB membership of any individuals who are not fulfilling their member responsibilities or obligations.

The Associate Chief of Staff for Research and Development (ACOS/R&D) is delegated by the Medical Center Director with overall responsibility for the R&D program, including the HRPP, at the facility.

He/she will:

- Ensure compliance with federal regulations, policy and procedures to guarantee the protection of human subjects participating in research
- Evaluate on an on-going basis the HRPP program for adherence and compliance with federal, state, and local policy and regulations.

- Evaluate (at least yearly) the IRB workload in regard to timely and thorough review.
- Respond to and resolve reports of IRB member coercion or undue influence.

AO is responsible for the oversight of daily operations of the HRPP and oversight of the daily operations of the IRB.

He/she will assist the ACOS with:

- Ensuring compliance with federal regulations, policy and procedures to guarantee the protection of human subjects participating in research
- Evaluating on an on-going basis the HRPP program for adherence and compliance with federal, state, and local policy and regulations.
- Evaluating (at least yearly) the IRB workload in regard to timely and thorough review.

The IRB Coordinator will be responsible for the daily operations of the IRB.

The Program Assistant will be responsible for the daily operations of the IRB.

Standard Operating Procedures for Research
Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 2: IRB Committee Organization

October 19, 2011

1. THE MEMBERSHIP OF THE IRB

A. Membership Selection Criteria

The IRB members shall be sufficiently qualified through experience and expertise, for reviewing research proposals in terms of regulations, applicable law and standards of professional conduct and practice, knowledge and experience with vulnerable populations, and intuitional commitments. Therefore, the IRB shall include persons knowledgeable in these areas.

The membership shall be diverse, so selection shall include consideration of race, gender, cultural backgrounds, clinical experience, healthcare experience, and sensitivity to such issues as community attitudes, to assess the research submitted for review.

There shall be at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. There shall be one member who has no other affiliation with this institution, either self or family member. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. At least one member, designated as a "Community Member" must have no other affiliation with Providence VAMC other than his/her IRB membership. The IRB may consist entirely of members of one profession. At least one member is also a member of the R&D Committee.

The PVAMC IRB has at least five regular, voting members. Alternate members, with expertise similar to an IRB Committee Member, can be designated to substitute for that member, if that member cannot attend the meeting. Alternate members must meet qualifications of members and be selected by the same process as members and approved by the Medical Center Director.

The ACOS for R&D attends the meetings as an ex-officio without vote and is prohibited from voting in accordance with VHA Handbook 1200.05. The remaining administration officials including but not limited to the AO for R&D, are considered ex-officio without vote members. The Research

Compliance Officer is an invited guest. These members are sensitive to the occurrence or appearance of conflict of interest.

An alternate may only substitute for his/her designated member. Alternate members receive and review the same materials as the primary member. The IRB minutes document the attendance of the alternate member.

B. Composition of the Board:

Regular members: the backgrounds of the regular members shall be varied in order to promote complete and adequate reviews of the types of research activities commonly reviewed by the PVAMC IRB. Regular members must include:

- a. Nonaffiliated member(s): the nonaffiliated member(s), who can be either scientific or nonscientific reviewers, should be knowledgeable about local community and be willing to discuss issues and research from that perspective. Consideration should be given to recruiting individuals who peak for the communities from which the PVAMC will draw its research subjects. The nonaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB. The nonaffiliated member cannot be a member of the immediate family of a person who is affiliated with the PVAMC. In addition, the nonaffiliated member will have a WOC appointment to the PVAMC.
- b. Scientific members: Most IRB's include physicians and Ph.D. level physical or biological scientist. Such members satisfy the requirement for at least one scientist. When a IRB encounters studies involving science beyond the expertise of the members, the IRB may use a consultant to assist in the review, as provided by 21 CFR 56.107(f). However, when FDA regulated products are reviewed, the convened meeting must include a licensed physician member, and therefore at least one member of the PVAMC IRB must be a physician licensed in the state of Rhode Island.
- c. Nonscientific member: the intent of the requirement for diversity of disciplines is to include members whose main concerns are not in scientific areas. Therefore, nonscientific members are individuals whose education, work, or interests are not primarily in medical or scientific areas.
- d. Representatives of vulnerable populations or special groups of subjects: When certain types of research are reviewed, members or consultants who are knowledgeable about the concerns of certain groups may be required.
- e. Chairperson: The Chair should be an individual who highly respected in the VA research community and who is fully capable of managing the IRB, and the matters. The IRB Chair must have a VA appointment.

- f. At least one member who represents the perspective of a research participant.
- g. At least one member with expertise with mentally disabled persons or persons with impaired decision-making capacity, when reviewing this type of research.

h. Privacy Officer and Information Security Officer

The PVAMC Privacy Officer (PO) and Information Security Officer (ISO) are appointed to the IRB as ex-officio, non-voting members. The facility PO and ISO must be involved in the review of human subjects research to address and mitigate potential concerns regarding privacy and confidentiality, and information security, respectively.

An IRB Roster will be maintained for the IRB. The IRB members will be queried at the time of the IRB appointment and approximately each year to evaluate any changes. The IRB Roster will contain, but not limited to:

- Name of IRB member (primary and alternates)
- Earned Degrees
- Scientific Status
- Representative status
- Experience and credentials
- Employment or other relationship between each member and the organization
- Affiliation status
- Membership status
- Primary members who the alternate member can substitute for
- Representative capacities in terms of vulnerable populations, if any, each member is knowledgeable about or experienced in working with.
- Employment or other relationship between each IRB member and the PVAMC.

2. MANAGEMENT OF THE IRB

A. The Chairperson

(1) Selection and Appointment

The Research and Development Committee recommends the Chairperson, who is appointed by the Medical Center Director. The recommendation is based on qualifications and experience in the conduct

and regulation of Human Research and Human Research protections and willingness to serve. The Chairperson has a VA appointment.

(2) Length Of Term/Service

The Chairperson serves a 1-year term that may be renewed indefinitely.

(3) Duties

The Chairperson has primary responsibility for conducting Committee business. He/she directs Committee proceedings in accordance with institutional and federal requirements. He/she works with Committee members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are protected. He/she functions as a role model and conducts business fairly and impartially. He/she reviews and approves IRB records and correspondence and is the signatory official for official IRB correspondence. He/she in conjunction with the IRB Coordinator assigns protocols to primary reviewers.

(4) Removal

The Medical Center Director may remove the Chairperson with the concurrence of the Research and Development Committee, for causes such as non-performance of duties.

B. The IRB Members

(1) Selection and Appointment

The Research and Development Committee recommends the members, including alternates, who are appointed by the Medical Center Director in writing. The recommendation is based on qualifications and experience in the conduct and regulation of Human Research and Human Research protections and willingness to serve. Alternate member's qualifications are comparable to those of the primary member to be replaced. Great consideration is placed on appointing members of different genders, races, and cultural backgrounds.

(2) Length of Term/Service

Members serve one-year terms, which can be renewed indefinitely.

(3) Duties

Committee members, including alternates, conduct initial and continuing review of human research projects to ensure that the rights and welfare of research subjects are protected. Members vote to approve, require modifications (to secure approval), or disapprove submissions. These actions apply to: (a) initial reviews, (b) continuing reviews, (c) amendments, (d) serious adverse events and serious unanticipated protocol deviations, (e) advertisements, (f) noncompliance, (g) general policy issues, and (h) general procedural issues. Members evaluate the seriousness of noncompliance and may restrict, suspend or terminate approval of a protocol. In cases of serious or continuing noncompliance the Committee may suspend or terminate an investigator's privilege to

conduct research at Providence. Serious or continuing noncompliance resulting in suspension of privileges is reported to Providence VAMC management, VA Headquarters and relevant federal oversight agencies (e.g., FDA, OHRP). (See SOP Section 4, Review of Research, 4.9 Reporting Requirements)

(4) Attendance Requirements

Members are required to attend monthly meetings. When the primary member is unable to attend, his/her designated alternate may attend as their substitution. Members may have designated alternates, who are appointed by the Medical Center Director.

(5) Removal

Members may be allowed to resign or be removed from office at the discretion of the Director. Regular attendance at meetings of the IRB is expected, and a member may be removed because of repeated unexcused absences. Members should submit requests for resignation to the IRB Coordinator or the IRB Chair for inclusion on the IRB and R&D Committee agendas. The PVAMC Director will be informed through the review and signing of the R&D Committee minutes.

C. Training of IRB Chair and Members

(1) Orientation

The IRB Chairperson, R&D Chairperson, IRB members, R&D members, and investigators receive comprehensive educational materials including VA [38 CFR 16,17], VA [Handbook 1200.05], FDA [21 CFR 50,56], DHHS [45 CFR 46], the 1998 FDA Information Sheets, the Institutional Review Board Guidebook (DHHS), and The Belmont Report.

(2) VHA Mandatory Training

The HRPP requires the following VA mandated annual training of all IRB, R&D, subcommittee chairs and members involved with human research, investigators and research study staff: VA Privacy Awareness Training (HIPAA), Good Clinical Practice and Human Subject Protections from CITIprogram.org, and VA Information Security Awareness and Rules of Behavior (Cyber Security). In addition to the annual required training, a one-time completion of Information Security 201 for Research and Development Personnel is also required. All individuals are required to submit a certificate of completion to the Research Office. Training folders and a log of all Committee members, investigators, and study staff are maintained in the Research Administration Office by the Program Assistant for Research Education and Training. These references are used to validate required training is completed upon assignment to the Research Committee.

For Department of Defense sponsored protocols, persons who conduct, review, approve, oversee, support or manage human subject research

sponsored by the Department of Defense (DOD) must complete initial and continuing (i.e., annual) research ethics education. Current VA research training meets this requirement. DOD-specific research requirements are communicated to the Principal Investigator at the time a grant is awarded. The Investigator is responsible for ensuring that the study team is aware of these requirements. Other members of the research community, including IRB members, are informed of DOD-specific requirements through review of initial DOD-sponsored protocols, reviews of standard operating policies, meetings to develop and update the Research Strategic Plan, and/or presentations about new DOD-sponsored research studies. In addition, the RCO, who may obtain additional information about DOD requirements through Office of Research Oversight training, DOD policy review and national conferences, is available as a consultant to the IRB, the R&D Committee and investigators.

(3) Continuing Education and Reference Materials

(a) Providence VAMC research service will fund travel and registration to one IRB training conference per year for each member of the IRB or R&D upon request. PRIM&R, FDA, and OHRP sponsored meetings are recommended.

(b) The Research Service library contains instructional materials and training materials that may be checked out by investigators or IRB members.

(c) Ongoing education is an agenda item at each IRB meeting.

D. Evaluation of IRB Members, Chairs, and Staff

IRB members, Chair, Associate Chair, and staff members performance are evaluated annually. A member and Chair/Associate workload evaluation is conducted by the IRB Coordinator or another member of Research Administration. This evaluation focuses on attendance and number of protocol reviews. The Chair/Associate Chair evaluation includes, but is not limited to, the amount of effort put forth on functions associated with the position, such as expedited reviews, minutes, correspondence, and investigator contact. In addition, each member, chair and staff member completes an online anonymous survey that includes a self-assessment and quality measures that focus on the overall IRB meeting process, such as, pre-meeting protocol review time, meeting flow, IRB Administrative support and Chairperson evaluation. An aggregate summary of the surveys is presented to the IRB members, Chair, Associate Chair, staff, and the R&D Committee. Individual feedback is provided by the ACOS.

E. Compensation of IRB Members

IRB members who are not paid employees of the VA may be compensated for their time spent reviewing protocols and attending meetings. IRB members

who are VA employees are not compensated additionally for serving on the IRB.

F. Liability Coverage for IRB Members

IRB members are officially carrying out the VA mission and are protected from liability under the US Torts. Non-VA employees are registered as WOC (without VA compensation) employees with Human Resources Management Service, Providence VAMC. WOC employees are officially carrying out the VA mission and are protected from liability under the US Torts.

G. Use of Consultants

The IRB is authorized to obtain and/or purchase services of ad hoc reviewers or consultants when additional expertise is required due to a lack of expertise represented on the Committee.

The IRB Coordinator in consultation with the Chair will contact an appropriate expert (consultant) and arrange for their assistance. The consultant will be required to sign an IRB Member Conflict of Interest Statement and may not participate in a protocol review if it is determined that he/she has a conflict of interest. The use of consultants may be determined at any time during the review process, including but not limited to, at the time of protocol submission, during the review process prior to the IRB meeting, or during the presentation/discussion at an IRB meeting. If the need for a consultant is determined at an IRB meeting, the protocol will be tabled until next convened meeting that can be attended by the consultant.

The consultant will be given the same materials as the Primary and Secondary reviewer per at least 7 days prior to the next scheduled IRB meeting. The consultant is required to submit a written report to include all elements of review to the Committee at the time of review. The report will be recorded in the minutes.

The consultant may be required to participate in all subsequent submissions. The consultant will attend the IRB meetings as a guest, where he/she may participate in the deliberations and make recommendations, but may not vote and shall not be used to reach quorum.

H. Administrative Support

Providence VAMC employs one full time IRB Coordinator and one full-time IRB Program Assistant. In addition, other employees of Research Service may assist with clerical and administrative activities, as necessary. The IRB Coordinator and Program Assistant are supervised by the Administrative Officer who reports to and is supervised by the ACOS for Research. The IRB Coordinator consults frequently with the IRB Chair. The duties of the IRB Coordinator include:

- Directing and overseeing all IRB support functions and operations

- Developing and implementing procedures to effect efficient flow of documents and maintenance of records
- Managing the process for receiving and responding to research-related complaints and allegations of noncompliance with PVAMC policies related to the HRPP, including recording complaints in a log, reporting the complaint to the ACOS for Research or other appropriate institutional official who will conduct an appropriate investigation, define remedial action, and report the nature of the complaint, the response, and the remedial action to the IRB, institutional officials and other appropriate officials.
- Providing guidance to investigators to assist them in complying with requirements concerning informed consent. The IRB Coordinator will meet with principal investigator and study coordinators to inform them of the following:
 - The IRB has the authority to observe the consent process.
 - Prospective participants may not be entered into a study, and procedures may not be conducted, until informed consent is obtained (unless consent is waived by the IRB).
 - The IRB will review proposed Consent Forms to ensure that the information given to the subject, or their legally authorized representative, is in understandable language.
 - Prospective participants, or their legally authorized representative, must have sufficient opportunity to consider whether or not to participate.
 - Prospective participants must give consent without coercion or undue influence.

I. Resources (meeting area, reproduction equipment, filing space)

The Research Conference Room, Building 32 is reserved for all IRB meetings. The IRB administrative office and files (300 sq. ft.) are maintained in Administrative area of the Research Office. Additional secure file space for storage is available in the basement of the research building. The IRB has a digital multi-purpose photocopier (50 copies/minute) and fax machine.

J. Committee Member Conflict Of Interest Policy

- (1) The Research and Development Committee nominates members to the IRB, who are appointed by the Medical Center Director.
- (2) The ACOS for Research and Development may not serve as a voting member on the PVAMC IRB in accordance with VHA Handbook 1200.05 or R&D Committee in accordance with VHA Handbook 1200.1.
- (3) The IRB and R&D Chairpersons, IRB and R&D members, alternates, and consultants are required to list on the IRB Member Conflict of Interest Form, any potential financial or non-financial conflicts of interests, including competing business interests, or update the form when information related to a conflict of interest changes materially, in writing to the Research Office.

Financial conflicts of interest are defined as:

- Involvement of immediate family in the design, conduct, or reporting of the research.
 - Ownership interest (equity or stock options) of \$10,000 or greater value when referenced to publicly traded prices or other measure of fair market value when aggregated for the immediate family.
 - Ownership interest (equity or stock options) of any amount when the value of the interest would be affected by the outcome of the research.
 - Ownership interest (equity or stock options) whose value represented 5% or more interest in any one single entity.
 - Compensation of \$10,000 or greater in the past year when aggregated for the immediate family.
 - Compensation of any amount when the value of the interest would be affected by the outcome of the research.
 - Board or executive relationship related to the research, regardless of compensation.
 - Non-financial conflicts of interest are defined as any VA duties that involve the management of research project or contracts other than those on which the member is a principal investigator, co-principal investigator or investigator. This includes oversight, approval, advising, recommending, or initiating actions on research related projects.
- (4) The Research Office monitors IRB member's actions during proceedings, annual Conflict of Interest Disclosure forms, and through a review of the minutes. Corrective action will be taken if this policy is not adhered to, including but not limited to, termination of protocol, censoring, and reporting to appropriate regulatory bodies.
- (5) IRB/R&D Chairperson and IRB/R&D members who have either a financial or non-financial conflict of interest on a specific item are prohibited from participating in the IRB/R&D's initial or continuing review of the involved research. The conflict of interest will be announced during the meeting and the IRB/R&D Chairperson and IRB/R&D members with a conflict of interest are required to recuse themselves from deliberations and from voting. However, recused members may answer questions from the convened IRB/R&D or IRB/R&D Chairperson if requested. Recused members do not count toward a quorum. Members who are recused due to a conflict of interest are recorded in the minutes.
- (6) Investigators may not select IRB reviewers for their protocols.
- (7) IRB members may not discuss protocols under review with investigators, except in the context of a convened meeting.

RESPONSIBILITY

The Medical Center Director is responsible for:

- The appointment of the IRB membership or for the removal of members.

- Assure availability of necessary resources, such as staff support, meeting area, filing space, reproduction and computer access to the IRB.

The R&D committee is responsible for nominating candidates for IRB membership.

The ACOS/R&D is responsible for

- The resolution of member Conflict of Interest non-compliance or complicated issues.
- Assure that all IRB members are provided with initial orientation and appropriate continuing education.

The AO/R&D will assure that all IRB members are provided with initial orientation and appropriate continuing education.

The IRB Chair is responsible for:

- Chair the IRB meeting.
- Reviewing the IRB minutes to ensure that the actions and reasons for actions of each presented protocol are accurately summarized.
- Reviewing requests for expedited review and, if the expedited process is appropriate, either approving the study on behalf of the IRB, requiring modification for approval or referring the request for full IRB review. Requests that do not meet the criteria for expedited review will be considered by a fully convened IRB. The chair may also delegate this task to another IRB member.
- Reviewing requests for exempt status.
- Reviewing the adverse event reports and available DSMB reports along with a primary reviewer from the IRB.
- Ensuring that if any amendment for VA research addresses an issue related to biosafety or radiation safety, the appropriate committee or subcommittee must first approve the amendment before IRB approval is given.
- Signing the final approval documents (VA Form 10-1223 Report of Subcommittee on Human Studies, Human Studies Subcommittee (IRB), letters, etc) on protocols approved by the IRB.
- Interacting with the Research Office staff and the ACOS/R&D about IRB matters.
- Reporting to the R&D Committee about IRB activities as needed.
- Determining, as necessary, the need for additional expertise.
- Educate IRB members.

The Associate Chair is responsible for chairing the meeting in the Chair's absence and will assume other duties of the chair as delegated by the Chair.

The IRB members are responsible for:

- Learning about and remaining current on ethical, legal and regulatory issues related to IRB business.
- Preparation of written reviews of proposals and other documents (such as adverse event reports or continuing reviews), as assigned by the Research Office.
- Review of all proposals submitted to the IRB.
- Review of minutes to ensure accuracy.
- Serving as primary reviewers as assigned by the Research Office or IRB Chairperson.
- Maintaining the integrity of the IRB review process. In particular, members must avoid discussing IRB protocols with investigators outside of a convened IRB meeting, except that the Chair and Primary Reviewers may contact investigators to provide advice and to obtain clarification regarding studies that are under review.
- Making recommendations for regular, alternate and ad hoc membership
- Reviewing reports of serious or continuing noncompliance with regulations that may endanger the well being of subjects and considering actions that might be taken, such as notification of current or past participants, modification of the research protocol, continuing review timetable, consent process, or consent document, and termination or suspension of the research.
- Reviewing reports of unanticipated problems involving risks to subjects and considering actions that might be taken.
- Alternate IRB members are responsible for reviews as assigned when substituting for a regular member. Alternate members receive and review the same material that the primary member receives.

The IRB coordinator will:

- Assist the Chair in determining the need for additional expertise.
- Monitor the member conflict of interest disclosures and report to the IRB Chair, ACOS and AO issues/concerns as they arise for resolution.
- Maintain education and training materials and provide to members.
- Maintain IRB member's files which will contain, at a minimum, Curriculum Vitae, training documentation and conflict of interest statement.
- Act as liaison between investigators and members as needed.

The Program Assistant will:

- Generate IRB member's appointment letters from the R&D Committee.
- Maintain IRB member's files which will contain, at a minimum, Curriculum Vitae, training documentation and conflict of interest statement.
- Act as liaison between investigators and members as needed.

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Providence, Rhode Island

Section 3: Functions and Operations

October 19, 2011

3.1 SUBMISSION REQUIREMENTS FOR IRB REVIEW

The IRB reviewers rely on the documentation that is submitted by Investigators for review. It is imperative that the documentation contain all information pertinent to the study so that the members may conduct a thorough review and to ensure that the study meets all approval criteria.

1. Submission Requirements for Initial Review

Investigators applying for initial review must submit:

- Completed Request to Review Research Proposal/ Project Form with all applicable signatures
- Completed IRB Submission Application
- ISO/PO Checklist for Reviewing Information Protection in Research
- Abstract
- Full protocol
- Grant Application (if applicable)
- Contract of funding agency
- Budget
- Data Use Agreement (if applicable)
- De-Identified Data Checklist (if applicable)
- Completed Principal Investigator's Conflict of Interest Disclosure Form (Note: all project staff will also need to complete this form)
- Completed Chief of Service Statement Supporting Research Project
- Completed Research Protocol Safety Survey
- Applicable training PVAMC training certificates
- CV of Investigators (new investigator only)
- Questionnaires
- Recruitment materials
- Proposed participant instructions
- Completion of the VA Form 10-1086 Informed Consent Form or the form requesting waiver of informed consent or Short Form Summary or Oral Presentation
- The DHHS – approved sample consent document (when one exists)

- The complete DHHS-approved protocol (when one exists)
- VA Form 10-3203, Consent for Use of Picture and/or Voice, if collecting this information.
- Investigator Plan for Addressing HIPAA Regulation (Include Authorization/Revocation form, waiver request form or check reason HIPAA does not apply)
- If applicable: Completion of VA Form 10-9012 Investigational Drug Information Record
- The Investigator Brochure (when one exists).
- FDA Form 1572 (drug study) or signed investigator agreement (device study)
- Device specifications
- Data Safety Monitoring Plan (DSMP) or Data and Safety Monitoring Board Plan (DSMB) (if applicable for more than minimal risk research.)
- If additional IRB review being sought at another institution: Name, Address and telephone number of IRB or approval letter

2. Exempt Research Submission Requirements

Investigators requesting Exemption status must submit:

- Request for Exemption From Ongoing IRB Review
- Completed Request to Review Research Proposal/ Project Form with all applicable signatures
- ISO/PO Checklist
- Abstract
- Full protocol
- Budget
- Completed Principal Investigator's Conflict of Interest Disclosure Form for all project staff
- Completed Chief of Service Statement Supporting Research Project
- Completed Research Protocol Safety Survey
- CV of Investigators (new investigator only)
- Applicable training PVAMC training certificates
- Questionnaires (if used)
- Recruitment materials (if used)
- Completion of the waiver of informed consent form or consent form if appropriate
- Investigator Plan for Addressing HIPAA Regulation (Include Authorization/Revocation form, waiver request forms or check reason HIPAA does not apply)
- If additional IRB review being sought at another institution: Name, Address and telephone number of IRB or approval letter(if applicable)
- Data Use Agreement (if applicable)
- De-Identified Data Checklist (if applicable)

- Completed Research and Development Information System Investigator Data sheet (Page 18) and Personal Data on VA Investigator sheet (new investigator only)
- Applicable training PVAMC training certificates

3. Modification and Continuing Review Requirements

A. Modification

In order to modify approved protocols, Investigators must submit requests to the IRB to modify approved including but not limited to:

- Investigator's Protocol or Sponsor's protocol (if applicable)
- Current approved consent (if applicable)
- Any other relevant documents provided by the investigator
- Interim results
- DSMB reports

B. Continuing Review of IRB Approval

Investigators must submit the following documents at least 30 days prior to the approval period expiration date:

- Cover letter explaining what is being requested
- Request for Continued Approval of Human Use
- A copy of the full protocol that incorporates all previously approved revisions.

Two unstamped copies of the currently approved PVAMC consent form with all revision dates or Short Form Summary or Oral Presentation.

- The modified consent form for approval.
- A copy of the most recent approved PVAMC informed consent form
- A narrative summary of the project progress and update the risk-benefit assessment on a separate page, including research results, if any.
- Abstract
- HIPAA Authorization Form, Waiver form or reason HIPAA still does not apply.
- If using any medications, the investigator brochure, drug package insert, or other source of information.
- DSMB report(s) or safety report(s) since initial review or last progress report, if applicable.
- If applicable, other IRB approval letters
- Any other relevant documents provided by the investigator

4. IRB Request for Additional Information

The IRB may request additional information if they find that the submitted documents are incomplete or lacking substantive information. Additionally, the IRB may request that the Investigator attend the IRB meeting to provide additional information. The IRB Coordinator will contact the investigator at least 3 days prior to the meeting with the proposed time of their protocol review.

RESPONSIBILITY

IRB Chair will:

- Review all proposals to determine if an expert consultant or the presence of the investigator is needed.
- Review claims for exemption from ongoing IRB review.

IRB Coordinator will:

- Assist investigators with submission requirements.
- Maintaining submission documents and forms.
- Program Assistant assembles reviewer packets, checklists and conduct pre-review of submitted documents when needed.
- Review all submissions for completeness
- Assign primary/secondary reviewers and/or expert consultation per Chair;
- Review protocols for eligibility for expedited review and forward to Chair or designated reviewer.

Program Assistant will:

- Maintain and organize the submitted documents including reviewing for completeness and request any missing information.
- Place in Upcoming IRB folder for preparation of the next meeting.

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Section 3: Functions and Operations

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3.2 IRB Meeting Administration

The IRB will review submitted protocols meeting full board criteria at a convened meeting where quorum is met and where the board consists of the appropriate expertise for the types of protocols being reviewed. The IRB will hold monthly meetings, however, the Chairperson, Associate Chair, Associate Chief of Staff of R&D, or Administrative Officer for R&D may call an additional meeting if deemed necessary.

1. Quorum

- A quorum is defined as the majority of the voting members.
- A quorum consists of regular and/or their alternate members and includes: at least one member whose primary concerns are in scientific areas, and one member whose primary concerns are in nonscientific areas.
- At least one unaffiliated member is present at convened meetings, which is documented on the attendance page of the minutes.
- At least one member who represents the general perspective of participants is present convened meetings, which is documented on the attendance page of the minutes.
- An alternate member may attend in the place of an absent regular member in order to meet the quorum requirements outlined above.
- Consultant will not be used to establish a quorum and may not vote with the IRB.
- IRB members who leave the room due to a conflict of interest cannot be counted towards quorum and are recorded as recused.
- When FDA regulated research at the VA Medical Center is reviewed at least one IRB member who is a licensed physician must be present at the meeting.
- Quorum will be documented as the first item in the minutes.
- If quorum is lost during the convened meeting, the IRB will not discuss issues requiring a vote (1200.5.13.a.2) or take votes until quorum is restored. In addition, if required members (e.g., non-scientific) leave the room and quorum is lost votes cannot be taken until the quorum is restored, even if more than half the members are still present.

- If there is not appropriate scientific or representational expertise, the protocols is deferred to another meeting or until appropriate consultation is obtained.

2. Primary and Secondary Reviewers

Prior to the meeting, the IRB Coordinator will designate primary and secondary reviewers for each research proposal according to their scientific or scholarly expertise, and if there are not IRB members with the appropriate expertise, an expert consultant will be arranged. Primary and secondary reviewers are utilized for new protocols and reinstatement requests. Primary reviewers are utilized for all other reviews, including but not limited to, continuing reviews, modifications, adverse events, study closures, protocol deviations, and unanticipated problems.

3. Consultants:

The IRB is authorized to obtain and/or purchase services of ad hoc reviewers or consultants when additional expertise is required due to a lack of expertise represented on the Committee.

The IRB Coordinator in consultation with the Chair will contact an appropriate expert (consultant) and arrange for their assistance. The consultant will be required to sign a Conflict of Interest Statement and may not participate in a protocol review if it is determined that he/she has a conflict of interest. The use of consultants may be determined at any time during the review process, including but not limited to, at the time of protocol submission, during the review process prior to the IRB meeting, or during the presentation/discussion at an IRB meeting. If the need for a consultant is determined at an IRB meeting, the protocol will be tabled until next convened meeting that can be attended by the consultant.

The consultant will be given the same materials as the Primary and Secondary reviewer per Section 6 of this SOP at least 7 days prior to the next scheduled IRB meeting. The consultant is required to submit a written report to include all elements of review to the Committee at the time of review. The report will be recorded in the minutes.

The consultant may be required to participate in all subsequent submissions. The consultant will attend the IRB meetings as a guest, where he/she may participate in the deliberations and make recommendations, but may not vote and shall not be used to reach quorum.

4. Pre-Review Procedures:

The IRB Coordinator and/or the Program Assistant pre-review each submitted protocol for completeness prior to distributing the packets to reviewers. The IRB Coordinator and/or Program Assistant will contact the investigator by email or phone to correct any discrepancies or omissions prior to distribution. Investigators are strongly encouraged to meet with the IRB coordinator prior to

submitting a protocol or other documentation to the committee to ensure that the correct forms and documents have been included.

The Information Security Officer (ISO) and Privacy Officer (PO) do a pre-review of all elements of the protocol submission to ensure they meet both information security and privacy regulations. Their review consists of a form that details all regulatory requirements that is signed by the PI, ISO and PO. PI's are encouraged to meet with the ISO and PO prior to submission of their protocol to the IRB. Both the ISO and PO are non-voting members of the IRB Committee.

5. Distribution of Meeting Materials

All IRB members will receive the documents that are required for review with sufficient time to conduct a thorough review. These materials include:

A. Agenda: a meeting agenda will be prepared by the Program Assistant and distributed to IRB members prior to each meeting. A copy of the agenda will be maintained on file with the meeting minutes.

The Agenda indicates the reviewer assignments. The Primary and Secondary reviewers will conduct in depth reviews of the proposals they are assigned and will present the study at the meeting. All other members are expected to review the study and contribute to the discussion.

All members will receive all the submission documents and will have access to the complete protocol file stored in the Research Office. The files may be accessed by contacting the IRB Coordinator or Program Assistant.

B. Initial Review Submission Materials

- Completed Request to Review Research Proposal/ Project Form with all applicable signatures
- Completed IRB Submission Application
- Completed Information Security-Privacy Checklist
- Abstract
- Full protocol
- Grant Application (if applicable)
- Contract of funding agency
- Budget
- Off-Site Data Removal form (if applicable)
- De-Identified Data Checklist (if applicable)
- Completed Principal Investigator's Conflict of Interest Disclosure Form (Note: all project staff will also need to complete this form)
- Completed Chief of Service Statement Supporting Research Project
- Completed Research Protocol Safety Survey
- Applicable training PVAMC training certificates
- CV of Investigators (new investigator only)
- Questionnaires
- Recruitment materials

- Proposed participant instructions
- Completion of the VA Form 10-1086 Informed Consent Form or the form requesting waiver of informed consent or Short Form Summary or Oral Presentation
- The DHHS – approved sample consent document (when one exists)
- The complete DHHS-approved protocol (when one exists)
- VA Form 10-3203, Consent for Use of Picture and/or Voice, if collecting this information.
- Investigator Plan for Addressing HIPAA Regulation (Include Authorization/Revocation form, waiver request form or check reason HIPAA does not apply)
- Completion of VA Form 10-9012 Investigational Drug Information Record (If applicable)
- The Investigator Brochure (when one exists).
- FDA Form 1572 (drug study) or signed investigator agreement (device study)
- Device specifications
- Data Safety Monitoring Plan (DSMP) or Data and Safety Monitoring Board Plan (DSMB) (if applicable for more than minimal risk research.)
- If additional IRB review being sought at another institution: Name, Address and telephone number of IRB or approval letter

C. Continuing Review Materials:

- Request for Continued Approval of Human Use
- A copy of the full protocol that incorporates all previously approved revisions.
Two unstamped copies of the currently approved PVAMC consent form with all revision dates or Short Form Summary or Oral Presentation.
- The modified consent form for approval.
- A copy of the most recent approved PVAMC informed consent form
- A narrative summary of your project progress and update your risk-benefit assessment on a separate page, including research results, if any.
- Abstract
- HIPAA Authorization Form, Forms for Waiver or reason HIPAA still does not apply.
- If using any medications, the investigator brochure, drug package insert, or other source of information.
- DSMB report(s) or safety report(s) since initial review or last progress report, if applicable.
- If applicable, other IRB approval letters
- Any other relevant documents provided by the investigator
- Summary of relevant recent literature concerning any changes in risks or benefits.

- Summary of adverse events, untoward events, or outcomes experienced by participants since last IRB review.
- Summary of unanticipated problems involving risk to participants and others since last IRB review.
- Relevant multi-center trial reports, if applicable

D. Modifications to Approved Research:

- Modification request memo
- Investigator's Protocol or Sponsor's protocol (if applicable)
- Current approved consent/assent document (if applicable)
- Track change and clean versions of any document requested to be changed from the previously approved protocol submission.

6. Minutes

The Federal regulations for the protection of human subjects [38 CFR 16.115(a)(2)] require that "Minutes of IRB meetings... shall be in sufficient detail to show attendance at the meeting; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution."

A. Recording: The Program Assistant will take minutes of each meeting following the IRB agenda and entering the minutes into the IRB Minutes Template. The meeting is also audiotaped. Minutes will be written in sufficient detail to show the following:

- Meeting attendance; including status of each attendee (regular member, alternate, consultant, etc), members who recuse themselves due to conflicts of interest, if any, and members or alternate members who are participating through teleconference and documentation that those attending through teleconference received all pertinent material prior to the meeting and were able to actively and equally participate in all discussion. It will be documented when the alternate member replaces a primary member;
- The minutes document the members present at the beginning of the meeting, and those who enter and leave during the meeting;
- Report of Exempt and Expedited Reviews;
- Determination of level of risk;
- Separate deliberations for each action;
- Actions taken by the IRB on each agenda item requiring full IRB action, including, the basis for requiring changes in, tabling, or disapproval of the research;

- Summary of the discussion of controverted issues and resolution;
- Summary of key information from consultant's verbal in-person report if a written report was not provided;
- Documentation of the basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs;
- Documentation of additional safeguards to protect vulnerable populations if entered as a study participant when this is not otherwise documented in IRB records;
- Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document;
- Documentation of the frequency of the next continuing review of each protocol's initial and continuing review as determined by the IRB;
- For initial and continuing review, the approval period.
- Notation that a waiver of HIPAA authorization was approved. (Note: Documentation of IRB approval of a HIPAA Waiver required by 45 CFR 161(i)(2) and VHA Handbook 1200.05 will be contained in both the IRB approval letter and the reviewer checklist for waiver of HIPAA contained in the protocol file. These specific requirements will not be recorded in the minutes).
- Documentation of the four required findings (38 CFR 16.116(c or d)) when approving a consent procedure that does not include or that alters some of all the required elements of informed consent, or when waiving the requirement to obtain an informed consent. (Note: documentation will be made in the minutes of research involving pregnant women, prisoners, and children ONLY when the research has received permission to be conducted by the CRADO).
- The rationale for significant risk/non-significant risk device determinations;
- Voting results, including the number for, against, abstaining, and abstaining;
- Documentation when an IRB member has a real or potential conflict of interest relative to the proposal under consideration, that the IRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained);
- Documentation of approval of research that was contingent on specific minor conditions reviewed and approved by the chair or designee. This documentation must take place at the first meeting that has taken place after the date of approval.

- Determinations required by the VHA Handbook 1200.05, Appendix D.3.c. for research involving persons with impaired decision making or who are mentally incompetent.
- For continuing review of research using the expedited procedure:
 - The specific permissible category
 - Description of action taken by the reviewer
 - Any findings required under the regulations

A majority of members must vote in favor of an action in order to be accepted by the IRB. Only regular and alternate members acting in place of absent regular members may vote. The vote will be recorded in the minutes. Members with a conflict of interest will recuse themselves from the discussion and voting and such will be noted in the minutes.

B. Approval of Minutes:

- i. Minutes must be written and available for review within 3 weeks of the meeting date.
- ii. Draft minutes will be distributed to members at the next IRB meeting for review and approval.
- iii. Corrections requested by the IRB will be made by the Program Assistant and the minutes will be printed in final form and made available to members at the following meeting. The Chairperson of the IRB shall sign and date final, approved minutes.
- iv. The Program Assistant will maintain copies of the minutes, as well as the agenda and pertinent materials on file.
- v. The approved minutes will be forwarded to the R&D Committee for review and approval.
- vi. A copy of the approved minutes will be forwarded to the Institutional Official for signature. Following this signature, a copy of the minutes is forwarded to the Quality Management Committee.
- vii. Once approved by the IRB members at a subsequent IRB meeting, the minutes may not be altered by anyone including a higher authority.

7. Telephone Use

A. Convened meeting using speaker phone:

Should a member not be able to be physically present during a convened meeting, but is available by telephone, the meeting can be convened using a speakerphone. The member who is not physically present will be connected to the rest of the members via speakerphone. In this manner, all members will be able to discuss the protocol even though one member is not physically present. Members participating by such speakerphone call may vote, provided they have had an opportunity to review all the materials the other members have reviewed.

B. Meetings Conducted Via Telephone Conference Calls:

On occasion, meetings may be convened via a telephone conference call. A quorum (as defined above) must participate for the conference call meeting to be convened. To allow for appropriate discussion to take place, all members must be connected simultaneously for a conference call to take place -- "telephone polling" (where members are contacted individually) will not be accepted as a conference call.

Members not present at the convened meeting, nor participating in the conference call may not vote on an issue discussed during a convened meeting (no voting by proxy).

Members who have a conflict of interest must terminate the connection during the discussion and vote. (*page 33, 1200.5*)

The minutes will document which members present by conference call.

8. Voting

Members of the IRB vote upon the recommendations made by the primary/secondary reviewers according to the criteria for approval. Members also will determine level of risk, the frequency of review for each protocol, monitoring of the investigative site, and whether third party assessment and follow-up will be needed.

RESPONSIBILITY

The Chair and Associate Chair are responsible for:

- IRB meeting procedural conduct and documentation.
- The conduct and leadership of the IRB.

The IRB Coordinator will:

- Assist Chair with IRB meeting procedural conduct and documentation.

The Program Assistant will:

- Assist Chair and IRB Coordinator with IRB meeting procedural conduct and documentation.
- Create IRB Notes Sheet based upon agenda.
- Assemble reviewers' packets.
- Attend meeting of the IRB, use IRB agenda as a template to record proceedings of the meeting.
- Provide IRB members with summary of administrative approvals, exempt and expedited reviews conducted since the last IRB meeting.
- Complete draft minutes in time to include in the reviewers' packets for the next meeting (within three weeks).

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3.3 REVIEW AND DISTRIBUTION OF MATERIALS

The efficiency and effectiveness of the IRB is supported by administrative procedures that ensure that IRB members not only have adequate time for thorough assessment of each proposed study, but that the documentation they receive is complete and clear enough to allow for an adequate assessment of study design, procedures, and conditions.

1. Exemptions

IRB Chair and delegated IRB members may review and approve Request for Exemption from Ongoing IRB Review submitted by Investigators. The IRB Coordinator may pre-review protocols that may be eligible for exemption and forward them to the Chair or delegated IRB members. Exempt protocols will be placed on the next convened meeting agenda and complete packets will be made available to committee members.

2. Incomplete Submissions

Incomplete applications will not be accepted for review until the Investigator has provided all necessary materials as determined by the IRB Coordinator or Program Assistant. The Program Assistant or IRB Coordinator will notify the submitting Investigator to obtain any outstanding documentation or additional information before the application is scheduled for review. Incomplete submissions will be stored in the IRB folder in the receiving filing cabinet until all documents have been received.

3. Expedited Review

The PVAMC IRB does not routinely use expedited procedures for approval of new protocols. The PVAMC does use expedited procedures for review of modifications in previously IRB-approved research and research that meets expedited review criteria for continuing review. Complete applications that appear to meet qualifications for expedited review will be submitted to the Chairperson, Associate Chair, or experienced member of the IRB. If a submission meets expedited review requirements, the review will be performed as described in Section 4.2 (Review of Research, Expedited Review). All other applications will be placed on the agenda for the next full board meeting.

4. Meeting Material Distribution

Copies of submitted documents described in Section 3.1 (Functions and Operations, Submission Requirements for IRB Review) will be distributed to all IRB members, generally at least seven (7) days prior to the meeting, unless deemed urgent by the IRB Coordinator or Chair. Each regular member of the IRB, and any alternate members attending the meeting in place of a regular member, will receive a complete copy of the submitted material. Consultants will only receive copies of material that pertain to their requested input.

The originals of submission materials will be retained in the Research Office and will be available for the IRB meeting.

5. Confidentiality

All material received by the IRB will be considered confidential and will be distributed only to meeting participants (regular members, alternate members, and consultants) for the purpose of review. All application materials will be stored in a project study file with access limited to the IRB members and Research Office staff. Investigators or their authorized study staff may be granted access by the IRB Coordinator or Program Assistant and must sign the access log.

6. Destruction of Copies

All materials received by the IRB will be considered confidential and in excess of the required original documentation. All packets will be collected at the end of the meeting and destroyed by a method deemed appropriate by the Administrative Officer.

4. RESPONSIBILITY

IRB Coordinator will:

- Pre-review documents prior to distribution in order to determine completeness, potential for expedited review, or request for exempt status.
- Contact Investigators for any missing elements.

Program Assistant will:

- Providing complete review material packets to IRB members and other relevant parties.
- Contact Investigators for any missing elements.

Chairperson or Associate Chair will:

- Support and assist the IRB Coordinator in submission triage activities.

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3.4 DOCUMENTATION AND DOCUMENT MANAGEMENT

The IRB files must be maintained in a manner that contains a complete history of all IRB actions related to review and approval of a protocol, including continuing reviews, modifications and adverse event reports. All records regarding a submitted study (regardless of whether it is approved) must be retained in an appropriate manner as required by regulatory requirements and/or institutional policy.

Records must be accessible for inspection and copying by authorized representatives of the Sponsor, funding department, or agency, regulatory agencies, and institutional auditors at reasonable times and in a reasonable manner.

Required documents must be submitted to the appropriate funding entity as required.

1. Document Retention

Per VA Office of Research and Development (ORD) guidance and until ORD and the Central Privacy Office can complete a records retention schedule specifically for the Research Service, all records will be maintained Per the Record Control Schedule (RCS-10).

A. Study-related documents:

Adequate documentation of the IRB activities will be prepared, maintained and retained in a secure location. Retained documents include:

- Copies of all original research protocols reviewed, scientific evaluations, if any, that accompany the proposals, approved consent documents, progress reports submitted by Investigators and reports of adverse events, unexpected adverse events, unanticipated events occurring to subjects and reported deviations or violations from the protocol.
- Agendas and minutes of all IRB meetings.
- Copies of all submitted monitoring reports, site visit reports, and other continuing review activities.
- Copies of all correspondence between the IRB and the Investigators.
- Copies of all correspondence between the VA and R&D Committee.

- Statements of significant new findings provided to subjects as submitted by the Investigator.
- Reports of any complaints received from subjects.
- DHHS-approved sample consent documents (when one exists)
- DHHS – approved protocol (when one exists)
- The investigator’s brochure (when one exists)
- Reports of injuries to subjects
- Records of continuing review activities
- For continuing review of research using the expedited procedure:
 - The specific permissible category
 - Description of action taken by the reviewer
 - Any findings required under the regulations
- Each protocol’s initial and continuing review, the frequency for the next continuing review

IRB Records will be accessible for inspection and copying by authorized representatives of the VA, VA R&D Committee, OHRP, FDA and other authorized entities at reasonable times and in a reasonable manor.

2. IRB Administration Documents

Until disposition instructions are approved by the National Archives and Records Administration and are published in VHA’s Records Control Schedule (RCS 10-1), the Research Office must maintain and retain all records regarding IRB administrative activities that affect review activities and all records regarding protocols that are approved and the research initiated.

- A. Rosters of IRB members will contain but are not limited to: 1) Name of IRB member (primary and alternates), 2) Earned Degrees; 3) Scientific Status; 4) Representative status; 5) Experience and credentials; 6) Employment or other relationship between each member and the organization; 7) Affiliation status; 8) Membership status; 9) Primary members who the alternate member can substitute for.

Alternate members shall be included on the roster. In addition to the above information, the roster shall indicate the primary member for whom the alternate may substitute.

Current and obsolete membership rosters will remain in the Research Office and then archived according to VA policy.

The roster of IRB members must be submitted to OHRP.

Resumes of all IRB members and alternates are maintained in the Research Office.

- B. Maintain current and obsolete copies of the Standard Operating Policies and Procedures.

- C. Delegation of specific functions, authorities, or responsibilities by the Chairperson must be documented in writing within and maintained in the Research Office
- D. IRB records regarding the justification for exemption determinations, determinations required by laws, regulations, codes, and guidance, and protocols cancelled without subject enrollment.

3. Destruction of IRB Packets

All materials received by the IRB, which are considered confidential and in excess of the required original documentation, will be collected at the end of the meeting and destroyed per VHA approved methods.

4. Archiving and Destruction

After project closure, all documents and materials germane to IRB determinations will be archived by the Research Office in accordance with VHA Records Control Schedule (RCS 10-1), applicable FDA and DHHS regulations, or as required by outside sponsors. As required, all of these records will be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA, and other authorized entities at reasonable times and in a reasonable manner in accordance with 38 CFR 16.115(b).

5. Department of Defense

For DoD-sponsored research, the DoD may require submitting records to the DoD for archiving.

RESPONSIBILITY

IRB Coordinator will:

- Maintain complete files on all research reviewed by or submitted to the IRB and for all applicable regulatory compliance requirements.
- Conduct periodic review of stored files to determine if stored files may be archived.
- Consult with the Information Security Officer for guidance on media destruction (e.g., audio tapes).
- Report changes in the IRB membership to OHRP as they occur.

Program Assistant will:

- Maintaining complete files on all research reviewed by or submitted to the IRB and for all applicable regulatory compliance requirements.
- Create protocol files after the study has been approved.
- Maintain submitted documents in an organized manner.

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4.1 RESEARCH EXEMPT FROM ONGOING IRB REVIEW

Research activities in which the only involvement of human subjects will be in one or more specific categories, which are listed in section 3.1 of this policy, may be exempt from IRB review. Determination of exemption must be based on regulatory and institutional criteria and documented.

Research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review:

(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.

- The research does not involve prisoners as participants [45 CFR 46.301(a)].
- The research is not FDA-regulated. (See Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions) [FDA 21 CFR 56.104]

(2) Research involving the use of one or more of the following: 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, reputation, or loss of insurability .

- If the research involves children as participants: the procedures do not include any of the following: 1. survey procedures, 2. interview procedures, 3. observation of public behavior where the investigators participate in the activities being observed.
- The research does not involve prisoners as participants [45 CFR 46.301(a)].
- The research is not FDA-regulated. (See Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions) [FDA 21 CFR 56.104]

(3) The research is not exempt under Category 2. 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.

- The research does not involve prisoners as participants [45 CFR 46.301(a)].
- The research is not FDA-regulated. (See Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions) [FDA 21 CFR 56.104]

(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.

- The research does not involve prisoners as participants [45 CFR 46.301(a)].
- The research is not FDA-regulated. (See Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions) [FDA 21 CFR 56.104]

(5). Research and demonstration projects, which are conducted by or subject to the approval of Federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine one or more of the following:

- (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.
- The program under study delivers a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
 - The research is conducted pursuant to specific federal statutory authority.
 - There is no statutory requirement that an IRB review the research.
 - The research does not involve significant physical invasions or intrusions upon the privacy of participants

- The research does not involve prisoners as participants. [45 CFR 46.301(a)]
- The research is not FDA-regulated. (See Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions) [FDA 21 CFR 56.104]

NOTE: 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.

- (6) Taste and food quality evaluation and consumer acceptance studies,
 - (a) if wholesome foods without additives are consumed or
 - (b) 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.

- The research does not involve prisoners as participants. [45 CFR 46.301(a)]
- Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.
- Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy
- Compliance with this policy requires compliance with pertinent federal laws or regulations, which provide additional protections for human subjects.
- This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.
- This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.
- When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (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.

- 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.

1. Assessment of the research

The review of the research will also include;

- Does the research have a sound research design?
- Is there minimal risk to the subject?
- Can the research be ethically carried out?
- Is subject selection equitable?
- If there is recording of identifiable information, are there adequate provisions to maintain the confidentiality of the data?
- If there are interactions with subjects, is there a consent process that discloses the following information:
 - That the activity involves research.
 - A description of the procedures.
 - That participation is voluntary.
 - Name and contact information for the investigator.
 - There are adequate provisions to maintain the privacy interests of subjects.

2. R&D Committee Review

The R&D Committee must review all protocols deemed exempt from ongoing IRB review and are subject to annual reviews per R&D regulations.

3. Notification of Exemption

The investigator is notified in writing indicating the category of exemption. The IRB will be provided a list of exempt protocols performed by the IRB Chair or designee at the next convened meeting and distribute complete packets to all committee members.

RESPONSIBILITY

The IRB Chair will:

- Make the exemption determination or designated an experienced member to conduct review.
- Document the findings, including a reason of denial if the request is denied, in correspondence with the investigator indicating the category of exemption.

The Program Assistant will:

- Provide the Chair or experienced member designated by the Chair with a complete packet, including the required forms for new protocol submission, abstract, protocol, and the Request for Exemption from Ongoing IRB Review form.
- Send out approval correspondence to the investigator.
- Provide a listing of exempt protocols performed by the IRB Chair or designee at the next convened meeting and distribute complete packets to all committee members.
- Forward exempt protocol to the R&D Committee for review at the next convened meeting.

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4.2 EXPEDITED REVIEW

An expedited review procedure consists of a review of research involving human subjects by the Chairperson, Associate Chairperson, or a designee appointed by the Chairperson who has demonstrated clear understanding of the federal regulations governing IRBs and has demonstrated a dedication to the protection of human subjects with their actions and comments. The designee must be a voting member and has served on the Committee as a primary reviewer for at least 10 initial and/or continuing review submissions reviewed at the convened IRB. The list of designees is maintained electronically in the Research Office and is located on the Research Server in the IRB folder. A hard copy is maintained with the minutes.

The PVAMC IRB may use expedited review procedures to review and approve specific categories of research as defined in the Federal Register: Volume 63, Number 216, Pages 60364-60367, November 9, 1998. Studies on marketed drugs that significantly increase the risks or decrease the acceptability of the risks associated with the use of the drugs are not eligible for expedited review. Therefore, eligible research activities include activities that 1) present no more than minimal risk to human subjects, and 2) involve only procedures listed in one or more of the categories listed in the above mentioned document. The activities listed should not be deemed to be minimal risk simply because they are included on the 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 subject. See Appendix A, for Activities Appropriate for Expedited Review.

This policy pertains to continuing IRB review, modifications to previously approved research during the period for which approval is authorized and to determine if a protocol meets criteria for expedited review. The PVAMC IRB does not routinely use expedited review protocols to approve research for initial review approvals.

1. Definitions

Minimal risk is defined as "...the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those

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

“Minor changes that involve no more than minimal risk, or risks to subjects are not increased, and/or the revision is not a significant alteration of the study design“.

2. Cautions

- A. The activities listed should not be deemed to be of minimal risk simply because they are included on the list of eligible research. 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 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.

3. Authority of the Expedited Reviewer

- A. The Chairperson or designated reviewers may exercise all of the authorities of the IRB, except that he/she may not disapprove the research. A research proposal may be disapproved only after review by the full IRB.
- B. The reviewers conduct expedited review with the same depth and criteria as those by a convened IRB. Additionally, the reviewers must follow the PVAMC IRB member conflict of interest policy and take into consideration the need for additional expertise.
- C. If modifications to the submission are requested by the reviewer and the investigator does not want to make the requested modifications, or modifications have been made that were not requested, the reviewer may refer the study to the full Committee.

4. Notification of the IRB

When the expedited review procedure is used, all regular members shall be informed of actions taken by the IRB at the next convened meeting. The expedited actions will be listed in the IRB agenda and minutes, along with the criterion that was met that allowed expedited review. Documentation provided to the members involves the complete submission, the determination, and the criterion for expedited review.

5. New Protocol Review

Expedited review of new protocols is conducted only to determine if a new protocol meets criteria for exemption.

6. Other Items That May be Reviewed by the Chairperson or Designee (Reviewer)

A. Minor Changes to previously approved research

- i. The Chairperson or designee may use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. The research activities must 1) present no more than minimal risk to human subjects and 2) involve only the procedures in one or more of the categories listed in “Categories of Research that May be reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure”, 63 FR 60364-60367, November 9, 1998 and VHA Handbook 1200.05, Appendix B, The activities listed should not be deemed to be minimal risk simply because they are included on the 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 subject.
- ii. Protocol revisions that entail no more than minimal risk to participants are considered “minor” changes.
- iii. Revisions to informed consent and/or HIPAA Authorization documents: Changes to informed consent and/or HIPAA Authorization documents that do not affect the rights and welfare of study participants, or do not involve increased risk are considered minor changes and may be reviewed by the reviewer.
- iv. Advertisements: The Chair or reviewer may approve new or revised recruitment advertisements or scripts.

B. Continuing review

- i. Continuing review of research previously approved by the convened IRB where (1) the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or (2) where no subjects have been enrolled and no additional risks have been identified; or (3) where the remaining research activities are limited to data analysis.
- ii. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption but the IRB has determined and documented at a

convened the research involves no greater than minimal risk and no additional risks have been identified.

The reviewer at the time of continuing review will receive the following documents:

- Request for Continued Approval of Human Use
- A copy of the full protocol that incorporates all previously approved revisions.
- Two unstamped copies of the currently approved PVAMC consent form.
- A copy of the most recent approved PVAMC informed consent form showing the dated approval stamp.
- A narrative summary of your project progress.
- Updated risk-benefit assessment.
- Abstract of the study.
- HIPAA Authorization Form, Forms for Waiver or reason HIPAA still does not apply.
- If using any medications, the investigator brochure, drug package insert, or other source of information.
- DSMB report(s) or safety report(s) since initial review or last progress report, if applicable.
- If applicable, other IRB approval letters
- Any other relevant documents provided by the investigator
- Summary of relevant recent literature concerning any changes in risks or benefits.
- Summary of adverse events, untoward events, or outcomes experienced by participants since last IRB review.
- Summary of unanticipated problems involving risk to participants and others since last IRB review.
- Relevant multi-center trial reports, if applicable

RESPONSIBILITY

The Chair will:

- Identify submissions that qualify for expedited review.
- Conduct and document expedited review.

The IRB Coordinator will:

- Identify submissions that qualify for expedited review and forward to Chair or designated reviewer.

The Program Assistant will:

- Provide a listing of expedited reviews performed to IRB members at convened meetings.
- Distribute letter to investigator.

Designated reviewer will:

- Conduct and document expedited review.

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4.3 INITIAL REVIEW

All research proposals that intend to enroll human subjects must meet certain criteria **before** study related procedures can be initiated. The criteria are based on the principles of justice, beneficence and autonomy as discussed in the Belmont Report, VHA Handbook 1200.05, and 38 CFR 16. In addition, certain other criteria that are unique to the Providence VA Medical Center may apply and must be met as well. Trials involving pharmaceuticals are also reviewed according to 21 CFR 50.

1. Minimal Criteria for Approval of Research

In order for a research project to be approved, the IRB must find that:

- A. Evaluation of Risks: In their review of the protocol the IRB evaluates the risk with consideration of potential physical, psychological, social, legal, and economic harms. The anticipated risks are identified. With the totality of their evaluation of the risk of these possible harms, the reviewers consider the level of risk for the protocol.
- B. Risks to subjects are minimized by using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk, and risks to subjects are minimized, when appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- C. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
 - In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that 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.
 - The IRB will consider the risks and benefits related to both biomedical (including genetic) research and non-biomedical research.

- Determines the scientific appropriateness of the protocol and determines whether the degree of risk (physical, social, psychological, legal, or economic) to human subjects is justifiable. The IRB determines whether risks are minimal or greater than minimal (the PVAMC categorizes greater than minimal risk as moderate, high or unacceptable) and that they have been minimized to the fullest extent possible. In order to make this determination, the IRB will examine the research plan, including the research design and methodology, to determine that there are no obvious flaws that would place participants at unnecessary risk. This includes the risk that, because of poor design or lack of statistical power, meaningful results cannot be obtained.
- Payment for participation in research (remuneration) will be considered to be reimbursement, and will not be considered to be a benefit.
- Data Safety Monitoring Plan (DSMP) or Data and Safety Monitoring Board (DSMB): If the research study is more than minimal risk, the PVAMC IRB requires that each new research application include a Data Safety and Monitoring Plan (DSMP) or Data and Safety Monitoring Board (DSMB). Often in externally sponsored studies, the DSMP is incorporated into the protocol. If the proposed study has a DSMB, a copy of the plan or charter will need to be attached to the IRB application. The term Data Monitoring Committee (DMC) will be used interchangeably with DSMB in this document.

For DoD regulated research, an independent research monitor shall be appointed to studies involving more than minimal risk. The IRB may require a research monitor be appointed for studies involving no more than minimal risk if appropriate. The research monitor must be appointed by name and has the authority to stop a research study in progress, remove individuals from the study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the research monitor's report.

For an investigator-sponsored study greater than minimal risk, the principal Investigator is responsible for creating and implementing a data and safety monitoring plan. The plan will need to detail how confidentiality is protected and, to the extent possible, risks are reduced to a minimum. The plan does not have to be complicated but should be appropriate for the risks associated with it. The intensity and frequency of monitoring should be tailored to fit the expected risk level, complexity, phase and size of the particular study.

The DSMP needs to address:

- Items to be monitored (i.e. subject eligibility, adherence to treatment plan, documentation of dropouts, evaluation of primary and secondary endpoints, adverse events, and/or unanticipated problems)
- Data management: who is responsible for the collection and storage of data, where will it be stored (i.e. lab notebook, database), security

measures needed to protect the data from inadvertent loss or inappropriate use, who will perform analysis on the data and how often.

- A plan to assure compliance with reporting adverse events and/or unanticipated problems involving risk to participants or others.

A DSMB is normally required for Phase III, clinical trials, and many multi-site trials.

C. Selection of subjects is equitable.

The IRB will determine that selection of research participants is equitable. It will take into account the purposes of the research and the setting in which the research will be conducted, and the scientific and ethical reasons for the inclusion/exclusion of individuals or groups of individuals. The IRB will be particularly cognizant of the special problems of research involving vulnerable populations. Non-veterans may be entered into research studies only when there are insufficient veterans available to complete the study.

If vulnerability is determined to exist, the IRB must ensure that additional safeguards have been included in the study to protect the rights and welfare of these participants.

D. Informed consent:

- The IRB must find the 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 appropriate local, state and federal regulations, except when a waiver of written informed consent or exemption from ongoing IRB review has been granted.
- Ensure the informed consent form is consistent with the protocol and, when relevant, with the HIPAA Authorization.
- The informed consent will be appropriately documented as required by local, state and federal regulations.

See Section 7, Informed Consent, for required elements.

E. Compliance with the Health Insurance Portability and Accountability Act.

The IRB will assure that the required language for a valid authorization to release health information is included. The HIPAA Authorization form will be employed and signed except when the investigator formally requests a Waiver of Requirement for Authorization for Release of Protected Health Information for Research Purposes or marks the appropriate block as to why HIPAA does not apply. The IRB will review these forms to ensure that the criteria are met. Please see Section 11, HIPAA Compliance, for more information.

F. Recruitment.

The IRB will determine that recruitment practices, including advertisements and compensation (both to investigator and participant) are reasonable.

Advertisements must be reviewed by the IRB before they are used. Advertisement used to recruit participants should be limited to the information the prospective participants need to determine their eligibility and interest. The PVAMC IRB does not allow researchers to solicit sensitive information (e.g., a patient's social security number) over the telephone or other communication. Researchers must make initial contacts with veterans in person and/or by letter prior any telephone contact and provide a telephone number or other means that veterans can use to verify the validity of the study. See Section 4.13, Recruitment of Participants.

G. Privacy and Confidentiality.

Where appropriate, there are adequate provisions to protect the privacy of participants, and to maintain the confidentiality of individually identifiable data. The provisions must consider the requirements of local, state, and federal regulations. The IRB will determine that privacy and confidentiality of research participants are maximized. The IRB will assess whether the planned research has adequate provisions to protect the privacy and confidentiality by evaluating methods used to obtain information about participants and about individuals who may be recruited to participate in studies, be evaluating the use of personally identifiable records, by evaluating methods to protect confidentiality with regard to identifying and recruiting participants, obtaining information about participants, and storing and using data. The IRB will consider the nature, probability and magnitude of harms that would be likely to result from a disclosure of collected information outside research. The IRB will evaluate the effectiveness of proposed techniques to protect the anonymity of subjects (including coding systems, etc.). Obtaining and disclosing individually-identifiable patient records must be in compliance with all applicable confidentiality statutes and regulations discussed in VHA Handbook 1200.05, subparagraph 7a(7).

H. Information Security.

The IRB must determine that applicable VHA and VA information security policies pertaining to research are implemented and continually monitored to ensure compliance as set forth in VA Directive 6500 and its Handbooks.

I. The IRB determines the frequency of continuing review of each study appropriate to the degree of risk research subjects are exposed to due to their participation in the study, but at least annually. For any protocol that involves greater than minimal risk, the IRB must consider whether the protocol needs review more than annually.

Criteria for Review Schedule that is more frequent than annually:

- Studies may be reviewed more frequently than annually if the IRB believes that the study population is especially vulnerable.
- Studies may be reviewed more frequently than annually if the IRB believes that previous studies indicate an expected high incidence or high severity of adverse events related to study procedures.

- Studies may be reviewed more frequently than annually if the IRB believes close monitoring is indicated due to the risk level, due to past noncompliance on the part of the investigator, or due to concerns about investigator experience level.
 - The reasons for such a determination will be included in the minutes and communicated to the investigator.
- K. Conflict of Interest. The IRB must ensure that steps to manage, reduce or eliminate potential or real conflict of interest (financial, role (investigator/patient relationships), and/or institutional) have been taken. Research Service staff members family members and/or family may not participate in research at the PVAMC due to a conflict of interest.
- L. Investigator's Educational Requirements and Certification. The IRB must determine that the Principal Investigator has the training required to be able to properly conduct the research protocol. The IRB must determine that the investigator(s) is qualified through education, training, and experience to conduct the research. The IRB must determine that the PI and all other investigators of the proposed research activity have met all current educational requirements for the protection of human research subjects as mandated. The investigator Curriculum Vitae is maintained in the Research Office. ADD DOD piece here
- M. The IRB has the authority to suspend or terminate a study at any time, at the IRBs discretion. The IRB has the authority to place any restrictions on a study that the IRB deems appropriate.
- N. The IRB has the authority to require that information, in addition to that specifically required by applicable regulation, be given to the participants when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of participants.
- O. The IRB must determine that there are adequate resources for human research protection, care of research participants, and safety during the conduct of the research, i.e.:
- Adequate Facilities
 - Adequate Numbers of Qualified Staff
 - Availability of medical or psychological resources that participants might require as a consequence of the research
 - Access to a population that would allow recruitment of the required number of participants
 - Sufficient Time To Complete Study
 - A process to assure persons assisting with the research are adequately informed of protocol and their research related duties and functions

Other Criteria

A. The IRB may require verification of information submitted by an Investigator. The need to verify any information will be determined by the IRB at a convened meeting. The purpose of the verification will be to provide necessary protection to subjects when deemed appropriate by the IRB.

B. Flagging a Medical Record. The IRB needs to determine if the patient's medical record (electronic or paper) must be flagged to protect the subject's safety by indicating the subject's participation in the study, and the source of more information on the study.

The medical record must be flagged if the participant's participation in the study involves:

- Any invasive research procedure (e.g., muscle biopsy or bronchoscopy)
- 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);
- Clinical services that will be used in the medical care of the subject (e.g., orders for laboratory tests or x-rays ordered as a part of the study), or that could interfere with other care the subject is receiving or may receive; or
- 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 of victims of sexual assault).
- In other situations, the IRB determines if flagging is necessary.

Flagged Health Record Contents. If IRB determines and documents that the patient health record must be electronically flagged in Computerized Patient Record System (CPRS) as participating in a research study then, in accordance with VHA Handbook 1907.01), the health record must:

- Identify the investigator, as well as contact information for a member of the research team that would be available at all times. **NOTE:** *The research team must have an appropriate member available (on-call) at all times.*
- Contain information on the research study or identify where this information is available.

Duration of Flagging. The duration of flagging is determined by local policy.

C. If this is collaborative research, the IRB assures that IRB approval from the coordinating site is obtained or if the PVAMC is the coordinating site, that IRB approvals from all coordinating sites are attained.

For research administering medications, the IRB determines whether an IND is needed, and if so, whether it has been obtained,

RESPONSIBILITY

The Chair will:

- Provide IRB members adequate submission review training and ongoing guidance

The Primary and Secondary Reviewer will:

- Conduct a thorough review and presents findings at a convened IRB meeting.
- Complete reviewer checklist.
- Determine whether any special considerations exist that may influence the review of proposal.
- Determine whether the evidence exists that third party verification of submitted information is needed.

The IRB Coordinator will:

- Select primary/secondary reviewers and/or consultants with the relevant expertise to perform reviews and make necessary recommendations on approval decisions by the IRB.
- Obtain other expertise is needed, obtain consultant.

The Program Assistant will:

- Ensure that IRB reviewers have all the tools and resources they need to complete their research reviews.

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4.4 CONTINUING REVIEW

The IRB conducts continuing review of research taking place within its jurisdiction at intervals appropriate to the degree of risk, but not less than once per year. The IRB has the authority to observe or have a third party observe the consent process; inspect signed consent forms, and inspect respect case files for compliance.

1. Interval for Review for purposes of Renewal

- A. The IRB must conduct continuing review of protocols for purposes of renewal of the IRB approval period, at intervals determined at the initial review, but not less than once per year. "Not less than once per year" means that the research must be renewed on or before the one-year anniversary of the previous IRB review date, even though the research activity may not have begun until sometime after the IRB gave its approval. For example, with an approval period of September 1, 2007 to August 31, 2008, the expiration date is after 11:59 p.m. on August 31, 2008.
- B. The date of continuing review is determined at the time of initial review or at annual review based upon the degree of risk. The approval period is listed in the IRB and R&D approval letters .
- C. Investigators are required to submit a periodic report prior to the expiration of the study or as specified by the IRB, but at least annually. The report should normally be filed at least 30 days before the study approval period ends.

2. Expiration of Approval Period

If the continuing review does not occur on or before the expiration date, the research is automatically lapsed. The PVAMC considers such lapsed approval as an automatic action. However, it will be reported to the sponsoring agency, private sponsor, ORD (if funding the research), and funding agencies as appropriate.

The IRB office will promptly notify the investigator of the expiration via e-mail followed by a signed letter that expiration of IRB has occurred and all study

activities must stop immediately, including data analysis. The investigator must immediately submit a list of subject names to the IRB Chair for whom cessation of study interventions would cause harm. Continuation of research interventions or interactions in previously enrolled subject will only continue when the IRB Chair in consultation with the VA Chief of Staff, finds that it is in the best interest of individual subjects to do so (VHA Handbook 1200.05, section 7g). If the study is FDA regulated, the VA Chief of Staff and IRB must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.

The IRB must review and re-approve the study prior to allowing any study activities to occur on research that has expired IRB approval.

3. Primary Reviewer

- A. At continuing review a Primary Reviewer system is used. All IRB members (and alternates) receive the entire continuing review submission. If at all possible, the same reviewer will be used that reviewed the initial submission of the study. The entire protocol file containing the initial submission and previous continuing reviews (if applicable), modifications, adverse events, and correspondence is available to all IRB members. Please see Section 3, Functions and Operations, 3.2 IRB Meeting Administration for complete list of required documents.
- B. If the IRB determines that it needs verification from sources other than the Investigator, that no material changes have occurred since the previous IRB review, the IRB may request an independent assessment of information or data provided in the renewal application. Studies with complicated protocols or atypical risks that are conducted by investigators who fail to respond to the IRB or Chair are examples of when verification may be needed.
 - The scope and extent of such an independent assessment is determined on a case-by-case basis.
 - Sources for such outside information could include copies of FDA audits, literature searches, an audit of documents by the IRB's designated quality improvement monitor, and/or phone call to the sponsor.

4. Criteria for Continuation and Renewal

- A. Research activities initially reviewed by full board review must be reviewed by the full board at continuation, unless:
 - i. study has been modified in such a way that it is now eligible for expedited review as defined in the regulations (as published in the Federal Register); or
 - ii. The study meets one of the following expedited review criteria:
 - The research is not FDA regulated; and

- The research is permanently closed to the enrollment of new participants; and
 - All participants have completed all research-related interventions; and
 - The research remains active only for long-term follow-up of participants; or
 - No participants have ever been enrolled at any site and no additional risks have been identified; or
 - The remaining research activities are limited to data analysis.
- B. Research activities that had previously met criteria for expedited review may change as a result of the review and approval of amendments, such that IRB Committee review would be required at the time of continuing review (e.g., risk has changed to be greater than minimal).
- C. When conducting research under an expedited review procedure, the Chairperson or experienced IRB member conducts the review on behalf of the full IRB using the same criteria for continuation as stated in Section 3.4 of this policy. If the reviewer feels that there has been a change to the risks or benefits, he or she may refer the study to the full IRB for review.

5. Continuation Review

- A. Continuing review must be substantive and meaningful. When considering whether or not to renew a study, the IRB revisits the same criteria used to grant initial approval (see Section 4.3, Initial Review, for complete list of minimal criteria for approval of research). Therefore, the IRB (or the reviewers for protocols reviewed under an expedited procedure) must determine that:
- The risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
 - The selection of subjects continues to be equitable and reasonable in relation to anticipated benefits;
 - Informed consent continues to be appropriately documented or criteria for waiver of informed consent continue to be met;
- Additionally, there are appropriate:
- Provisions for safety monitoring of the data,
 - Protections to ensure the privacy of subjects and confidentiality of data,
 - Appropriate safeguards for vulnerable populations.

- B. Because it may be only after research has begun that the real risks can be evaluated and the preliminary results used to assess the actual risk/benefit ratio, the IRB can then determine whether or not the study can be continued or continued only with protocol modifications.
- C. In order to determine the status of the study, the following will be reviewed:
- Request for Continued Approval of Human Use Form: All IRB members shall receive an annual report prepared and submitted by the Investigator requesting continued approval. The progress report shall summarize the project progress to date including an update of risk-benefit assessment, adverse event experiences, modifications, number of subjects enrolled, the gender and racial identity breakdown, and the number who refused to participate or withdrew from the study.
 - Consent document: Each member of the IRB shall review the currently approved consent document and ensure that the information is still accurate and complete. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in an updated consent document. Each member of the IRB shall review the currently approved HIPAA Authorization or "Investigator Request for Waiver of Requirement for Authorization for Release of Protected Health Information for Research Purposes" The exceptions to reviewing these documents occur when; a) if a study is closed to enrollment, or b) a study qualifies for waiver of informed consent and/or waiver or does not require Authorization for Release of Protected Health Information.
 - Currently approved protocol including any modifications to protocol since last approval date: All IRB members shall receive the protocol and abstract. Modifications and addenda to a research protocol should be submitted as generated during the course of the study. They also may be submitted at the time of continuing review. A separate cover letter describing the change and all appropriate documentation (approved consent form) must accompany the continuing review.
 - Continuing IRB review of research must occur even where the remaining research activities are limited to the analysis of identifiable private information described in the IRB protocol.

- Medication information: All IRB members shall receive an investigator brochure, drug package insert, or other source of medication information, to ensure that the risks are appropriately documented in the informed consent document and protocol.
- Other IRB approval documents: All IRB members shall receive documentation of other IRB approvals if the study is being conducted at another site and PVAMC is the central or coordinating site, and documentation if IRB approval from the central or coordinating site if PVAMC is secondary site.

6. Possible Outcomes

- A. As an outcome of continuing review, the IRB may authorize continuation of the research, require that the research be modified or require that it be halted altogether. The IRB may need to impose special requirements or relax special requirements it had previously imposed on the research protocol.
- B. Appropriate continuing review intervals are addressed with each review conducted by the IRB. The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:
 - Involvement of vulnerable populations;
 - Involvement of recombinant DNA or other types of gene transfer protocols;
 - Level and types of risk (e.g. minimal or greater than minimal)
 - The number of participants that are expected to be enrolled during the period (e.g., too few may be available per year for a shorter review period to result in useful information about risks)
 - Withdrawal of therapy, whether or not it is replaced by experimental treatment, when there is significant risk of morbidity or mortality;
 - Use of waiver of informed consent procedures; and
 - Previous suspensions of the research due to non-compliance, record-keeping or other concerns
- C. Any changes required to obtain continued renewal approval shall be provided to the investigators by the IRB staff.

RESPONSIBILITY

The IRB Coordinator will:

- Generate a monthly summary of all studies with IRB approvals due to expire in 9 weeks.
- Generate email and mail corresponding notification letters and continuing review forms.

- Monitor continuing review submissions with summary of studies due to expire in order to remind investigators of impending expiration.

The Program Assistant will:

- Notify the Investigator as to the outcome of the review.
- If the IRB does not re-approve the research by the specified expiration date, an expiration letter will be sent. The letter will outline the terms of the expiration according to the three regulatory categories (screening, enrollment of new subjects, and continuation of interactions/interventions in already enrolled subjects and the re-instatement procedure) as decided by the IRB or reviewer

The Primary Reviewer will:

- Conduct a thorough review and presents findings at a convened IRB meeting.
- Complete reviewer checklist.
- Determine whether any special considerations exist that may influence the review of proposal.
- Determine whether the evidence exists that third party verification of submitted information is needed.

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4.5 REQUEST FOR MODIFICATION TO APPROVED RESEARCH

All changes in approved research, including premature study completion, during the period for which approval has already been given, may not be initiated without prior IRB review (full or expedited review, as appropriate) and approval, except where necessary to eliminate apparent immediate hazards to human subjects. In such cases, the investigator must promptly inform the IRB of the implemented change.

Note: Research following DoD regulations must undergo scientific review prior to IRB review for all substantive amendments to previously approved research. Scientific review is conducted by the PVAMC IRB. The IRB Surveys performed on DoD personnel must be submitted, reviewed, and approved by the DoD after the research protocol is reviewed and approved by the IRB.

1. Information Needed For Review of Project Modifications

Investigators or Sponsors must submit requests for changes to the IRB in writing. Each Modification request will include:

- Description of the changes;
- Reason for the change;
- Whether or not changes are need to the Informed consent document;
- The impact the change will have on the study and/or the participants;
- All appropriate documents;
- Revised informed consent (if affected, submit both marked change and clean versions of revision);
- Sponsor correspondence concerning the amendment (if affected);
- Amended protocol (if affected, submit both marked change and clean versions of revision).

2. Determinations and Full Board Review

- A. Upon receipt of the protocol modification, the IRB Coordinator with the assistance of the chair will determine if the revision meets the criteria for minimal risk. If the change represents more than a minimal risk to subjects, it must be reviewed and approved by the IRB at a convened meeting.

- B. For a project modification to be considered more than minimal risk, the proposed change would increase risk or discomfort or decrease the benefit. The IRB must review and approve the proposed change at a convened meeting before the change can be implemented unless, the change is necessary to eliminate an immediate hazard to the research participants. In the case of a change implemented to eliminate an immediate hazard to participants, the IRB committee will review the change to determine that is consistent with the ensuring the participant's continued welfare.
- C. The review of project modifications will be done using a primary reviewer system. If possible, the prior primary reviewer of the initial IRB submission will be assigned as the reviewer. All other members will receive all the materials.
- D. If the project modification might affect the willingness of a participant to continue in the study or changes the risk benefit for the participants already enrolled, the investigator will be directed to notify the participants. Depending on the seriousness, the investigator may be directed to contact the participants by letter, re-consent at next opportunity, or phone participants to schedule a visit for immediate re-consent.
- E. If the project modification involves requested changes related to biosafety or radiation safety, the request must achieve approvals at these local subcommittees prior to submission to the IRB.

3. Notification of Investigator

All approvals or requested revisions will be reported to the investigator via e-mail followed by a signed copy of the letter.

RESPONSIBILITY

The IRB Chair or designated IRB member will:

- Review of modifications that are minor and can be expedited.

The IRB Coordinator will:

- Triage the modification for expedited review or assigning a primary reviewer to review at a full board meeting.

The Primary Reviewer will:

- Review modification.

The IRB Program Assistant will:

- Document receipt of the modification and correspondence pertaining to the modification.

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4.6 STUDY COMPLETION

The completion or closure of the study is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report submitted to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

1. Determining When a Project Can Be Closed

- A. All research-related interventions or interactions with human subjects have been completed, and all data collection and analysis of identifiable private information described in the IRB-approved protocol have been finished. For multi-site clinical trials when the PVAMC investigator is not the coordinating investigator, the study can be closed if specified by the sponsor.

2. Investigator Initiated Study Closure

Investigators may submit a request for closure, including a final report with available results, in memoranda to the IRB at any time during the approval period. In addition, the investigator may choose to close their study at the time of continuing review by checking the appropriate item on the continuing review form and providing a final report.

3. Expired Project Status

If the continuing review does not occur on or before the expiration date, the research is automatically lapsed. The PVAMC considers such lapsed approval as an automatic action and therefore not an action reportable to ORO, although may require reporting to the study sponsor or FDA if a drug or device study. The IRB will consider the project closed and will require formal reinstatement by the investigator if the investigator chooses to re-open the study

RESPONSIBILITY

The IRB Coordinator and/or Program Assistant will:

- Instruct Investigators to submit written notification of the study completion along with a final report or at the time of continuing review.

- Review written notification of the study completion and obtain any outstanding information or documentation from the Investigator to close the study. If there are inconsistencies or if clarification is needed, request additional information.
- Add the study closure to the next month's agenda for review.
- Follow-up per instructions of the Board
- If study can be closed, generate study closure acceptance letter.

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4.7 CATEGORIES OF ACTION

As a result of its review, the IRB may decide to approve, require modification in to secure approval by either conditional approval or tabling, or disapprove the proposed research activity. Except when the expedited review procedure is used, these actions will be taken by a vote of a majority of the regular and alternate members present. When reviewed via expedited review, the Chairperson, Associate Chairperson, or experienced IRB member can take any of the following actions except to table or disapprove a study.

1. Determinations

The IRB may make one of the following determinations as a result of its review of research submitted for initial review or for continuing review:

- A. Approval: The protocol and accompanying documents are approved as submitted. Final IRB approval will commence on the day the study is approved by an action of the convened IRB or Chairperson, Associate Chairperson or and experienced member of the IRB and expire within (1) year of the approval date, but not later than the day preceding the date of review.
- B. Conditional Approval: Approval is contingent on specific conditions agreed and voted on by the convened IRB. The IRB will stipulate specific revisions that require a response by the investigator in order for the IRB to evaluate whether the conditions are met to allow the research to be approved. Upon submission of the IRB contingent items to the IRB Chair or designee, an expedited review is provided without subsequent review by the convened IRB. However, if the contingent approval from the convened IRB requires substantive clarifications or modifications that are directly relevant to the determinations required by the convened IRB, the review will not be expedited and must return to the next convened IRB meeting for review and approval.

Upon satisfactory review:

Approval Date: is issued as of the date the fully convened IRB conditionally approved the protocol rather than the date that the minor changes were approved by the IRB Chair, or designee.

Expiration Date: is the last day the research is approved. For example, for an approval period of September 1, 2007 to August 31, 2008, the expiration date is after 11:59 p.m. on August 31, 2008. Approval is usually one year,

but may be given for a lesser period of time (less than one year) based on the relative perceived greater than minimal risk to the subject population, previously reported issues with the drug, biologic or device, previous compliance issues with the PI, nature and location of the study, or the vulnerability of the study subject population.

- C. Tabled: The IRB requests any additional information, any clarifications, or substantive modifications that cannot be described as specific revisions that require simple concurrence by the investigator. In addition, a protocol will be tabled if significant questions are raised by the proposal requiring its reconsideration after additional information is received from the Investigator and/or Sponsor. The convened IRB must review the responsive materials when re-submitted by the investigator.
- D. Disapproval: The proposal fails to meet one or more criteria used by the IRB for approval of research. Disapproval cannot be given through the expedited review mechanism and may only be given by majority vote at a convened meeting of the IRB.

2. R&D Committee Approval

- A. No research may begin until R&D approval has been granted. Research that has been modified by the R&D Committee must be re-reviewed and approved by the IRB Committee. Approved and stamped study consent forms will not be distributed to the investigator until R&D approval has been granted to, therefore, participants will not be recruited into the study until final approval has been issued.
- B. Only research that has been approved by the IRB may be reviewed by the R&D Committee.
- IRB approved studies are automatically placed on an IRB Action Report signed by a voting member, then placed on the next R&D agenda with no further action required by the investigator.
 - Conditionally approved items are placed on the IRB Action Report but not submitted to the R&D until the conditions are met and the study is fully approved by the IRB. The investigator is responsible for responding to the conditions in a timely fashion. If the conditions are not met by the cutoff date for submission to the R&D, the study will be placed on the IRB Action Report for the following months R&D meeting, provided the PI has met the conditions of approval.
- C. The R&D Committee may decide to approve, require modification in to secure approval by either conditional approval or tabling, or disapprove the proposed research activity. All revisions requested by the R&D committee must be reviewed and approved by the IRB at either a convened meeting or expedited review if appropriate. See PVAMC R&D Standard Operating Procedures for additional information.

RESPONSIBILITY

The IRB Chair and/or Associate Chair will:

- Ensure the appropriateness of all IRB decisions and actions.
- Ensure that all IRB decisions and actions are based on institutional and regulatory requirements.
- Review and sign all IRB decision letters

The IRB Coordinator will:

- Assist Chair/Associate Chair to ensure that all IRB decisions and actions are based on institutional and regulatory requirements.
- Prepare the IRB Action Report for submission to the R&D.

The Program Assistant will:

- Document IRB decisions in the minutes.
- Drafts IRB issued decision letters.
- Drafts R&D issued decision letters.

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4.8 NONCOMPLIANCE WITH HUMAN RESEARCH PROTECTION PROGRAM

Reports of noncompliance will be directed to the Research Compliance Officer, appropriate IRB staff and to the IRB for investigation and corrective action. Reports of misconduct, as defined by VHA Handbook 1058.2, and are limited to plagiarism, fraudulence or fabrication are covered under the Research Misconduct Section (See Section 12: Research Misconduct). Complaints about the IRB process or the conduct of research may or may not involve noncompliance with IRB policies or federal regulations and will be handled as potential unanticipated problems involving risks to participants or others. Complaints that do not have elements of noncompliance should be handled in accordance with the IRB policy for addressing complaints. In addition, all employees or agents of the PVAMC, whether involved in research or not, are required to notify the IRB within five business days if they become aware of any noncompliance, including serious or continuing, with human subject regulatory requirements or with the determinations of the IRB.

Definitions:

Noncompliance: Failure to comply with applicable Federal Regulations, VHA policies for the protection of human subjects (including 38 CFR Part 16; 45 CFR Part 46; 21 CFR Parts 50, 56, 312 or 812; and VHA Handbook 1200.05), ethical treatment of participants PVAMC IRB policies and procedures, PVAMC policy, or the determinations of the PVAMC IRB.

Allegation of noncompliance: An unproved assertion of noncompliance.

Finding of non-compliance: A proven assertion of non-compliance.

Serious non-compliance. Serious noncompliance refers to willful and neglectful failure to adhere to IRB or HRPP regulations, requirements, or determinations or violations of procedures, policies, regulations, or laws (including VHA policies for the protection of human subjects (including 38 CFR Part 16; 45 CFR Part 46; 21 CFR Parts 50, 56, 312 or 812; and VHA Handbook 1200.05) involving substantive harm, or a genuine risk of substantive harm, to the safety, rights or welfare of human research subjects, research staff, or others; or substantively compromising the effectiveness of a facility's human research protection or human research oversight programs.

Examples of serious noncompliance:

1. Failure to adhere to the federal regulations governing the use of humans in research;
 - a. Failure to obtain IRB approval prior to initiation of research procedures;
 - b. Failure to notify the IRB of changes in approved procedures;
 - c. Failure to obtain informed consent;
 - d. Failure to document informed consent;
 - e. Failure to maintain complete record of informed consent;
 - f. Failure to notify the IRB of changes in the scope/intent of the study; or
2. Failure to adhere to institutional policies where subject's well-being or rights have been affected.

Continuing non-compliance. Continuing noncompliance refers to a pattern of non-compliance that suggests an inability or unwillingness to maintain compliance with IRB or HRPP regulations, requirements, or determinations.

Examples of continuing noncompliance:

- a. Failure to implement IRB-required changes to an on-going protocol within the time period specified by the IRB.
- b. Deficiencies in informed consent or HIPAA Authorization procedures or documentation for ten or more participants.
- c. Failure to maintain documentation required by the IRB or by the IRB-approved protocol for ten or more participants.

Non-Serious and Non-Continuing Non-Compliance. Noncompliance that is neither Serious Noncompliance nor Continuing Noncompliance.

1. Receiving Reports of Noncompliance

Reports of noncompliance may be provided to the Research Compliance Officer (RCO), IRB Chair, IRB members, IRB Staff, or Research Office staff from anyone inside or outside of the PVAMC Community who has reason to believe that the noncompliance with the IRB Policies and procedures has occurred. These complaints will be accepted verbally or in writing.

- A. Receipt of verbal reports. . Allegations received by the IRB Coordinator will be reported to the Administrative Office (AO), RCO, Associate Chief of Staff for Research (ACOS/Research), and the IRB Chair immediately.

If the report is made via telephone, the recipient of the call should take care to record all relevant information in a thorough manner and request that the caller provide a contact number for follow-up calls, unless the caller desires to remain anonymous.

Anonymous Callers. The person making the allegation may choose to remain anonymous. The recipient of an anonymous call should inform the caller that the matter will be investigated to the extent possible given the information provided.

The recipient of the call should ask the caller for any available evidence that the caller is willing to give that will facilitate an investigation into the matter, but should not encourage the caller to provide a name or contact information if the caller has expressed a desire to remain anonymous. It is permissible to advise the caller to provide additional information at a later date if new information becomes available or if the caller remembers details that were not presented originally.

Investigator. The investigator will be contacted in writing by the AO, ACOS/R, or the RCO to discuss the allegation of noncompliance. The AO, RCO, or ACOS/R will begin the investigation at this time.

B. Noncompliance Identified During an Audit:

Noncompliance discovered by the RCO during a routine informed consent audit or regulatory audit follows a separate reporting schedule as described in Section 4.9, Reporting Requirements.

Examples of noncompliance identified during an RCO informed consent audit that require the 5-day reporting to the Medical Center Director include but are not limited to: 1) lack of signed informed consent or HIPAA privacy rule authorization for one or more participants; 2) use of consent documentation that lacks VA-required information on loss of benefits or treatment in case of injury; 3) pervasive or persistent use of unapproved, unstamped, or outdated consent documentation; 4) pervasive or persistent failure to obtain dates of participant or witness signatures; and 5) pervasive or persistent failure to document informed consent as required by applicable VA policy.

Examples of noncompliance identified during an RCO regulatory audit that require 5-day reporting to the Medical Center Director include but are not limited to: 1) lack of IRB approval or lack of VA approval before initiating research; 2) initiating research procedures before obtaining required informed consent; initiating changes in research without IRB approval, unless necessary to prevent immediate hazards to the subject; 3) implementing substantive protocol amendments without IRB approval; 4) failure of one or more members of the research team to satisfy research credentialing, privileging, or scope of practice requirements; 5) pervasive or persistent failure to comply with IRB determinations or requirements; 6) pervasive or persistent failure to report AEs or problems in research per IRB or VA requirements; and 7) pervasive or persistent failure to maintain required study documentation.

All allegations of noncompliance will follow the standard procedures, regardless of the discovery. The IRB is responsible for determining whether serious or continuing noncompliance actually did occur and the nature of required remedial actions.

2. Allegations of Non-Compliance

A. Investigation.

The AO, RCO, and/ or the ACOS/R&D will investigate the allegation upon notification of the alleged noncompliance. The investigation will focus on the review of findings and will determine whether the allegation has basis in fact. The IRB Chair and IRB Coordinator will be made aware of the progress of the investigation.

- If the AO, RCO, and/or the ACOS/R&D is unable to make a determination, the IRB Chair will involve the convened IRB and has the IRB make a determination of whether the allegation has a basis in fact.
- If the allegation has no basis in fact, no further action is undertaken under this policy.
- If the allegation has a basis in fact, it is handled under this policy as finding of non-compliance.

B.. Report to IRB of an Investigation of Allegations of Non-Compliance:

If the investigation of the allegation has not been completed prior to the next scheduled meeting of the IRB, the IRB will be notified that an allegation of noncompliance has been received and that an investigation has been initiated by Research Administration (AO, or ACOS) or by the Research Compliance Officer. This information will be presented in a manner that does not identify the investigator, study or facility. However, if the allegation will impact other IRB business at that or another meeting, the IRB will be informed as needed to ensure effective decision-making by the IRB relative to that investigator, protocol or facility. The IRB will also be notified that they may be called upon to make a determination if the AO, RCO, or ACOS is unable to reach a determination.

3 . Determinations.

After the investigation, the AO, RCO, or ACOS, will report the investigation to the IRB, which is responsible to determine whether:

- a. the non-compliance might be serious or continuing or
- b. the non-compliance is not serious and not continuing.

If the IRB determine that the non-compliance is neither serious nor continuing, the IRB Chair or IRB will work with the investigator on a corrective action plan with the assistance of Research Administration and the Research Compliance Officer. If the convened IRB determine that the non-compliance is serious or continuing, the IRB Chair reports it to the regulatory agencies following the procedures outlined in Section 4.9, Reporting Requirements.

4. Convened IRB Review of Serious or Continuing Non-Compliance:

1. Review by the IRB Committee (Serious or Continuing): Incidences of non-compliance determined to be Serious or Continuing will be presented to the IRB and the IRB votes to determine whether the non-compliance was serious or continuing

(or defers the decision to a future meeting pending receipt of additional information), and that the results of the vote are documented in the minutes.

At a convened IRB meeting the RCO and Chair will present the issue to the IRB. All IRB members and the primary reviewer will receive the following:

- the investigation report,
- synopses of any communication between Research Administration and the investigator,
- the last approved IRB application or continuation,
- the approved consent,
- protocol and any other pertinent information.

All members attending the IRB meeting will review all the documents prior to the meeting and determine:

1. There is no issue of serious and continuing non-compliance
2. There is serious and continuing non-compliance
3. More information is needed and determination is deferred to future meeting pending receipt of additional information

Actions that may be taken by the IRB::

1. No action;
2. Suspension of the research: Suspend enrollment and/or all research procedures for the specific research study in question; (in accordance of Section 4: Review of Research, 4.10 Suspension and Termination of IRB Approval)
3. Termination of the research; (in accordance of SOP on Suspension and Termination of IRB approval)
4. Notification of current participants when such information may relate to the participant's willingness to continue to take part in the research.
5. Require a response from the investigator with a plan for corrective action;
6. Initiate audits of all or some part of the Investigator's active protocols;
7. Modification of the research protocol;
8. Modification of the information disclosed during the consent process;
9. Additional information provided to past participants;
10. Modification of the continuing review schedule;
11. Obtain more information pending final decision;
12. Conference with other IRBs involved with the research
13. Requirement that current participants re-consent to participation;
14. Monitoring of the research
15. Monitoring of the consent process

If the investigator offers a timely and satisfactory explanation for the concern and a plan to eliminate future incidents of such noncompliance, and the IRB accepts the explanation and plan, the IRB may elect to terminate the noncompliance investigation process and report that the noncompliance issue was satisfactorily resolved with no further corrective action. The IRB will still determine if the noncompliance was serious and continuing.

If the corrective action plan call for any changes to the previously approved research and the change involves more than minor modifications the modification must be reviewed by the convened IRB. If the change is only a minor modification the change can be reviewed by expedited review.

If the Investigator does not provide a timely response, or offers an unsatisfactory explanation or corrective action plan, the IRB may ask the investigator to meet with the chair or attend an IRB meeting to discuss the issue.

Meeting with the IRB Chair: The investigator may be asked to attend a meeting with IRB Chair and other appropriate members of the IRB or others in Research Administration or the Research Compliance Officer to discuss the allegations and/or findings and/or requests for more information.

If the investigator has attended an informal meeting with the IRB Chair or provided a written response, the IRB will receive a summary of the conference or the investigator's written response included with the other documentation relating to the allegation, investigation and findings.

Attendance at IRB Meeting: The investigator may be asked or may choose to attend a meeting of the full IRB. The investigator would be scheduled to appear at the meeting only after the full IRB had the opportunity to discuss the issues and findings.

If the investigator initiates the request to attend the full IRB meeting, the request must be received by the Research office (2) weeks in advance of the IRB meeting.

If the investigator attends the IRB meeting, the investigator shall have an opportunity to present a response to the IRB immediately following the presentation of the allegation and investigation.

Note: During the investigation, the IRB may impose restrictions to the research study until satisfactory answers are received by the IRB.

5. Investigator Notification:

Not serious and not continuing: If it is determined by the IRB that the noncompliance is not serious and not continuing, the investigator will be notified in writing by the IRB. In addition, the AO, RCO, ACOS/R, or Chair will discuss the issue with the investigator and an action plan will be drafted. The final action plan will be forwarded to the investigator via letter or e-mail and the information will be included in the IRB agenda as an information item.

Non-Compliance that may be Serious or continuing:

The investigator will be notified by the IRB, of the findings and/or requests for information by phone call, letter or e-mail. The investigator will be asked to respond in writing to the allegation and depending on the response, the investigator may be asked by the A O, ACOS/R, R C O, or Chair to attend the IRB meeting and/or a meeting with the IRB Chair.

Written Response: The investigator will be asked to respond in writing to the allegation and/or finding and/or request for information. The investigator will have 14 days to respond. If the investigator needs more time, an extension may be granted by the IRB Chair. The written response will be presented to the full board at a convened meeting for review.

H. Notification of Relevant Parties of Reports and Findings of Serious or Continuing Noncompliance. Upon determination by the IRB that an incident of noncompliance was either serious or continuing noncompliance the incident will be reported according to Section 4: Review of Research, 4.9 Reporting Requirements. If the identity of the person who reported the allegation, complaint, or concern is known, a summary of the findings of the investigation will be forwarded to this person as well.

RESPONSIBILITY

IRB Chair, Administrative Officer, ACOS/R&D and Research Compliance Officer will:

- If report of noncompliance is unbeknown to the investigator, notify the investigator (unless notification could jeopardize the investigation) that an investigation is being conducted.
- Conduct investigation into alleged noncompliance to determine basis in fact.
- Notify the investigator of the IRB determination and corrective action
- Notify all appropriate parties of the allegation and outcome

The Chair will:

- Upon completion of the investigation, present the facts and findings to the IRB
- Review, along with the members, the information at a convened meeting of the full board and make a determination to close investigation or assign corrective action.

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The IRB Coordinator will:

- Keep the IRB Chair, ACOS/R, AO, RCO, and R&D Committee informed of developing issues.

IRB Members are responsible for the review of reports of investigation of non-compliance and determination of actions needed to be taken by the IRB and investigator.

The Program Assistant:

- Disseminate written actions/determinations to the investigator.

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4.9 REPORTING REQUIREMENTS

It is the policy of the VA to comply with all applicable local, state, and federal regulations in the conduct of research studies and to communicate certain actions to entities that may have an interest in the status of the research being conducted.

DEFINITIONS

- a. **Unanticipated (unexpected) problem involving risks to participants or others.** Events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a new or greater risk of harm or discomfort related to the research than was previously known or recognized.
 - b. **Serious non-compliance.** Serious non-compliance refers to willful and neglectful failure to adhere to IRB or HRPP regulations, requirements, or determinations or violations of procedures, policies, regulations, or laws involving substantive harm, or a genuine risk of substantive harm, to the safety, rights or welfare of human research subjects, research staff, or others; or substantively compromising the effectiveness of a facility's human research protection or human research oversight programs.
 - c. **Continuing non-compliance.** Continuing non-compliance refers to a pattern of non-compliance that suggests an inability or unwillingness to maintain compliance with IRB or HRPP regulations, requirements, or determinations.
 - d. **Suspension.** An action initiated by the IRB to stop temporarily some or all research procedures, including but not limited to the enrollment of new subjects and activities involving previously enrolled subjects, pending future action by the IRB or by the Investigator or his/her study personnel.
 - e. **Termination.** An action initiated by the IRB to stop permanently some or all research procedures, including but not limited to the enrollment of new subjects and activities involving previously enrolled subjects.
1. The Medical Center Director is directly notified in writing of all terminations and suspensions and the identification of apparent serious or continuing noncompliance within five businesses days. The Director has five business days upon receiving notification to report the incident to the Northeast Regional Office of ORO and others listed in 4.

2. IRB Coordinator in consultation with the IRB Chair and RCO prepares a letter that contains the following information:

- The nature of the event
 - Unanticipated problem involving risks to participant or others, or
 - Serious or continuing non-compliance, or
 - Suspension or termination of approval of research
- Title of the research project and/or grant proposal in which the problem occurred
- Name of the principal investigator on the project
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (i.e., grant, contract, or cooperative agreement)
- A detailed description of the problem including the findings of the IRB and the reasons for the IRB decision
- Actions the institution is taking or plans to take to address the problem (e.g., suspend subject enrollment, terminate the research, revise the protocol and/or informed consent, inform enrolled subjects, increase monitoring, etc.)
- Plans, if any, to send a follow-up or final report by the earlier of:
 - A specific date.
 - When an investigation has been completed or a corrective action plan has been implemented.

3. The IRB Chair, Research Compliance Officer, ACOS for R&D, and Medical Center Director review the letter and modify as needed. The final letter is approved and signed by the Medical Center Director and returned to the IRB Coordinator for distribution and follow up.

4. The IRB Coordinator, or designee, sends copies of the letter to the following as appropriate:

(Bolded items are required by regulations. Others are optional.)

- **The Institutional Official**
- The ACOS/R&D
- The Chair of the R&D Committee
- **The IRB**, by including the letter in the next agenda packet as an information item
- The VISN Director
- **The Northeast Regional VA Office of Research Oversight**
- **The Office of Research and Development**
- **FDA**, if the study is subject to FDA regulations
- **OHRP**
- **DoD**, if the study is subject to DoD regulations
- **Any “Common Rule” Federal Agency** that is supporting research
- Principal Investigator
- Principal Investigator’s Supervisor
- Sponsor, if the study is sponsored
- Contract research organization (CRO), if the study is overseen by a CRO
- **The VA Privacy Officer** if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information

- **The VA Information Security Officer** if the event involved violations of information security requirements
 - Office of Risk Management
 - Regional Counsel
 - VA Central Office when the unanticipated problem involving risks to participants or others was an adverse event.
5. The IRB Coordinator will provide copies of the letter within five business days of the IRB action with a follow-up report when the investigation has been completed or a corrective action plan has been implemented. The letter and reports will be sent to the appropriate officials, committees, and agencies listed above.
6. Noncompliance discovered by the RCO during a routine informed consent audit or regulatory audit follows a specific reporting schedule:
- The Medical Center Director, IRB, ACOS/R, AO, and R&D Committee are to be notified as soon as possible, but no later than 5 business days after discovery.
 - The Medical Center Director must report to ORO Regional Office (RO), VISN Office, and the Office of Research and Development (ORD) as soon as possible, but no later than 5 business days after being notified by the RCO.
 - The Facility Director must provide follow-up reports as directed by ORO RO, including subsequent IRB determinations.
 - If the IRB ultimately determines that serious or continuing noncompliance actually did occur, the Medical Center Director must report promptly to OHRP, FDA and/or DoD.

RESPONSIBILITIES

The IRB Coordinator in consultation with the IRB Chair and RCO is responsible for drafting a letter to be sent to appropriate individuals and agencies once the IRB takes any of the following actions:

- Determines that an event represents an unanticipated problem involving risks to participants or others,
- Determines that non-compliance was serious or continuing, or
- Suspends or terminates approval of research.

The RCO is responsible for initiating the special reporting procedures when noncompliance is identified during an audit.

The Medical Center Director is responsible for reviewing and approving the draft.

The IRB Coordinator is responsible for distributing the letter to the appropriate individuals, committees, and agencies.

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4.10 SUSPENSION AND TERMINATION

The IRB shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with IRB, federal, state or local requirements, or has been associated with unexpected serious harm to participants. A project may be suspended or terminated for the following reasons, including but not limited to:

- Serious and Continuing non-compliance with federal regulations and IRB policy
- Failure to obtain appropriate informed consent
- New information regarding the increased risk to the participant

If someone other than the IRB suspends or terminates approval of research, that party must report this action to the IRB Chair, ACOS for Research, Research Compliance Officer and/or the IRB Coordinator in writing immediately. This report will be reviewed by the convened IRB (see Section 1 below).

Definitions:

Suspension: An action initiated by the IRB to stop temporarily some or all research procedures, including but not limited to the enrollment of new subjects and activities involving previously enrolled subjects, pending future action by the IRB or by the Investigator or his/her study personnel.

Termination: An action initiated by the IRB to stop permanently some or all research procedures, including but not limited to the enrollment of new subjects and activities involving previously enrolled subjects.

Administrative Hold: An administrative hold is a voluntary interruption of research enrollments and ongoing research activities by an appropriate facility official, research investigator, or sponsor (including the VHA ORD when ORD is the sponsor).

(1) The term "administrative hold" does not apply to interruptions of VA research related to concerns regarding the safety, rights, or welfare of human research subjects, research investigators, research staff, or others.

(2) An administrative hold must not be used to avoid reporting deficiencies or circumstances otherwise covered by VHA Handbooks or other Federal requirements governing research.

Suspensions and terminations do not include:

- a. Interruptions in research resulting solely from the expiration of a project approval period.
- b. "Administrative holds" or other actions initiated voluntarily by an appropriate facility official, research investigator, or sponsor for reasons other than those described in preceding items.

1. Suspension and Termination

- I. At a convened meeting of the IRB, the Chair, Administrative Officer, ACOS/R&D, Research Compliance Officer, and/or IRB Coordinator will present the facts for consideration and vote. The IRB will review a study for suspension or termination for the following types of conditions, including but not limited to:
 - Falsification of study safety data;
 - Failure to comply with prior conditions imposed in writing by the IRB under a Suspension for Investigation;
 - Repeated or deliberate failure to obtain or document informed consent from human participants, which may include:
 - Repeated or deliberate omission of a description of serious risks of the experimental therapy when obtaining informed consent; and/or
 - Repeated or deliberate failure to provide informed consent in a language understandable to the subject;
 - Repeated or deliberate failure to limit administration of the investigational drug or device to those participants under the Investigator's supervision;
 - Repeated or deliberate failure to comply with conditions placed on the study by the IRB, sponsor, or FDA;
 - Repeated or deliberate failure to obtain prior review and approval of new protocols and on-going human subjects research by the IRB;
 - Repeated or deliberate failure to follow the signed Investigator statement or protocol, e.g., by enrolling participants who should have been excluded because of concomitant illnesses that put those participants at greater risk;
 - Repeated or deliberate failure to maintain accurate study records, submit required adverse event reports, report changes to the research or report unanticipated events to the IRB;
 - Repeated or deliberate falsification or concealment of study records, e.g., by substituting in study records the results of biological samples from participants who met the inclusion criteria for samples of participants who did not meet the inclusion criteria, or by fabricating participants.
- II. The IRB will decide on a course of action and establish a time line for the completion of that action. The discussion, action and vote will be recorded in the meeting minutes. The IRB may act at any time during the investigation to modify the terms of the suspension or termination.

The IRB or person ordering the suspension or termination must consider the following when determining the action:

- Actions to protect the rights and welfare of currently enrolled subjects.

- Whether procedures for withdrawal of enrolled subjects take into account their rights and welfare.
 - Informing current subjects of the termination or suspension.
 - Whether any adverse events or outcomes were reported to the IRB.
- III. The Chair may act alone to suspend or terminate previously approved human research or an investigator's privilege to conduct human subject research if the alleged serious or continuing non-compliance with the requirements or determinations of the IRB, or any incidence that has been associated with the unexpected serious harm to participants appears to pose imminent threat to subject safety.
- IV. The IRB may request an ad hoc review from an independent source with expertise in the type of research being conducted or expertise in the specific area of concern.
- V. For suspensions; the IRB deliberates and determines the category(s) of suspension which are:
- Suspension to recruitment
 - Suspension to screening and enrollment
 - Suspension to interaction and intervention; and/or
 - Suspension to follow-up
- VI. The IRB notifies the Medical Center Director and investigator in writing of its decision by letter (within 5 working days) and a copy of the unsigned letter will also be emailed by the Research office. The letter will include:
- Reason and rationale for the suspension or termination
 - IRB action plan and established timeline for response and reporting progress to the IRB
 - If appropriate, require the investigator to submit:
 - Procedure for the withdrawal of currently enrolled participants that considers their rights and welfare.
 - Letter or script notifying all currently enrolled participants that are affected by the suspension or termination.
 - A reminder that all study activities such as, reporting adverse events, revisions to investigator brochures, and updated package inserts must still be reported to the IRB.
 - If appropriate, require the investigator to:
 - Attended investigator training
 - Provide a plan for oversight for current and future research
 - Notification that an internal audit of the study will be conducted by the Research Office
- G. To reinstate a project that has been suspended, the investigator must satisfactorily resolve any pending issues required by the IRB. If the issues have not been resolved after one year, the study will be terminated.

- H. To reinstate a project that has been terminated, the investigator must submit the project to the IRB as new and past issues must be resolved to the satisfaction of the IRB.
- I. The R&D Committee will be notified of the action taken by the IRB at the next convened meeting.

2. Reporting Suspension and Terminations

All suspensions and terminations will be reported to the appropriate individuals and agencies per Section 4: Review of Research: 4.9: Reporting Requirements.

RESPONSIBILITY

The Chair will:

- Presenting the facts to the IRB at a convened IRB meeting.

The IRB Coordinator will:

- Notify the appropriate individuals and agencies of the suspension or termination.
- Assist Chair with presenting the facts to the IRB at a Convened IRB meeting.
- Notify, through the Institutional Official, within 5 business days all appropriate individuals and agencies of IRB determination. and appropriate individuals and agencies

The members will:

- Determine if the facts are sufficient to require suspension or termination of the research.
- Determine course of action and establishing a timeline for completion of that action.

The Program Assistant will:

- Notify Investigators within 5 business days of IRB determination.

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4.11 INVESTIGATIONAL DRUGS AND DEVICES

1. Investigational Drugs

All investigational drug studies will be reviewed and approved by the IRB and R&D Committee prior to initiation. Investigators who employ a test article classified by the Food and Drug Administration (FDA) as an investigational drug must assure the IRB that it is complying with the FDA's IND regulations (21 CFR 312).

The exemption categories from the requirement of an IND (21 CFR 312.2(b)) are as follows.

- Exemption 1:
 - The drug product is lawfully marketed in the United States.
 - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
 - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
 - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
 - The investigation is conducted in compliance with 21 CFR 50 and 56.
 - The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
- Exemption 2:
 - A clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following:
 - Blood grouping serum.
 - Reagent red blood cells.
 - Anti-human globulin.
 - The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.

- The diagnostic test is shipped in compliance with 21 CFR 312.160.
- Exemption 3:
 - A drug intended solely for tests in vitro or in laboratory
 - research animals is exempt from the requirements of this part if shipped
 - in accordance with Sec. 312.160.
- Exemption 4:
FDA will not accept an application for an investigation that is exempt under the provisions of 21 CFR 312 (b)(1).
- Exemption 5:
A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

Investigational drugs used in humans require an IND if they are used to develop information about their safety or efficacy. Approved, marketed drugs may also require an IND if the proposed use is:

- Different from its previous FDA-approved use,
- Administered by an unapproved route or method of delivery, or
- An altered dosage form,
- Shipped by interstate commerce in order to conduct a clinical trial.

The IND number assigned to the test article and a source document supporting the IND Number and the holder, must be submitted to the IRB when the protocol is submitted for initial review. The IRB Committee will verify that the IND is valid by confirming that the number supplied by the investigator matches the sponsor's protocol, a letter from the FDA, or correspondence from the sponsor or Contract Research Organization (CRO). Such confirmation will be documented in the IRB minutes. An investigator's brochure will not be used to validate an IND.

The FDA has published several exemptions to the IND requirements. Roughly, a clinical investigation may be exempted from the IND requirements if the drug is lawfully marketed in the U.S. and all the following apply:

- The results will not be reported to the FDA to support a new indication for Use, nor to support any other significant change in the labeling of the drug;
- The investigation will not be used to support a significant change in the advertisement of a prescription drug that is already on the market;
- The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR Part 56 and with the requirements for informed consent set forth in 21 CFR Part 50; and
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7, which concerns the promotion and sale of investigational drugs.

The IRB evaluates each of the above criteria during a convened meeting when research involving investigational drugs not having an IND is reviewed to determine whether an IND is needed and/or whether the investigator should consult FDA prior to IRB approval. Documentation of IRB deliberations will be described in IRB minutes. No protocol will be approved by the IRB prior to the IRB validating the IND (if applicable).

2. Investigational Devices

The IRB will conduct the review of research involving investigational devices in compliance with FDA regulations, VA requirements, and any other applicable requirements. Research approval involving an FDA-regulated investigational device will only occur after the IRB has received documentation that the research will be conducted under an applicable Investigational Device Exemption (IDE) **or** has formally determined that satisfactory justification has been provided by the investigator as to why an IDE is not required. The IRB will make the following assessment of the protocol:

- The IRB will determine the risk level based on proposed use of the device and not the device alone.
- The IRB may agree or disagree with the sponsor's assessment of significant risk or nonsignificant risk. The IRB chair will notify the Sponsor and investigator of its decision on significant risk either electronically or by written communication.
- The IRB will review significant risk device studies only after the sponsor obtains an IDE.
- Protocols involving significant risk devices will not qualify for expedited review.
- The rationale for the IRB's determination of significant/non-significant risk will be documented in the IRB minutes.

3. Categories of Research Involving Medical Devices Exempt from the IDE Regulations

There are seven categories of device studies that are exempt from the FDA regulations on IDEs. These exemptions apply only so long as the investigator remains qualified to conduct the research (see FDA regulations, 21 CFR 812.119 for Disqualification).

- Exemption 1:
Devices, other than transitional devices*, in commercial distribution prior to May 28, 1976, when used or investigated in accordance with labeling in effect at that time;
- Exemption 2:
Devices, other than transitional devices*, introduced into commercial distribution on or after May 28, 1976, that the FDA determines to be substantially equivalent to a device in commercial distribution prior to May 28, 1976, and which is used or investigated in accordance with approved labeling;
- Exemption 3:
A diagnostic device (including in vitro diagnostic products in compliance with 21 CFR 809.10(c)) if the testing:

- a. Is non-invasive
- b. Does not require an invasive sampling procedure that presents significant risk
- c. Does not by design or intention introduce energy into a subject, and
- d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- Exemption 4:
Devices undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution , if the testing is not for the purpose of determining safety or effectiveness and does not put the subject at risk.
- Exemption 5:
The device is intended solely for veterinary use.
- Exemption 6:
The device is shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).
- Exemption 7:
Custom devices, as defined by FDA in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

A. SIGNIFICANT RISK (SR) AND NON-SIGNIFICANT RISK (NSR) DETERMINATIONS

The IRB will use the following procedures to assess SR and NSR. The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" and "non-significant risk" . An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure.

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

- **Distinguishing Between SR and NSR Device Studies**

FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the

device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs must review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)] and the IRB must review the sponsor's justification for the non-significant risk determination.

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion. If the IRB determines that the device study is NSR, the IRB must also ensure that the device meets abbreviated IDE requirements.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

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

could be caused by the procedure in addition to the potential harm caused by the device.

B. ABBREVIATED IDE REQUIREMENTS

- Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation (§812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use.";
- IRB Approval – The sponsor must obtain and maintain Investigational Review Board (IRB) approval throughout the investigation as a nonsignificant risk device study;
- Informed Consent – The sponsor must assure that investigators obtain and document informed consent from each subject according to 21 CFR 50, Protection of Human Subjects, unless documentation is waived by an IRB in accordance with §56.109(c);
- Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (§812.46). Guidance on monitoring investigations can be found in "Guideline for the Monitoring of Clinical Investigations";
- Records and Reports - Sponsors are required to maintain specific records and make certain reports as required by the IDE regulation.
- Investigator Records and Reports – The sponsor must assure that participating investigators maintain records and make reports as required (see Responsibilities of Investigators); and
- Prohibitions –Commercialization, promotion, test marketing, misrepresentation of an investigational device, and prolongation of the study are prohibited (§812.7).

C. IDE Validation

The IDE number assigned to the test article and a source document supporting the IDE Number and the holder, must be submitted to the IRB when the protocol is submitted for initial review and/or if the IRB determines that the device is SR and requires an IDE issued by FDA. The IRB Committee will verify that the IDE is valid by confirming that the number supplied by the investigator matches the sponsor's protocol, a letter from the FDA, or correspondence from the sponsor or Contract Research Organization (CRO). Such confirmation will be documented in the IRB minutes. An Investigator's Brochure will not be used to validate an IDE.

D. Investigational Device Accountability

Any investigator submitting a research proposal involving investigational devices must describe in a cover letter or in the proposal the plan for control of the investigational device. The plan must include at a minimum:

- (1) How the device will be obtained
- (2) Control for access
- (3) Security
- (4) Recording/Accountability log

The IRB will evaluate the plan when during the review of the research involving an investigational device. The IRB must approve the plan for receipt, control, custody, and dispensing of the investigational device in order to approve the research.

E. Investigator-Sponsor Requirements for Studies Requiring an IND/IDE

In reviewing research involving FDA regulated articles, the IRB will determine if the study involves an investigator-sponsor. If so, the IRB informs the investigator that sponsor responsibilities, including reporting requirements to the FDA, (as well as the investigator responsibilities) are his/her responsibility as required by FDA regulations. Investigators who are assuming the sponsor function must submit in their protocol or cover letter a plan for how they are going to fulfill their sponsor functions. The IRB will evaluate the plan and determine whether the investigator can assume the sponsor function for an IND or IDE study prior to approving the study.

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Providence, Rhode Island

Section 4: Review of Research

October 19, 2011

4.12 ADVERSE EVENT AND UNANTICIPATED PROBLEMS

1. Definitions:

Adverse Event (AE): Any untoward physical, social, psychological, or legal/economic occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or with the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research.

Unexpected Adverse Event (UAE): Any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

Serious Adverse Event (SAE): An event involving a death; life-threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or a event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes. Life threatening is defined as “immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.”

Related AE or a Related Problem. A “related” AE or a “related” problem in VA research is an AE or problem that may reasonably be regarded as caused by, or probably caused by, the research (see 21 CFR 312.64).

Unanticipated (Unexpected). The terms “unanticipated” and “unexpected” 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.

Risks: The occurrence of harm or probability that harm might occur. The harm may be physical, psychological, financial, social, economic, or legal.

Others: Individuals who are not research subjects.

Serious Problem. A serious problem is a problem in human research that may reasonably be regarded as:

- (1) Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
- (2) Substantively compromising the effectiveness of a facility's human research protection or human research oversight programs.

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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unexpected adverse drug experiences: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g. included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

2. Investigator Reporting

A. Unanticipated (Unexpected) Problems Involving Risks to Participants or Others, including Serious Unanticipated Problems

The investigator or other members of the VA research community must report all unanticipated problems involving risk to subjects or others in VA research in writing to the IRB within 5 business days of becoming aware of the event or problem.

Examples of these events include:

- Any event (adverse events, injuries, side effects, deaths, or other problems), which in the opinion of the principal investigator (1) was unanticipated, (2) involved risk to the participants or others, and (3) was related to the research procedures;
- Any event that requires prompt reporting according to the sponsor;
- Any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur;
- Any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant;
- Protocol violation/deviation (meaning a change or alteration in a procedure or procedures as outlined in the IRB approved protocol, health care system or IRB policies and standard operating procedures);

- Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research;
Any complaint or a participant that indicates an unanticipated risk or which cannot be resolved by the research staff;
- Any adverse event that is both a serious adverse event and an unexpected adverse event, which in the investigators opinion is more like than not to be related to the research procedures;
- Any DMC, DSMB, or DSMC report describing a safety problem;
- Breach of confidentiality of research data;
- Breach of privacy/confidentiality/data security/loss of study data/destruction of study data due to noncompliance, or incorrect labeling/dosing of study medication or test article
- Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death.
- Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects. **NOTE:** *PBM generally forwards such communications directly to the ACOS for Research, who is responsible for determining if any of the facility's research projects are affected and, if so, reporting the alert to the IRB and the relevant investigators. Local SOPs should address the obligations of the ACOS for Research, individual investigators, and the IRB in reviewing such alerts.*
- Any sponsor analysis describing a safety problem for which action at the facility level may be warranted. **NOTE:** *Sponsor AE reports lacking meaningful analysis do not constitute "problems" under this paragraph.*
- Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;
- Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs
- The IRB will accept other reports when the PI is unsure whether the event should be reported.

B. Local Unanticipated Serious Adverse Events

Within five (5) business days of becoming aware of any local (i.e., occurring in the reporting individual's own facility) unanticipated serious adverse event, the investigator or other members of the VA research community are required to ensure that all serious adverse has been reported in writing to the IRB. It is noted that this requirement is in addition to other applicable reporting requirements (e.g., reporting to the sponsor under FDA requirements). In addition, the unfounded classification of an SAE as "anticipated" constitutes serious non-compliance.

Note: If a DSMB or DMC is used, events must be reported to these boards and a summary of the DSMB or DMC findings must be reported to the IRB when available.

3. Written Report Format

Reportable events include serious adverse events or unanticipated problems involving risks to subjects or others, including unanticipated adverse device effects, must be reported as follows;

- In the form of a memoranda that includes:
 - i. Name of Principal Investigator
 - ii. Date of the event/problem
 - iii. Description of the study procedures
 - iv. Description of the event/problem
 - v. PI's evaluation of the event/problem, including the need for revisions to the informed consent protocol
 - vi. Corrective action planned or corrective action implemented to prevent a reoccurrence, if applicable
 - vii. Other relevant information
 - viii. Signature of the PI
 - ix. Copy of Med Watch, DSMB/DMC or other reports (FDA regulated research, cooperative studies) as applicable

In addition, the investigator must informed consent document and other protocol documents as applicable (protocol, sponsor reports, Medwatch Reports, etc)..

The investigator is responsible for the documentation, investigation and follow-up of all serious adverse events and unanticipated problems that occur at the site in which the investigator is responsible for the conduct of the research.

4. Review of the Event or Problem

- a. The IRB Coordinator conducts an initial review of all SAE, unanticipated problems involving risk to others, DSMB reports, and deviation reports and determines which require immediate attention by the IRB based upon the seriousness of the event (i.e., death of a patient related to the study).
- b. In addition to the pre-reviewed items listed above, the IRB will make the decision whether the problem meets the definition of "unanticipated problem involving risks to participants or others" by evaluating whether the problem reported is both:
 - Unforeseen
 - or

Indicated that participants or others are not at increased risk of harm before determining whether any other actions are needed.

If neither criterion is met, the problem is NOT an unanticipated problem involving risks to participants or others, and no further IRB action is required. However, further action may be required if the problem involves non-compliance and the non-compliance policy will be followed.

- c. If the problem is determined in pre-review to be serious and unanticipated problem involving risks to participants or others and related, the IRB Coordinator will notify the IRB Chair no later than one day of receiving the report. Within five (5) business days, the convened IRB or a qualified IRB member-reviewer must determine and document whether or not the reported incident was serious and unanticipated and related (as defined above) to the research.
1. 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 report the problem or event directly (without intermediaries) to the medical center director within five business days after the determination.
 2. The report must be made in writing, with a simultaneous copy to the Associate Chief of Staff for research and the Research and Development Committee.
 3. The Medical Center Director must report the problem or event to the Northeastern ORO Regional Office within five business days after receiving such notification.
- d. If the convened IRB or the qualified IRB member-reviewer determines that the problem or event was serious and unanticipated and related to the research, a simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii).
- e. All determinations of the qualified IRB member-reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting.
- f. If it was determined that the problem or event is serious and unanticipated and related to the research, the convened IRB must determine and document whether or not a protocol or consent document modification is warranted.
- g. If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document:
1. Whether or not previously enrolled subjects must be notified of the modification and, if so,
 2. When such notification must take place and how such notification must be documented.
- h. A primary reviewer will be assigned to review and present the event or problem. The reviewer is chosen by experience, expertise and work load. The reviewer and all members will receive the following:
- Memorandum describing the event
 - Protocol
 - Informed consent

- Other study documents as applicable (i.e., investigator brochure, sponsor protocol, etc.)
- i. The IRB will review these documents at a convened meeting according to the risk and will determine whether changes are needed to the protocol or informed consent document or if any other action is necessary (e.g., remove participants from the study, etc.). In addition to the findings the Committee must make for a serious and unanticipated and related problem, as noted above, the Committee may take the following actions:
- No action;
 - Modification of the research protocol;
 - Modification of the information disclosed during the consent process;
 - Additional information provided to past participants;
 - Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research);
 - Requirement that current participants re-consent to participation;
 - Modification of the continuing review schedule;
 - Monitoring of the research;
 - Monitoring of the consent;
 - Suspension of the research;
 - Termination of the research;
 - Request for more information pending final decision;
 - Refer to other organizational entities (e.g. legal council, institutional official) or
 - Other actions appropriate for the local content.
- j. The determination whether this is an unanticipated problem involving risk or not and vote will be reported in the minutes and the investigator will be notified.
- k. If the modification made in response is determined by the IRB to be more than minor modification to previously approved research, the modification must come back to the convened IRB for review and vote.

5. Notification

- A. The Investigator will be notified promptly of IRB findings other than acceptance as presented. This letter will be generated from the IRB Committee. See Section 6: IRB Communication and Notification, for further information.
- B. The Office of Research Oversight will be notified of any event that meets its reporting requirements set forth in VHA Handbook 1058.01. The reporting to the officials will follow the procedures outlined in Section 4: Review of Research, Section 4.9. The reporting requirements are as following:
- Any adverse event (i.e., an untoward physical, psychological, social, legal, or economic occurrence) in a human subject, or an imminent threat of an

adverse event, that results in a substantive action by the Institutional Review Board (IRB) under VHA Handbook 1058.01 on *Reporting Adverse Events in Research*. Definition of Substantive Action: An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including by not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

- Any unexpected death of a human subject under VHA Handbook 1058.01
NOTE: Such deaths must be reported within 24 hours of the IRB's determination that the death was unexpected or within 10 working days if the IRB has not yet made a determination about whether the death was unexpected. Definition of Unexpected Death: The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of this Handbook.
- Any unanticipated problem involving risks to subjects or others that result in a substantive action by the IRB.

RESPONSIBILITY

IRB Coordinator will:

- Draft notification if appropriate, to individuals and agencies of the event
- Conduct initial review of Adverse events, unanticipated problems or protocol deviations for problems that require pre-review and action prior to a convened IRB meeting and notification to higher authority.

The Chair or designee will pre-review all Adverse Events or Unanticipated Problems triaged by the IRB Coordinator involving Risk to Participants or Others for immediate action and present the action taken (if any) to the full IRB at a convened meeting.

IRB members will determine if the event represents a serious adverse event or unanticipated problem involving risks to subject or others.

Program Assistant is responsible for sending our letters to Investigators and appropriate individuals and agencies.

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4.13 RECRUITMENT OF PARTICIPANTS

It is the policy of the PVAMC Human Research Protection Program to protect the rights and safety of research participants, including privacy and data security.

1. EQUITABLE SELECTION OF SUBJECTS

To approve research, the IRB must determine that the selection of subjects is equitable. This is the concept of “Justice” from the Belmont Report. In making this determination, the IRB should evaluate the purposes of the research, the research setting, and the inclusion/exclusion criteria.

The IRB should be especially cognizant of the problems of research involving vulnerable subject populations (mentally disabled, pregnant women, fetuses, prisoners, economically disadvantages, educationally disadvantaged). Generally, a population that stands no chance of benefiting from the research should not be selected to assume the risk.

In addition, the IRB should be cognizant of the scientific and ethical justification for excluding classes of persons who might benefit from the research.

The IRB should be 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. The IRB should also ensure that subjects are not taken from one group of people because it is convenient.

The IRB should be 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.

(Note: With regard to children, it is VA policy that children cannot be included in VA-approved research unless Chief Research and Development Officer has granted a waiver. See VHA Handbook 1200.05, Appendix D, dated July 31, 2008.)

At the time of initial review and continuing review, the IRB considers subject selection criteria to ensure that subject selection criteria are appropriate to the purposes of research and consistent with VA and DHHS policies.

This facility prohibits compensation to investigators, physicians and other health care providers for identifying/enrolling subjects.

Military personnel require additional protections; refer to Section 5, Vulnerable Populations, I. Military Personnel for guidance.

2. ADVERTISING FOR SUBJECTS

All advertisements, including audio and video tapes, and flyers intended to recruit subjects for approved research projects will be reviewed and approved by the IRB prior to release. IRB review and approval of listings of clinical trials on the Internet is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information.

The IRB will review the final copy of printed advertisements, and the final audio/video taped advertisements to assure that advertisements do not

1. State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol
2. Make claims, explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation.
3. Make claims, explicitly or implicitly, that the drug, biologic or device is known to be equivalent or superior to any other drug, device or biologic.
4. Use terms such as “new treatment,” “new medication” or “new drug” without explaining that the test item is investigational.
5. Promise: free medical treatment”: when the intent is to say participants will not be charged for taking part in the investigation.

Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Advertisement to recruit participants should be limited to the information the prospective participants need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements:

1. The name and address of the clinical investigator or research facility
2. The condition under study or the purpose of the research
3. A brief list of participation benefits (e.g. a no-cost health examination.)
4. The time or other commitment of the participants, and
5. The location of the research and the person or office to contact for further information.

No advertisement includes any exculpatory language. Any credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to the participants who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not

withdrawn. The IRB should determine that the amount paid as a bonus for completion of the study is reasonable and not so large as to unduly induce participants to stay in the study when they would have otherwise withdrawn. Compensation for participation in a trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

3. PAYMENT TO SUBJECTS

(Adapted from VHA HANDBOOK 1200.05, Section 12)

The PVAMC IRB shall review any proposed payments to research subjects associated with the research that they oversee. Payments to research subjects may not be of such an amount as to result in coercion or undue influence on the subject's decision to participate. Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation. For example, payment may not be withheld as a condition of the subject completing the research. If the subject withdraws early, payment must be prorated to reflect the time and inconvenience of the subjects participation up to that point.

The IRB allows nonveterans to be entered into VA-approved research studies only when there are insufficient veterans available to complete the study.

VA policy prohibits paying patients to participate in research when the research is an integral part of a patient's medical care and when it makes no special demands on the patient beyond those of medical care. Finders fees and bonus payments are not permitted. Payment may be permitted, with the approval of the IRB, in the following circumstances:

- *There is no direct subject benefit* - When the direct intention of the study to be performed is not to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice of affiliated, non-VA institutions is to pay subjects in this situation.
- *Others being paid* - In multi-institution studies, where 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 subject volunteers is appropriate.
- *Transportation Expenses* – When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

- *Payments not coercive* - Payment must not be coercive, in the sense of persuading subjects to take risks they might not otherwise be willing to take.

A. Procedure

Principal Investigators who wish to pay research subjects must indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, must:

1. Substantiate that the proposed payments are reasonable and commensurate with the expected contributions of the subject;
2. State the terms of the subject participation agreement and the amount and schedule of payment in the VA informed consent document (Form 10-1086); and
3. Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran subject to volunteer for the research study; and
4. Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study.

The IRB will review all proposals involving the payment of subjects (in excess of reimbursement for travel) in light of the above policies. The deliberations will be recorded in the IRB minutes.

5. COMPENSATION FOR ENROLLING SUBJECTS

The FDA requires a sponsor in a marketing application of any drug, device, or biologic to submit certain information on financial interests and arrangements of clinical investigators conducting studies to FDA. This includes any relationship between the study outcome and the value of the compensation made to the investigator.

This facility requires that Principal Investigators and their staff disclose any financial interests or arrangements of concern to the IRB. The PVAMC Investigator Conflict of Interest Disclosure Worksheet serves this purpose, and must be completed by the Principal Investigators, on-site co-investigators and research staff submitted with all initial IRB applications.

6. CONTACTING POTENTIAL PARTICIPANTS

- A. Investigators and study personnel may not contact veterans via phone calls, e-mails, or other communications to ask for or to confirm personal information.
- B. Investigators must restrict their telephone and other contacts with research participants (both veteran and non-veteran) to only those procedures and data elements outlined in IRB approved protocols. In these contacts, the Investigators or study personnel may not request social security numbers.
- C. Investigators and study personnel must make initial contacts with research

participants (veteran and non-veteran) in person and/or by letter prior to any telephone contact and provide a telephone number or other means that veterans can use to verify the validity of the study. One source of information about clinical trials that can be shared with veteran is <http://www.clinicaltrials.gov/> where VA clinical trials are listed. The research participants may also be informed to contact the PVAMC Research Office for more information regarding the validity of study.

- D. Informed consent documents need to include information about where and how a veteran could verify the validity of a study and authorized contacts.
- E. After recruitment and during the follow-up phase, a researcher should begin calls by referring to previous contacts and the information provided on the informed consent form.

RESPONSIBILITIES

The IRB is responsible for the review of the methods of contacting research participants for both initial contact and continuing contact as part of the study.

Investigators are responsible for protecting the confidentiality, privacy and data security of all research participants.

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4.14 Emergency Use of a Test Article

The FDA regulations exempt research from prior IRB review for the use of a test article in a life-threatening situation in which no standard acceptable treatment is available and there is insufficient time to obtain IRB approval. FDA requirements for emergency use of a test article must be met {21 CFR 56.101(d); 21 CFR 56.102(d); 21 CFR 104(c)} must be met. The IRB requires notification of any emergency use of a test article to evaluate whether the situation met the FDA regulatory requirements that allow exemption from IRB review. FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had time to convene a meeting. However, if subsequent use of the test article is contemplated on the same subject or others, a complete IRB application must be submitted for full board review prior to any additional use of the test article. The IRB will make the determination that the activity meets the HHS and VA definition of research, and thereby, subject to HHS and VA regulations.

1.0 DEFINITIONS

- a. Emergency Use: The use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.
- b. Unapproved Use: Use of a drug, biologic, or device in a way or on a population different from that for which it was approved by the FDA.
- c. Test Article: Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.
- d. Life-Threatening: Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

d. Severely Debilitating: Diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

2.0 PROCEDURES

A. Prior to Administration of the Emergency Use of the Test Article:

- Emergency use of an investigational drug or biologic requires an IND (Investigational New Drug Application). The principal investigator (PI) must obtain an IND number from the manufacturer, if possible. If the manufacturer elects not to name the PI on the IND, the PI must then contact the FDA directly for an IND or obtain evidence of an IND Exemption.
- Emergency use of an investigational device requires an IDE (Investigational Device Exemption). Therefore, the principal investigator must contact the manufacturer to determine if the product can be made available for use under the company's IDE. If an IDE does not exist, the FDA expects the principal investigator to determine the following:
 - whether the criteria for emergency use have been met;
 - assess the potential for benefits from the unapproved use of the device and to have substantial reason to believe that benefits exist; and
 - assure the decision of the principal investigator that an "emergency" exists is not based solely on the expectation that IDE approval procedures may require more time than is available.
- If an investigational device is being used, the investigator is responsible for assuring that the device sponsor/manufacturer notifies the FDA immediately after an unapproved device is shipped for emergency use.
- PIs are strongly encouraged to contact the IRB Chair or the designated physician member to act as Chair if the Chair is not a physician to review whether the circumstances will follow regulatory requirements for the emergency use of test article, discuss how written informed consent will be obtained, or whether circumstances meet the exception to the requirement for informed consent. The IRB Chair (or physician member Chair designee) will discuss the circumstances with the PI as to whether FDA regulatory requirements are met before advising the PI to proceed with administration of emergency use of the test article.
- The principal investigator must enter a progress note into the subject's medical record documenting that the conditions of emergency use of a

test article are met. The progress note will contain, at a minimum, the following information:

- The subject is in a life-threatening situation,
- There is no standard acceptable treatment available,
- There is not sufficient time to obtain IRB approval,
- Discussion with IRB Chair or physician member Chair designee if the Chair is not a physician whether regulatory requirements were met (if applicable),
- Rationale for test article use,
- The diagnosis and test article to be used, and
- Contact information for the principal investigator

The PI must obtain the consent of the subject or the legally authorized representative of the subject and enter a progress note into the subject's medical record documenting the informed consent process as required by VHA 1200.05. No subject may receive an investigational drug, biologic, or device without obtaining informed consent from the subject or the subject's legally authorized representative unless the principal investigator and an independent physician who is not otherwise participating in the emergency use certify in writing all four of the following specific conditions to the IRB within 5 working days after the use of article and in a progress note entered into the subject's medical record:

1. The subject is confronted by a life-threatening situation, necessitating the use of the test article,
 2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject,
 3. Time is not sufficient to obtain consent from the subject's legally authorized representative, and
 4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
- If time is not sufficient to obtain the independent physician determination before use of the test article, the principal investigator must enter a progress note into the subject's medical record certifying the previous four conditions and rationale for proceeding without an independent physician determination. The actions of the PI must be reviewed and evaluated in writing by an independent physician within 5 working days following use of the test article.
 - The PI must provide a copy of the subject's signed informed consent form or a copy of the progress note entry if informed consent was not obtained, and order for the test article prior to the investigational

pharmacist dispensing the investigational drug or biologic under this emergency use of a test article policy. A VA Form 10-9012 must also be submitted with the principal investigator's signature if an investigational drug or biologic is prescribed. No approval signatures will appear on VA Form 10-9012 because the emergency use does not represent IRB or R&D Committee approval.

- Any subsequent use of the investigational product at the institution will have prospective IRB review and approval.

B. Principal Investigator Reporting Requirements Following Administration of the Emergency Use of a Test Article

- Emergency use of all test articles must be reported to the IRB. The following written certification documenting emergency use of a test article must be submitted to the IRB by the PI within 5 working days:
- A written certification containing the items listed in Section A above must be received from the PI to the IRB office within 5 days after the request for emergency use of the test article has been received by the IRB Chair. If a certification is not received within 5 days, the IRB Coordinator will contact the investigator on Day 5 to obtain the status of the emergency use and reiterate reporting procedures to the principal investigator. In addition to the above named criteria, the certification must also include the following information:
 - Name of investigational drug, biologic, or device
 - Subject's diagnosis and outcome if known,
 - Name of test article used,
 - Rationale for test article use,
 - IND number or IDE number (if applicable),
 - Supporting documentation of IND or IDE number, FDA correspondence, or sponsor correspondence,
 - Any adverse events or unanticipated problems,
 - Likelihood of needing to use the test article again,
 - Copy of the signed informed consent form (if applicable),
 - Copy of the subject's progress note entry if informed consent not obtained
 - All adverse events and unanticipated problems associated with the emergency use of the test article must be reported to the IRB as described in the IRB Standard Operating Policies.
 - Other information about the subject or emergency use of the test article if not included in the preceding forms

C. IRB Chair Responsibilities Following Confirmation of Emergency Use Request of a Test Article

Review the follow-up report to determine whether FDA regulatory requirements are met. The IRB Chair (or physician Chair designee if the Chair is not a physician) is responsible for making the following evaluations:

- The emergency use of the test article met the FDA criteria allowing the exemption from IRB review.
- Written informed consent was obtained and documented.
- If written informed consent was not obtained by applying the exception from informed consent requirements for emergency use of a test article, the situation met the FDA criteria.
- IF FDA regulations were not met, the matter will be handled according to IRB policies and procedures for non-compliance.

The IRB Chair (or physician Chair designee) has the authority to require an additional 30-day follow-up report from the Principal Investigator that includes information of the subject's outcome and any adverse events or unanticipated problems.

- If subsequent use of the investigational drug is contemplated, a complete IRB application must be submitted for full board review prior to any additional use of the test article.
- Arrange for full committee notification on next available IRB meeting agenda.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 5: Vulnerable Subjects

October 19, 2011

In accordance with VHA Handbook 1200.05 and 38 CFR 16.111(b), the IRB considers the following classes of subjects to be vulnerable to coercion or undue influence:

- (1.) Pregnant women and fetuses;
- (2.) Prisoners;
- (3.) Children;
- (4.) Mentally disabled and those with impaired decision-making capacity;
- (5.) Economically disadvantaged; and
- (6.) Educationally disadvantaged.

When research targets vulnerable populations, the IRB will obtain the scientific and ethical reasons for their inclusion, and will determine whether their inclusion is justified and will evaluate if additional safeguards are included to protect their rights and welfare.

When the IRB reviews research that involves subjects likely to be vulnerable to coercion or undue influence, the IRB Chair and/or Coordinator will indicate who evaluates each protocol and ensures that at least one IRB member knowledgeable about or experienced in working with such subjects will be present at the meeting.

Research involving children is not permitted to be conducted at the Providence VA Medical Center by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer and the research is in accordance with DHHS Subpart D (see VHA Handbook 1200.05, Paragraph 48).

Research involving the prospective recruitment of prisoners is not permitted at the PVAMC. If during the course of a research study a participant becomes incarcerated, the investigator must provide the IRB and ACOS for R&D justification as to why this participant must maintain contact during their incarceration. The ACOS and/or AO for R&D will contact the Office of Research and Development at VA Central Office to request a waiver by the Chief Research and Development Officer to contact the incarcerated participant. The ACOS, AO or other Research Administrative person will inform the IRB and investigator of the request outcome in writing within 5 days of Central Office notification (see VHA Handbook 1200.05, Paragraph 47).

Permission to conduct international research involving human subjects or human biological specimens must be obtained from CRADO prior to initiating the research. Instructions for requesting permission to conduct international research are found in VHA Handbook 1200.05, Paragraph 56.

Research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue) is not permitted to be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities at the Providence VAMC per VHA Handbook 1200.05, Paragraph 45.

Research related to pregnant women is not permitted at the PVAMC.

A. Fetuses

Research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue), or related to in vitro fertilization, cannot be conducted by VA investigators while on official duty or at VA facilities, or at approved off-site facilities.

B. Pregnant Women

(1.) For research involving the participation of pregnant women as research subjects, the IRB will:

- i. Determine that the proposed research meets the requirements;
- ii. Determine that adequate provisions have been made to monitor the risks to the subject and the fetus; and
- iii. Determine that adequate consideration has been given to the manner in which potential subjects are going to be selected, and that adequate provisions have been made to monitor the actual informed consent process, such as:
- iv. Overseeing the actual process by which individual consents required by this policy are secured, either by approving enrollment of each individual into the activity or by verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed; and
- v. Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

(2.) Activities related to pregnant women will not be undertaken unless:

- i. Appropriate studies on animals and non-pregnant individuals have been completed and data for assessing potential risks to pregnant women and fetuses is provided.

- ii. The purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal, and, in all cases, is the least possible risk for achieving the objectives of the activity.
- iii. Individuals engaged in the activity will have no part in:
 - Any decisions as to the timing, method and procedures used to terminate the pregnancy; or
 - determining the viability of the fetus at the termination of the pregnancy, or introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy.
- iv. No inducements, monetary or otherwise, may be offered to terminate the pregnancy for purposes of the research activity.

(3.) No pregnant woman may be involved as a subject in a research activity unless:

- i. The purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs;
 - or
- ii. The risk to the fetus is minimal.
- iii. The mother and father are legally competent and have given their full informed consent after having been fully informed regarding the possible impact on the fetus, except that the father's informed consent need not be secured if:
 - a. The purpose of the activity is to meet the health needs of the mother;
 - b. His identity or whereabouts cannot reasonably be ascertained;
 - c. He is not reasonably available; or
 - d. The pregnancy resulted from rape.

C. Prisoners

- (1.) Prisoners are considered a vulnerable population because both their incarceration, and the constraints imposed on them during their incarceration, may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Accordingly, research in which the subject is a prisoner cannot be conducted by VA investigators while on official duty or at VA facilities, or at approved off-site facilities.
- (2.) If an investigator enrolls a subject in a research protocol and the subject subsequently becomes incarcerated, the IRB must be notified. The subject will be removed from the study unless the IRB finds that it is in the best interest of the subject to continue participating.

D. Children

VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of care to veterans. Accordingly, research

in which the subject is a child cannot be conducted by VA investigators while on official duty or at VA facilities, or at approved off-site facilities unless a waiver is obtained from the Chief Research and Development Officer and the research be in accordance with 45 CFR Part 46, Subpart D 46.401-46.409.

E. Mentally Disabled Persons or those Persons with Impaired Decision-Making Capacity

- (1.) Research involving subjects who are mentally ill or subjects with impaired decision-making capacity warrants special attention. Research involving these populations frequently presents greater than minimal risk; may not offer direct medical benefit to the subject; and may include a research design that calls for washout, placebo or symptom provocation. In addition, these populations are considered to be vulnerable to coercion or undue influence.
- (2.) In order to review such research, the IRB membership will include at least one member who is an expert in the area of the research and one member who is knowledgeable about and experienced in working with the mentally impaired or those with impaired decision-making capacity. The IRB may utilize consultants to ensure appropriate expertise, such as a member of the population or a representative of an advocacy group for that population.
- (3.) Research involving persons with impaired decision-making capacity will only be approved when the following conditions apply:
 - i. Only incompetent persons or persons with impaired decision-making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research, unless there is a scientifically sound rationale. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
 - ii. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent persons or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

- iii. Procedures have been devised to ensure that participants' representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision-making capacity. Health care agents [appointed under Durable Power of Attorney for Health Care (DPAHC)] and next-of-kin, or guardians, must be given descriptions of both the proposed research and the obligations of the person's representative. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.
- (4.) The IRB will make a determination in writing of each of the criteria listed above. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives.
- (5.) For some subjects, decision-making capacity may fluctuate. For subjects with fluctuating decision-making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. Conversely, if a subject regains decision-making capacity, the investigator must obtain informed consent from the subject.
- (6.) Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representative. Under no circumstance may subjects be forced or coerced to participate.
- (7.) Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent) (per VHA Handbook 1200.05, July 31, 2008):
 - i. Such consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note.
 - ii. The practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
 - iii. Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.
 - iv. If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

F. Economically Disadvantaged

For research involving economically disadvantaged subjects, special care must be taken to assure that the financial inducements offered for participation do not constitute the sole grounds for the subject's participation in the research protocol. Financial inducements should not cause subjects to assume risks that they would not otherwise accept.

G. Educationally Disadvantaged

The consent form for educationally disadvantaged subjects should be written with special attention to assure that terminology has been sufficiently simplified. The investigator should present key elements of the informed consent orally to ensure comprehension.

H. Prisoners of War

DoD regulations prohibit the involvement of prisoners of war as human subjects in research.

A Prisoner of War is a person as defined in Articles 4 and 5 of the Geneva Convention Relative to the Treatment of Prisoners of War of August 12, 1949. In particular, one who, while engaged in combat under orders of his government, is captured by the armed forces of the enemy.

I. Military Personnel

DoD regulations require the following additional protections for military research participants (including temporary, part-time, and intermittent appointments) in order to minimize undue influence:

- Officers are not permitted to influence the decision of their subordinates.
- Officers and senior non-commissioned officers may not be present at the time of recruitment.
- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman is present.
- When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
 -
 - Prohibit an individual from receiving pay of compensation for research during duty hours.
 - US military personnel may be compensated for research if the subject is involved in the research when not on duty.

J. Protection of Vulnerable Populations

When some or all of the participants, mentally disabled persons or persons with impaired decision-making capacity, and economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence.

When a vulnerable group is studied, the IRB assures that an expert on that group is represented on the IRB .

- The IRB staff checks the agenda before the meeting, and if a vulnerable population is involved, the IRB staff ensure that an IRB member or consultant knowledgeable about or experienced with the involved vulnerable population will review the research and be at the meeting, or defers the research to another meeting at which such representation cannot be obtained. If a vulnerable population is the subject of the research, the protocol should be referred to the IRB Administrator, IRB Chair, AO, or ACOS R&D to determine if an appropriate expert is on the IRB as required for IRB review.
- In order to conduct research on a prisoner all the conditions under subpart C must be met:
 - At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, the IRB must determine that additional safeguards have been included in the study to protect the rights and welfare of these subjects and whether inclusion of vulnerable subjects is justified. If the research proposes to exclude classes of persons who might benefit from the research, the IRB must consider the scientific and ethical reasons for this exclusion. Safeguards include, but are not limited to:

- (1.) Surrogate consent;
- (2.) Subject assent;
- (3.) Use of a consent monitor;
- (4.) Use of a medical monitor;
- (5.) Use of a waiting period;
- (6.) Inclusion of a patient advocate in the informed consent process; and
- (7.) Presenting key elements of the informed consent orally.

The IRB will also evaluate research submitted for initial review, continuing review or review of modifications to judge whether the study targets other classes of subjects who may be vulnerable to coercion or undue influence, but are not identified in the federal regulations. For example, if the investigator wishes to include students in their subject pool, the IRB must consider that their participation

is sought only under circumstances that minimize the possibility of coercion or undue influence and assess whether equivalent alternatives to participation are available.

If during the course of a research study a participant becomes incarcerated, the investigator must provide the IRB and ACOS for R&D justification as to why this participant must maintain contact during their incarceration. The ACOS and/or AO for R&D will contact the Office of Research and Development at VA Central Office to request a waiver by the Chief Research and Development Officer to contact the incarcerated participant. The ACOS, AO or other Research Administrative person will inform the IRB and investigator of the request outcome in writing within 5 days of Central Office notification.

Employees of the Providence VA Medical Center or of the investigator will be considered vulnerable if the quality of their performance is being studied or if their consent could involve undue influence or coercion.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 6: IRB Communication and Notification
2011

October 19,

1. COMMUNICATION FROM THE IRB

A. To the Investigator for Additional Information

The IRB may request additional information from the Principal Investigator or sponsor to enable appropriate review. Communications to the investigator will be in writing and will be signed by the Chair or a voting member for the IRB who reviewed the research.

B. To the Investigator Conveying IRB Decision

1. The IRB promptly communicates in writing and in e-mail conditions of approval or reasons for tabling or disapproval of all initial submissions, continuing reviews, and modification requests. The communications include the reasons for non-approval and suggested changes to the protocol and/or consent form required before approval will be reconsidered.

The IRB promptly communicates in writing and in e-mail decisions concerning serious adverse events, unanticipated problems or protocol deviations that require action by the investigator.

The IRB promptly communicates in writing and in email modification request approvals, as these are not reviewed by the R&D Committee.

2. Exempt and Expedited Decisions: The Investigator will be notified by e-mail and in writing of the decision as soon as possible after review of the proposal.

3. Non-Human Research Determinations: The IRB Chair or designee reviews all requests that check "no" to meeting the definition of human research as defined in VHA Handbook 1200.05: 3 (g) and 38 CFR 16.102 (f) of the code of federal regulations. Upon validating the non-human designation, the IRB communicates in writing this decision to the investigator. The IRB also places this action on the next IRB agenda under the Non-Human Research category of the agenda.

4. Notification of final approval: Following final approval at the Research and Development Committee, the ACOS will generate approval letters for initial reviews and continuing reviews, as no research can be initiated without this approval. Investigators are notified in writing and via e-mail promptly after the

review of the protocol. The IRB-approved consent form will be stamped with the approval and expiration date and the HIPAA Authorization form will be stamped with approval date and submitted to the Investigator with the final approval letter along with a letter stating an overview of the Investigator's responsibilities.

5. Expiration: The investigator will be sent a notice that the study has expired and that no study activity can take place while in the expired state. The notice will include the options to either close the study officially or reinstate the study using the Reinstatement SOP procedures.

C. To the Institution Administration Conveying IRB Decision

The IRB submits reviewed and approved minutes to the Providence VAMC Research and Development Committee. Committee minutes are reviewed and approved by the Medical Center Director, who is the Institutional Official responsible for the Human Research Protection Program. Reviewed and approved Research and Development Committee minutes and IRB minutes are submitted to the Department of Veterans Affairs Headquarters, when requested. The Providence VAMC Compliance, Business Integrity Committee and Quality Management Committee also review IRB committee minutes.

D. To Sponsor of Research Conveying IRB Decision

Unless specifically required by a sponsor or the IRB no written notifications of IRB decisions will be provided to sponsors. The Principal Investigator usually serves as the communications link between the IRB and the sponsor. The sponsors and Principal Investigators agree to such linkage when they sign Forms FDA -1571 and FDA -1572.

E. Investigator and IRB Communications

The Investigator and their staff can call or e-mail the IRB office at anytime with questions, concerns or suggestions. The phone call or e-mail will be triaged to the appropriate personnel. All attempts will be made to respond to messages or e-mails within 48 hours.

2. APPEAL OF IRB DECISIONS

A. Criteria for Appeal

Appeals of an IRB decision to disapprove or table a submission may be addressed to the IRB in person or in writing. If you are submitting a resubmission, the documentation should be accompanied by a cover letter signed by the Principal Investigator detailing changes made or a justification of why recommended revisions were not made. Principal Investigators and/or sponsor representatives may attend, or be requested to attend the IRB meeting at which their submission is being reconsidered to provide additional information. They may not be present for the vote. There is no limit to the number of times a protocol may be re-submitted for review to achieve approval.

Criteria for appeal of suspension or termination of research privileges must be submitted to the Providence IRB. The IRB will vote to sustain or lift privileges. Their findings will be submitted to the Research and Development Committee for 2nd level review and to the Medical Center Director for concurrence. The Director has the final action on all appeals.

B. To Whom Appeal is Addressed

Chairman, Providence VAMC Institutional Review Board (151)
Providence VA Medical Center
830 Chalkstone Avenue
Providence, RI 02908

C. How Appeal is Resolved (override of IRB disapproval by external body/official is prohibited)

The IRB shall approve or disapprove all appeals. All research activities, including any IRB decision regarding an appeal is subject to further review and approval or disapproval by the Providence VAMC Research and Development Committee. The R&D Committee may not approve research if it has not been approved by the IRB but it may disapprove previously IRB approved research. No one may approve research that has not been approved by the IRB.

3. RESPONSIBILITY

Administrative Officer and IRB Coordinator are responsible for overseeing all IRB communications.

The Chairperson will:

- Review and sign IRB decision communications.

Program Assistant will:

- Generate appropriate correspondence in response to IRB meetings and decisions.
- Distributing IRB correspondence to appropriate parties.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 7: Informed Consent

October 19, 2011

INFORMED CONSENT

The investigator's responsibilities for obtaining informed consent are outlined in VHA Handbook 1200.05, Appendix C, entitled, Procedures for Obtaining Informed Consent. There are no Rhode Island state laws regarding the content of research informed consents. However, R.I. Gen. Laws § 23-17.5-7 (2008); and R.I. Gen. Laws § 23-17.16-2 (2008) require written informed consent for studies involving nursing home patients, mental health patients, and home health care patients. The IRB will consult with the PVAMC legal counsel to resolve differences between federal and local laws.

An investigator may not involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the person or the person's legally authorized representative. [*Note: This policy does not apply to research ruled exempt from Institutional Review Board (IRB) review or if a waiver of consent was obtained.*] Informed consent must be obtained prior to initiation of any research-related activity, including clinical screening procedures that are performed solely for the purposes of determining eligibility for research.

The IRB has the authority to observe the consent process, including direct observation and review completed consent forms as found in the medical record, pharmacy files, and research folders.

Research Involving Human Subjects with Surrogate Consent

Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a participant (surrogate consent). This policy is designed to protect human subjects from exploitation and harm, and at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have impaired decision – making capacity (e.g., a study of treatment options for comatose persons can only be done with incompetent subjects).

(Under VHA Handbook 1200.05, such consent may be obtained from: a health care agent appointed by the person in a DPAHC or similar document; court-appointed guardians of the person, or from next-of-kin in the following order of priority, unless otherwise specified by applicable state law: spouse, adult child (18 years or older),

parent, adult sibling (18 years or older), grandparent, or adult grandchild (18 years or older). (Note: The preceding list contains the only entities who are allowed to provide consent for research purposes.) RI Gen. Law § 15-12-1 (2008) states that the age of majority is 18 years of age and R.I. Gen. Law § 23-4.6-1 (2008) indicates that any person who is 16 or older or who is married may consent to routine emergency medical or surgical care. For purposes of PVAMC research involving surrogate consent, VA regulations apply. The IRB will consult with the PVAMC legal counsel for research that occurs outside of Rhode Island to determine appropriate state laws regarding legally authorized representatives.

The Principal Investigator determines who may inform the prospective participant about all aspects of the trial and who may conduct the informed consent process. In addition to the mandatory trainings, the PI must properly train the project staff member(s) in all study and consent procedures and indicate these responsibilities on the Scope of Practice form for the project staff member(s). Scope of Practice forms are submitted to the IRB Chair and maintained in the Research Office in the Training folders. The investigator delegating these responsibilities is reminded that they are ultimately responsible for these activities.

Data Retention when Participants Withdraw from a Clinical Trial

When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.

The investigator 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 would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

The investigator must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document.

If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, an investigator 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.

A. The Proposed Informed Consent Document

(1) Guidance on Informed Consent.

a. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

b. The information that is given to the subject or the representative will be in language understandable to the subject or the subject's representative. Language that approximates a sixth grade reading level is usually appropriate for most populations. When the population of potential research subjects includes those who do not speak English, the information given to the subject should be translated into the subject's native language.

c. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative 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.

d. VA Form 10-1086 or electronic version of VA Form 10-1086, VA Research Consent Form, must be used as the consent form, and all required elements must be completed including the subject's (or representative's) signature, investigator's signature, and witness's signatures. The consent form must be approved by the IRB and the official stamped version, with both approval and expiration date, must be used.

(2) Basic Elements of Informed Consent

[21 CFR 50.25(a)(b)] requires that in seeking informed consent basic criteria must be met. The information that should be provided to each subject has been incorporated in a VA FORM 1086 informed consent template. The template is available via the Research SharePoint site and must be submitted in the proscribed format for review by the IRB. The elements of informed consent are:

a. The name of the study and the name of the study's Principal Investigator(s)

b. A statement that the study involves research, and 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 which are experimental.

c. A description of any reasonably foreseeable tangible or intangible risks and/or discomforts to the subject including for example privacy risks (legal, employment, and social).

- d. A description of any benefits to the subject or to others that may reasonably be expected from the research.
- e. A disclosure of appropriate alternative procedures of courses of treatment, if any that might be advantageous to the subject.
- f. A statement describing the extent to which confidentiality of records identifying the subject will be maintained and how they will be maintained. If federal agencies (FDA, OHRP, ORO, or other regulatory entities) may have access to the records, this should be stated. If a Federal Certificate of Confidentiality has been obtained, the nature and limits of this protection should be described.
- g. If any compensation or reimbursement of patient costs is to be provided, this should be stated and described in detail, including the amount and schedule of payments and the circumstances under which subjects may or may not receive compensation.
- h. For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs and where further information may be obtained.
- i. A statement of any additional costs to the subject that may result from participation in the research. If the research is a VA approved research project (VA funded, funded by another sponsor, DoD, or unfunded), appropriate language consistent with 38 CFR 17.85 must be included in the consent form. Suggested language is as follows: "The VA medical facility shall provide necessary medical treatment to you as a research subject injured as a result of participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees in accordance with Federal regulations." This applies to research subjects that are either veterans or non-veterans.
- j. If the research's sponsor is other than the VA (including for profit organizations) information on whether the sponsor will be responsible for research-related injury must be addressed in the contract, but VA language consistent with 38 CFR 17.85 will be included in the consent form. It is strongly suggested that the investigator make provisions for coverage of such cost in research awards and contracts. For Department of Defense sponsored studies, the disclosure includes that provisions for research-related injury follow the requirements of the DoD component.
- k. An explanation of whom to contact for answers to questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject. At least one contact's name and phone number must be other than the investigators or study personnel.

l. A place for the signature of the subject and for the signature of a subject's legally authorized representative, if the subject is unable to sign. A written signature is required unless the IRB has specifically waived or modified the informed written consent process. A legally authorized representative is defined as: an individual or 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. For the purposes of this Handbook, a "legally authorized representative" includes not only persons appointed as health care agents under Durable Power of Attorney for Health Care (DPAHC), court appointed guardians of the person but also next-of-kin in the following order of priority: spouse, adult child (18 years of age or older), parent, or adult sibling (18 years of age or older).

m. A place for a witness to sign and a witness's written signature, unless the IRB has specifically waived or modified the informed written consent process. The witness should not have a direct relationship with the Principal Investigator and other personnel, such as being an immediate supervisor or subordinate, relative or close co-worker. The witness should directly observe the informed consent process and be able to attest that the subject read and understood the nature of his/her involvement in the research.

n. 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.

o. A statement that a veteran-subject will not be required to pay for treatment received as a subject in a VA research program. Investigators should note, however, that veterans in the "discretionary work load" category are subject to making a co-payment if so indicated by a means test (Reference M-1, Part 1, Chapter 4, Admissions – Hospital and Domiciliary Care, paragraph 4.02, or

(3). Additional Elements of Informed Consent.

One or more of the following elements of information also shall be provided to each subject when appropriate:

a. A statement that the particular treatment or procedure may involve currently unforeseeable risks to the subject, or to the embryo or fetus if the subject is or becomes pregnant.

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

c. Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. This shall include information about the anticipated use of all data and specimens already collected.

e. A statement that significant new findings developed during the course of the research which may relate to this subject's willingness to continue participation will be provided to the subject.

f. The approximate number of subjects involved in the study.

g. If the investigators believe that the human biologic specimens obtained could be part of or lead to the development of a commercially valuable product or if the specimens will be retained after the end of the study, guidance and regulations found in the VHA Handbook, "Banking of Human Biological Specimens" must be followed.

[Note: Storage or banking of all human biologic specimens must be in accordance with current VA policy. If genetic testing is to be done, requirements pertaining to genetic testing must also be met.]

h. A statement regarding any payment the subject is to receive and how payment will be made.

i. If applicable, the financial or other arrangements with a sponsor or institution that may pose a conflict of interest.

j. The statement that about where and how a participant (veteran and non-veteran) could verify the validity of a study and authorized contacts.

B. Documentation of the Informed Consent

1. The long form informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by:

- a. The subject or the subject's legally-authorized representative,
- b. A witness whose role is to witness the subject's or the subject's legally authorized representative's signature, and
- c. The person obtaining the informed consent.

2. VA Form 10-1086, or an electronic version of the VA Form 10-1086, must be used as the consent form. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the subject's signature; if the same person needs to serve both capacities then a note to that effect must be placed under the witness' signature line.

- a. The consent form must be the most recent IRB-approved consent form. The approval is documented by the use of a stamp on each page of the consent form that indicates the date of the most recent IRB approval of the form. A VA Form 10-1086 that has been amended during the approval period will indicate the approval date of the amendment rather than the date of approved protocol. The IRB maintains a copy of the approved form in its records.
- b. The original signed consent form must be filed in the subject's case history.
- c. A copy of the signed informed consent must be provided to the subject or the subject's legal representative.

3. Flagging a Medical Record. The IRB needs to determine if the patient's medical record (electronic or paper) must be flagged to protect the subject's safety by indicating the subject's participation in the study, and the source of more information on the study.

The IRB may not want to require the medical record to be flagged if:

- The subject's participation in the study involves:
 - Only one encounter,
 - Only the use of a questionnaire, or
 - The use of previously collected biological specimens.
- The identification of the patient in a particular study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk.

The PVAMC IRB limits flagging of medical records to PVAMC participants receiving any intervention (behavioral, physical or pharmacologic).

4. Consent Form: Except when the informed consent requirements are waived or altered, the consent form may be either of the following:

- a. Written Consent Document: VA Form 10-1086 (either paper or electronic version), must be used as the consent form and must embody the elements required by this policy and 38 CFR 16.116. In addition, it must contain any additional elements as required by the IRB. The consent form may be read to the subject or subject's legally authorized representative. The investigator must ensure that the subject (or representative) is given adequate opportunity to read the form and ask questions before signing it.
- b. Written Consent Document (Short Form). See Section C below for specific details

5. Progress Note. A progress note documenting the informed consent process must be placed in the subject's medical record.

- a. At a minimum, the progress note must include:

- i. The name of the study,
 - ii. The person obtaining the subject's consent,
 - iii. A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,
 - iv. A Statement that the study was explained to the subject, and
 - v. A statement that the subject was given the opportunity to ask questions.
- b. An entry must also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated. (*Note; Consent and entry notes can be combined when both occur at the same visit*).

C. Written Consent Document with a Short Form

With IRB approval, the short form may be used in place of the full written consent document. A shortened written consent document stating that the elements of informed consent required by VHA Handbook 1200.05 and 38 CFR 16.116 have been presented orally to the subject or the subject's legally-authorized representative. When this method is used, there must be a witness to the oral presentation. This process includes the following:

(a) The IRB must approve a written summary of what is to be said to the subject or the subject's legally-authorized representative.

(b) Only the short form is to be signed by the subject or the subject's legally-authorized representative.

(c) The witness must sign both the short form and a copy of the summary. The person actually obtaining the consent must sign a copy of the summary. The original short form and summary must be filed, as required.

(d) A copy of the summary must be given to the subject or the subject's legally-authorized representative, in addition to a copy of the signed short form.

(e) For participants who do not speak English, the witness is conversant in both English and the language of the participant.

D. Waiver or Alteration of Informed Consent Requirements

Under the Common Rule, the IRB has authority to alter or waive the requirement to obtain informed consent. However, FDA regulations do not provide for a waiver or alteration of the informed consent process; the only exception from obtaining informed consent is for planned emergency research, which is not allowed in the VA and exception from informed consent requirements used with emergency use of a test article. In addition, DoD regulations prohibits an exception from consent in emergency medicine research unless a waiver is obtained from the Secretary of Defense. Accordingly, for research that is not subject to FDA regulations, the IRB may approve an investigator's request to waive or alter the requirement to obtain informed consent if the investigator demonstrates with specificity that the criteria under 38 CFR 16.116(c) or (d) are met. To approve such a request, the IRB must find and document the following per 38CFR16.116(d):

a) The research involves no more than minimal risk to the participants;

b) The waiver or alteration will not adversely affect the rights and welfare of the

- subjects;
- c) The research could not practicably be carried out without the waiver or alteration; and
- d) Whenever appropriate, participants will be provided with additional pertinent information after participation.

Alternatively, the IRB may find and document the following for research that is not subject to FDA regulations per 38CFR16.116(c):

- a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials;
- b) The research is designed to study, evaluate, or otherwise examine public benefit or service programs, 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; and
- c) The research could not practicably be carried out without the waiver or alteration.

DoD regulations prohibit the waiver of the consent process if the research participant meets the definition of “experimental subject” (see Section 1. Role and Function, 10.A) unless a waiver is obtained from the Secretary of Defense. If the research participant does not meet the definition of “experimental subject”, a waiver of the consent process may be granted once the above requirements are met.

The IRB will not approve a request to waive or alter the informed consent process if the investigator does not demonstrate in the protocol application that each of the criteria is met for the given protocol.

E. Waiver of Documentation of Informed Consent

The IRB may waive the requirement to obtain **written documentation** of informed consent. This provision can be used only for the waiver of **documentation** of consent, not for waiver or alteration of the consent process itself. To approve a waiver of documentation, the IRBs must find and document in its minutes that the protocol-specific justification for waiving documentation satisfies regulatory criteria. Specifically, the IRB must determine the regulatory basis for the waiver as one of the following:

- a) Consistent with the Common Rule (38 CFR 16.117(c)) (but not the FDA regulations),
 - (i) the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; in this case each subject will be asked whether he/she wants documentation linking the subject with the research, and the subject’s wishes will govern; or
 - (ii) the research presents no more than minimal risk of harm to

participants and involves no procedures for which written consent is normally required outside of the research context; or

- b) For research subject to the Common Rule and FDA regulations, the IRB must find and document that the research involves no more than minimal risk to subjects and involves no procedures for which written consent is normally required outside of the research context. (38 CFR 16.117(c), 21 CFR 56.109(c))

In all cases in which the documentation requirement is waived, the IRB may require the principal investigator to provide subjects with the written consent document (i.e., with an option to sign the consent document) or a written statement regarding the research.

RESPONSIBILITY

Primary and Secondary reviewers are responsible for careful review of all incoming informed consent documents and for communicating revisions at the IRB meeting needed to bring documents into compliance.

IRB Members/Alternatives are responsible for review of informed consent documents prior to the IRB meeting.

Program Assistant is responsible for stamping each page of VA Form 10-1086 indicating the date of the most recent IRB approval of the document. A VA Form 10-1086 that has been amended during the approval period will indicate the approval date of the amendment rather than the date of approved protocol.

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Providence, Rhode Island

Section 8. Information and Data Protection

October 19, 2011

RESEARCH & DEVELOPMENT INFORMATION AND DATA PROTECTION

Adequate provisions must be taken to protect the privacy of subjects and to maintain the confidentiality of individually-identifiable data. The provisions must meet all local, state and federal regulations.

As part of the protocol review, the IRB, with guidance from the Information Security Officer and Privacy Officer, will determine that privacy and confidentiality of research participants are maximized. The IRB will assess whether the planned research has adequate provisions to protect the privacy and confidentiality by evaluating methods used to obtain information about participants and about individuals who may be recruited to participate in studies, by evaluating the use of personally identifiable records, by evaluating methods to protect confidentiality with regard to identifying and recruiting participants, obtaining information about participants, and storing and using data. The IRB will consider the nature, probability and magnitude of harms that would be likely to result from a disclosure of collected information outside research. The IRB will evaluate the effectiveness of proposed techniques to protect the anonymity of subjects (including coding systems, etc.)

1. Research incident reporting requirements related to Research Information

Protection: All research incidents related to Research Information Protection must be reported as prescribed in VHA Handbook 1058.01 as listed below:

a. **Research Information Protection Incidents – Immediate Reporting.** Within 1 hour of becoming aware of any situation described in subparagraphs a(1) and a(2) below, 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) **Unauthorized Access.** Unauthorized access to VA sensitive information, (including unauthorized use, disclosure, transmission, removal, theft, or loss) related to research, including but not limited to protected health information, individually-identifiable private information (as defined in 38 CFR 16.102(f)(2)), and confidential information protected by HIPAA, or by Federal records requirements at 38 U.S.C. §§5701, 5705, and 7332.

(2) **Reportable Network Security Operations Center (NSOC) Incidents.** Any research-related incident reportable to the Office of Information and Technology (OI&T) NSOC that impacts, inhibits, or compromises network security.

(3) **Notification of Facility Director.** The ACOS for Research 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 research information protection incident described in preceding subparagraph a(1) or a(2) above, and must ensure that the facility ISO and facility PO have also been notified.

(4) **Written Report.** Any oral report or notification of an incident described in subparagraph a(1) or a(2) above must be followed as quickly as possible by a written report.

b. Research Information Protection Incidents – Regular Reporting.

Independent of the reporting requirements described in subparagraph a. above, members of the VA research community are required to ensure that any situation described in subparagraphs b(1), b(2), and b(3) below has been reported in writing to the ACOS for Research, the facility ISO, and the facility PO within 5 business days of becoming aware of the situation,

(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. Subsequent reports to ORO based on findings made by entities external to the facility must include a copy of the official findings.

(2) **Other Deficiencies.** Any other deficiency that substantively compromises the effectiveness of the facility's research information protection program. (VHA HANDBOOK 1058.01)

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

(4) **Reports to Facility Director.** Within 5 business days of discovering, receiving a credible report of, or otherwise becoming aware of any situation described in subparagraphs b(1), b(2), or b(3) above, the ACOS for Research 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 facility PO have also been notified.

c. Reports to ORO RO. Within 5 business days of being notified of them, the facility Director must report the research information protections incidents listed in subparagraphs a and b above to the appropriate ORO RO, and must ensure that the facility ISO and facility PO have also been notified.

2. Notification of Veterans

The ACOS for R&D, ISO, Privacy Officer, other facility and/or VISN leadership will follow the Office of Information and Technology Standard Operating Procedures, for notifying veterans of a breach of personal information.

3 . Information Acquisition and Provisions for Maintaining Confidentiality

The investigator must address in the protocol the collection, use and/or storage of research information including subject identifiers and PHI. There must be specific information on all sites where the data will be used or stored, how the data will be transmitted or transported, specifically who will have access to the data, and how the data will be secured. If copies of the data will be placed on laptops or portable media a discussion of the security measures for these media must be included.

- The requested data may only be used in a manner that is consistent with the approved research.
- All forms used to gather information, whether by interview or dataset review, are to be included with the protocol submission for IRB review.

In most cases, data should be coded so that there are few if any subject identifiers. Access to data should be limited to only qualified personnel. According to VHA Handbook 1605.1, Appendix B, (1) the code or other means of record identification is not derived from, or related to, information about the individual and the code is not otherwise capable of being translated so as to identify the individual; (2) the code, or other means of re-identification, is not used or disclosed by VHA for any other purpose; and (3) VHA does not disclose the mechanism (e.g., algorithm or other tool) for re-identification. In addition, the code or other means of record identification is not considered one of the identifiers that must be excluded for de-identification. NOTE: When disclosing de-identified data to non-VA entities this code needs to be removed.

Research subjects or veterans names, addresses, and Social Security Numbers (real or scrambled) may only be stored within the VA and on VA servers. If the data is coded, the key linking the code with these identifiers must also be stored within the VA.

If data obtained can be potentially incriminating to subjects, a Federal Certificate of Confidentiality should be obtained for the protection of subjects.

4. Data Classification

Data is considered de-identified when it meets the requirements in VHA Handbook 1605.1 and the Common Rule.

- A. According to VHA Handbook 1605.1, Appendix B, “health information that does not identify an individual and to which there is no reasonable basis to believe that the information can be used to identify an individual is NOT individually-identified health information”.

De-identification requires the completion of the following steps:

- A person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually-identifiable applying such principles and methods:

- Determines that the risk by which the information could be use, alone or in combination with other reasonably available information, by anticipated recipient to identify an individual who is a subject of the information is very small; and Documents the methods and results of the analysis that justify such determination.

VHA does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information. All eighteen identifiers of the individual or of relatives, employers, or household members of the individual are removed. See HIPAA Worksheet form category (b) for a complete list of identifiers that must be removed.

- B. The Common Rule defines identified information as “Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and 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, or reputation.
- C. VA Office of Research & Development, Key Points Related to Privacy & IT Security, pg. 3 of 11 June 4, 2007 defines Sensitive Information as:
- a. Sensitive Information. Also see sensitive research data. VA sensitive information is all Department data, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, alteration, or destruction of the information.
- The term specifically 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 and the HIPAA Privacy Rule and information that can be withheld under the Freedom of Information Act.
 - Examples of VA sensitive information include the following: 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 information protected by the deliberative process privilege, attorney work-product privilege, and the attorney-client privilege; and other information which, if released, could result in violation of law or harm or unfairness to any individual or group, or could adversely affect the national interest or the conduct of federal programs.

- Clarification: The definition of Sensitive Information does not include ALL Department data. It does include Department data that require protection due to risk of harm that could result from inadvertent or deliberate disclosure, alteration, or destruction of the information. The term includes information whose improper use or disclosure could adversely affect the ability of an agency to accomplish its mission, proprietary information, records about individuals requiring protection under various confidentiality provisions such as the Privacy Act and the HIPAA Privacy Rule and information that can be withheld under the Freedom of Information Act.
- b. Sensitive research data. All research data that contain information about human subjects AND have not been de-identified are considered sensitive research data.
- Other research data including de-identified human subjects data, animal data, and data developed during other types of studies may be sensitive depending on what information is contained within the data, the topic of the research, and its impact of the VA.
 - An evaluation must be completed to identify any VA sensitive information that may be developed during the research. If VA sensitive information will be developed a risk assessment for impact of a data breach should be conducted. Based on this risk assessment appropriate privacy and security safeguards must be put in place. The local Privacy Officer and Information Security Officer (ISO) should be consulted to assist in developing such safeguards.

5. Data Access

1. 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. Investigators are referred to the PVAMC Privacy Officer for specific guidance to resolve privacy issues that may arise at any time, including protocol preparation, review process and post-approval.
2. Persons not employed by VA can be given access to medical and other VA records for R&D purposes only within the legal restrictions imposed by such laws as the Privacy Act of 1974 and 38 U.S.C. This applies to information requested from national, VISN, and local databases or sources. If the research involves human subjects, the requesting non-VHA Investigator must have received IRB approval for the research. If the research does not meet the definition of Human Subject Research per the Common Rule, the non-VHA Investigator's institution must approve the research. Requests for such use must be submitted to the CRADO in VA Central Office at least 60

days before access is desired. Requests for information filed pursuant to the Freedom of Information Act ordinarily require a response within 10 working days. VA guidelines and policy must be followed when making such requests to allow for a timely reply. This does not apply to those individuals having access for the purpose of monitoring the research. Obtaining and using records must be in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information. All related requests will be forwarded from the investigator to the ACOS. The ACOS (or AO, if so delegated by the ACOS) is responsible for generating the request to be submitted to the CRADO.

6. Storage of Data and Storage Media

1. VA sensitive research data may not be stored, transported, transmitted or accessed outside the VA unless applicable permissions have been obtained from the investigator's supervisor, the ACOS/R&D, the Privacy Officer and the Information Security Officer. This includes storage on non-VA computer systems/servers, desk top computers located outside the VA, laptops, or other portable media.
2. Data transfer to a non-VA computer system/server or site must only occur after the required permissions have been obtained and the transfer must be in compliance with requirements found in VA Handbook 6500.
3. VA Private Information is not transmitted by remote access unless VA-approved protection mechanisms are in place. See the ISO for further technical guidance.
4. Passwords or other authentication information are not stored on remote systems unless encrypted.
5. Approved encryption software is used when employees use VAGFE or non-VA OE in a mobile environment and VAPI is stored on the computer, file or electronic storage media. See the ISO for further technical guidance.
6. When VA data is stored on non-VA systems, the system must meet all requirements set forth in FISMA including the required Certification and Accreditation of the system.
7. Access to the VA Virtual Private Network (VPN) may be approved by an employee's supervisor through the ISO. Both VA owned Government Furnished Equipment and non-VA owned other equipment (OE) may be used to access the VA VPN through the CITRIX Access Gateway (CAG). The ISO will disable the remote access account if it is not used for a period of 90 days and removes the account if it is not used for 6 months. Please see the ISO for additional information and for a VA issued equipment, other equipment, security and encryption software, appropriate storage equipment and media, and VPN access.

8. Only VA personnel may access VA-owned equipment used to process VA information or access VA processing services.
9. Employees may only use computer and electronic storage media configured to conform to all VA security and configuration policies to store, transport, transmit, use and access VA Protected Information. See the ISO for further guidance.
10. Use of VAGFE and OE meets all requirements listed in VA Handbook 6500 This includes, VAGFE and OE that contain VAPI are equipped with, and use, VA-approved antivirus software and a personal firewall that is configured with a VA approved configuration. If the device is connecting remotely is simultaneously attached to a second network, the secondary network computer/devices are provided with similar AV and host-based/personal firewall protection. All VAGFE devices attempting to access the VA intranet remotely via One-VA VPN client have the AV and Host-based Intrusion Prevention System software installed and current, including critical updates and patches, in order to be granted access to the VA intranet. See the ISO for further technical guidance.
11. Employees using non-VA OE devices to access the VA intranet remotely comply with the policy set forth in "Anti-Virus/Firewall accepted for use on non-government owned equipment attached to the One-VA VPN". See the ISO for further technical guidance.
12. Employees using VAGFE or non-VA OE to connect to the internet outside the regular work site ensure that the computer is protected by a firewall.
13. Employees must inform the ISO immediately upon discovery when handling viral or malicious code infection.
14. Employees cannot simultaneously connect to VA and one or more non-VA networks while using VAGFE. See the ISO for further technical guidance.
15. Wireless routers and access points, even if not used at the enclave perimeter, are configured in accordance with the "VA Wireless and Handheld Device Security Guideline". See the ISO for further technical guidance.
16. Upon termination of required access privileges, supervisors confirm and notify the ISO that the employee has returned all VAGFE related to remotely access the VA system.
17. All Research Information residing on laptops, or other portable media, or personal computers not within a VA health care facility must be encrypted and password protected. Please note that the original data may not be stored on laptops or portable media and all laptops regardless of their location within or outside the VA must be encrypted if used for any research purposes.

18. Employees must make redundant copies (“backups”) of essential business data and software on remote or mobile computers at regular intervals. The backups must be stored in protected locations other than where the device is stored. Please see the ISO for more information.
19. When no longer needed, VA information classified as VA sensitive is destroyed by a method of rendering it unreadable, undecipherable, and irretrievable as prescribed in the most recent version of “Fixed Media Sanitation”. When media is to be destroyed, contact the ISO for further instructions.
20. Portable computers must be physically locked to an immovable object when the computers must be left in a meeting room, or other semi-public area to which individuals other than the authorized employee have access.
21. When traveling, employees must keep their portable computers or storage devices in their possession and not in checked baggage. It is also advised to maintain a copy of the authorization letter with your computer.

7. Alternative Work Locations

1. Employees may be authorized to remove confidential and Privacy Act-protected data from the PVAMC with prior written authorization from their supervisor and Information Security Officer (ISO).
2. Employees who are authorized to remove confidential and Privacy Act-protected data from the PVAMC are required to take all precautions to safeguard that data until it is returned.
3. The confidential and Privacy Act protected data must be properly encrypted and password-protected in accordance with VA policy. The ISO must be consulted to ensure that the data is properly encrypted.

8. RESPONSIBILITY

The ACOS is responsible for:

- Reporting loss or theft of research data/information or portable media to the Medical Center Director.
- Notify the PO, ISO and other facility and/or VISN leadership when the need to notify veterans in the case of a breach of personal information.

The ISO is responsible for:

- Advising investigators, research staff and the IRB on information technology issues, including but not limited to portable media encryption software, off-site data storage, and storage media.
- The ISO will also certify by signature, data use, storage, security and transfer plans submitted by the PI to the IRB.

The Privacy Officer is responsible for:

- Advising investigators, research staff and the IRB on Privacy issues, including de-identification of data and review of privacy related documentation approved by the IRB.
- Providing approval or disapproval of the HIPAA Authorization submitted by investigators to the IRB.
- Follow procedures on notifying veterans in the case of a breach of personal information.

The Investigator is responsible for adhering to the Information Security and Privacy regulations, mandates, and Handbooks.

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Section 9: Investigator Responsibilities

October 19, 2011

An **Investigator** is any individual who conducts research involving human subjects including, but not limited to, the PI, co-PI, and Local Site Investigator (LSI). The investigator must uphold professional and ethical standards and practices, adhere to all applicable Federal requirements, and comply with applicable local policies and procedures.

A **VA investigator** is any individual who conducts research approved by the VA R&D committee while acting under a VA appointment on VA time, including full and part-time employees, without compensation (WOC) employees, and individuals appointed or detailed to VA under the Intergovernmental Personnel Act (IPA) of 1970. In addition, a VA investigator must comply with all applicable VA and VHA requirements, and comply with applicable local VA facility policies and procedures.

A **Principal Investigator (PI)** is a qualified person or persons designated by an applicant institution to direct a research project or program and who usually writes the grant application. The PI oversees scientific, technical, and day-to-day management of the research. In the event of an investigation conducted by a team of individuals, the PI is the responsible leader of that team. **NOTE:** *FDA considers Investigator and PI to be synonymous.*

A **Co-Principal Investigator (Co-PI)** is when one of two or more PIs share equally in the accountability for a study. A Co-PI must meet the same qualifications of a PI.

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

The PI, LSI, and investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including this SOP, regarding the conduct of research and the protection of human subjects. The basic ethical principles governing research involving human subjects are described in the following documents:

The Nuremburg Code: The modern history of human subject protections began with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremburg Military Tribunal developed ten principles known as the Nuremburg Code. The Code is significant in that it addressed: 1) the necessity of voluntary consent on the part of the human subject, and

2) the personal responsibility of any individual “who initiates, directs, or engages in the experiment” to ensure the quality of consent.

The Declaration of Helsinki: Similar principles have been articulated and expanded in later codes, such as the World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, revised 1975, 1983, 1989, 1996, 2000). This code calls for prior approval and ongoing monitoring of research by independent ethical review committees. The Declaration states that all subjects and controls should not receive less than the best effective therapy.

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

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

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 (45CFR46.102(d)).

LISTING OF INVESTIGATOR RESPONSIBILITIES

a. The investigator must have the appropriate training and be credentialed to conduct research involving human subjects by a program that meets all VA requirements. They must also ensure the proper training and credentialing of their research staff as per VHA Directive 2009-054. When applicable, the investigator has read and understands the information in the investigator’s brochure including the potential risks and side effects of the drug. If required training lapses for PI’s or their staff, a letter is issued requiring the individual to stop all study work until training is back in good standing. A copy of this letter goes to the individual, the PI and the RCO. Once training is back in good standing, the training program assistant signs off on the letter maintained in the training folder so that study work can resume.

For Department of Defense sponsored projects, Investigators and project staff are responsible for completing any additional Department of Defense required trainings as noted by the DoD when the grant is awarded.

b. Research investigators shall prepare protocols giving complete descriptions of the proposed research. The investigator must develop a research plan that is scientifically valid, minimizes risk to the subjects while maximizing benefits, and contains a description of the data and safety monitoring plan that includes the reporting mechanism of adverse events (AE's) to the IRB, and when required to Office of Research Oversight (ORO), VA Central Office of Research and Development (ORD), and other Federal agencies or sponsors. The research plan must include provisions for the adequate protection of the rights and welfare of prospective subjects and ensure that pertinent laws and regulations are observed. Minimizing risks should include using procedures already required for diagnostic or treatment purposes in the protocol where possible. The Investigator determines that the resources necessary to protect participants are present before conducting the research study. Samples of informed consent documents and HIPAA authorization documents must be included with protocols. For DHHS supported clinical trials, the DHHS approved sample consent form must be submitted (if one exists). The plan may vary depending on the potential risks, complexity, and nature of the study. A Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) needs to be part of the monitoring plan when required by NIH or FDA. The use of a DSMB or DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are particularly high-risk, or vulnerable populations are included. Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, the investigator will provide information to the IRB on appropriate additional safeguards to protect the rights and welfare of these subjects. If a DSMB is used, all events must be reported to the DSMB and a summary of the DSMB findings must be submitted to the IRB and other entities as required.

c. The investigator is responsible for the submission of a clearly defined protocol and any relevant Merit Reviews or grant applications as well as a clearly defined consent procedure to the IRB for review.

d. The Principal Investigator must provide enough specific information for the IRB to assure adequate resources are in place for human research protection, care of research participants, and safety during the conduct of the research, i.e. facilities, staff, supplies, space, etc.

e. The investigator is responsible for obtaining initial and continuing IRB review and approval and for submitting to the IRB requests for modifications to the protocol. All proposed research involving human subjects must be reviewed and approved by the IRB and the R&D Committee prior to initiation of the research project. The investigator is expected to know the date of the continuing review and to be aware that IRB approval for the project expires automatically when the continuing review does not occur prior to the expiration date.

f. If the investigator requires a waiver or alteration of the HIPAA Authorization, the investigator must provide the IRB with information sufficient for the IRB to find that such waiver or alteration is necessary. The IRB must document its decision in IRB approval letter and the reviewer checklist filed in the protocol file. *[From: VHA HANDBOOK 1200.05 REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH]*

g. All advertisements, including audio and video tapes, and flyers intended to recruit subjects for approved research projects will be reviewed and approved by the IRB prior to release. IRB review and approval of listings of clinical trials on the Internet is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information.

The IRB will review the final copy of printed advertisements, and the final audio/video taped advertisements to assure that advertisements do not

1. State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol
2. Make claims, explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation.
3. Make claims, explicitly or implicitly, that the drug, biologic or device is know to be equivalent or superior to any other drug, device or biologic.
4. Use terms such as “new treatment,” “new medication” or “new drug” without explaining that the test item is investigational.
5. Promise: free medical treatment”: when the intent is to say participants will not be charged for taking part in the investigation.

Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Advertisement to recruit participants should be limited to the information the prospective participants need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements:

1. The name and address of the clinical investigator or research facility
2. The condition under study or the purpose of the research
3. A brief list of participation benefits (e.g. a no-cost health examination.)
4. The time or other commitment of the participants, and
5. The location of the research and the person or office to contact for further information.

No advertisement includes any exculpatory language. Any credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to the participants who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. The IRB should determine that the amount paid as a bonus for completion of the study is reasonable and not so large as to unduly induce participants to stay in the study when they would have otherwise withdrawn. Compensation for participation

in a trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

h. Conflict of Interest. Investigators and all project staff will complete a research Conflict of Interest Financial Disclosure Form as part of their application to conduct research. Investigators will be familiar with and comply with the stipulations in the PVAMC standard operating procedure document titled: Conflicts of Interest.

Investigators may be asked to take the following actions to better protect subjects:

- (1) Disclosure of the financial interest to potential subjects;
- (2) Not conducting the proposed research, or halting it if it has commenced;
- (3) Reducing or otherwise modifying the financial (equity or royalty) stake involved;
- (4) Increasing the segregation between the decision-making regarding the financial and research activities;
- (5) Requiring an independent data and safety monitoring committee or similar monitoring body;
- (6) Modifying of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change in investigator; or
- (7) Establishing a research monitoring process, so that the research can be closely scrutinized to ensure that potential conflicts do not undermine the integrity of the work and/or of the PVAMC.

i. The investigator is also responsible for ensuring education to employees conducting research (including mandated human subjects protection and good clinical practice training if applicable), the supervision of delegated responsibilities (i.e., data collection, consent process, etc.), and the conduct of the research. PI's must also ensure their research staff has a signed Scope of Practice form and are credentialed to perform the duties assigned per VHA Directive 2009-054.

j. Principal Investigators (PI's) are responsible for assuring that their research and research team complies with all IRB decisions, conditions, and requirements. The PI must apprise the study staff of their responsibility to report non-compliance to the IRB Coordinator or the AO/ R&D or ACOS R&D in the absence of the IRB Coordinator. (Non-Compliance refers to failure to follow medical center policies and procedures, regulatory requirements, ethical treatment of subjects, the requirements of VHA Handbook 1200.5, or the requirements or determinations of the IRB.) PI's must notify the Research Service office when anyone is added to the research staff and when anyone departs from their research staff. PI's are responsible to assure that all research staff, as applicable, are properly appointed and undergo processing by Human Resources Services and Employee Health.

k. Researchers are responsible for adhering to the approved protocol, notifying the IRB of protocol deviations, and unanticipated problems involving risks to subjects. Forms to report these events can be found on the PVAMC Research SharePoint and local shared drive. Investigators are responsible to assure that the research is conducted in compliance with all applicable regulatory requirements. Research

investigators are responsible for reporting the progress of the research to the IRB as often as and in the manner prescribed by the IRB but no less than once per year.

For research in which the local PI is the lead investigator, as in cooperative or multi-center studies, the investigator is responsible for notifying the IRB of the status of research at other sites through submission of: approval letters from all other sites; reports of protocol deviations and violations, serious adverse events and unanticipated problems involving risks to subjects; progress and other reports.

I. Investigator must observe policies for proper documentation, handling and use of investigational drugs, biologics, and devices as specified below:

(1) Investigator Responsibilities for Investigational Drug Studies

1. An investigator is responsible for: [21 CFR §312.60]
 - Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.
 - Protecting the rights, safety, and welfare of participants under the investigator's care.
 - The control of drugs under investigation.
2. An investigator shall administer the drug only to participants under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. [21 CFR §312.61]
3. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it. [21 CFR §312.61]
4. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants. [21 CFR §312.62]
5. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59. [21 CFR §312.62]
6. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. [21 CFR §312.62]
7. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes.
8. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
9. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication,

- until 2 years after the investigation is discontinued and FDA is notified. [21 CFR §312.62]
10. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under §312.33 to submit annual reports to FDA on the progress of the clinical investigations. [21 CFR §312.64]
 11. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately. [21 CFR §312.64]
 12. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation. [21 CFR §312.64]
 13. The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study. [21 CFR §312.64]
 14. An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. [21 CFR §312.66]
 15. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human participants or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.
 16. An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 21 CFR §312.62. [21 CFR §312.68]
 17. The investigator is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
 18. If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution. [21 CFR §312.69]
 19. As defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR §812.3(g)). Investigational devices include transitional devices (21 CFR §812.3(r)) that are objects of investigations.

20. However, for the purposes of VHA Handbook 1200.05, an investigational device may be an approved device that is being studied for an unapproved use or efficacy. [VHA Handbook 1200.05 3.j]
21. An investigational drug is a drug or biological drug that is used in a clinical investigation. The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug. [21 CFR §312.3] A copy of the IND or IDE will be provided by the investigator to the IRB copied from the sponsor's protocol or, the sponsor's response to the investigator's specific request for the IND or IDE.
22. However, for purposes of VHA Handbook 1200.05, an Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial. [VHA Handbook 1200.05 3.k]
23. An Investigational New Drug (IND) used to refer to either an investigational new drug application or to a new drug that is used in clinical investigations.]
24. IND is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." [VHA Handbook 1200.05 3.m]
25. See 21 CFR §312.2(a)-(b) for applicability and exemptions. [VHA Handbook 1200.05 3.m]
26. Use of investigational drugs must be conducted according to FDA IND regulations and other applicable FDA and VA regulations. [VHA Handbook 1200.05 14]
27. The use of drugs in research must be carried out in a responsible manner. [VHA Handbook 1200.05 14.a]
28. An investigational drug for clinical research use is one for which the principal investigator or a sponsor has filed an IND application. [VHA Handbook 1200.05 14.b]
29. Pursuant to these regulations an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or on earlier notification by FDA that the clinical investigation may begin (21 CFR §312.40). [VHA Handbook 1200.05 14.b]
30. For purposes of VHA Handbook 1200.05, an investigational drug is also defined as an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial. [VHA Handbook 1200.05 14.b]
31. The principal investigator is responsible for informing Pharmacy Service that IRB and Research and Development Committee approval has been obtained. [VHA Handbook 1200.05 14.c]
32. This must be through the use of VA Form 10-1223, Report of Subcommittee on Human Studies, to be sent to Pharmacy Service. [VHA Handbook 1200.05 14.c]
33. VA Form 10-9012, Investigational Drug Information Record or superseding forms must be provided to the pharmacy by the principal investigator as required in VHA Handbook 1108.04. [VHA Handbook 1200.05 14.c]

34. In addition a signed copy of VA Form 10-1086, must be sent to Pharmacy Service to document each participant's consent to participate in the study. [VHA Handbook 1200.05 14.c]
 35. The principal investigator must inform the Chief, Pharmacy Service, and the Research and Development Committee when a study involving investigational drugs has been terminated. [VHA Handbook 1200.05 14.d]
 36. All applicable requirements in VHA Handbook 1108.04 must be met. [VHA Handbook 1200.05 14.e]
 37. FDA regulations address the treatment use of an investigational drug (not approved for marketing, but under clinical investigation for a serious or immediately life-threatening disease condition) in patients for whom no comparable or satisfactory alternative drug or other therapy is available. Use of the investigational drug for this purpose must meet all applicable FDA requirements. [VHA Handbook 1200.05 14.g]
 38. The storage and security procedures for drugs used in research must follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations. [VHA Handbook 1200.05 14.a]
- (2) Investigator responsibilities for device studies
1. An investigator is responsible for: [21 CFR §812.100]
 2. Ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations.
 3. Protecting the rights, safety, and welfare of participants under the investigator's care.
 4. The control of devices under investigation.
 5. An investigator may determine whether potential participants would be interested in participating in an investigation, but shall not request the written informed consent of any participant to participate, and shall not allow any participant to participate before obtaining IRB and FDA approval. [21 CFR §812.110]
 6. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. [21 CFR §812.110]
 7. An investigator shall permit an investigational device to be used only with participants under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it. [21 CFR §812.110]
 8. A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. [21 CFR §812.110]
 9. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall

- return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs. [21 CFR §812.110]
10. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: [21 CFR §812.140(a)]
 11. All correspondence with another investigator, an IRB, the sponsor, a monitor or FDA, including required reports.
 12. Records of receipt, storage use or disposition of a device that relate to:
 13. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
 14. The names of all persons who received, used, or disposed of each device.
 15. Why and how many units of the device have been returned to the sponsor, repaired or otherwise disposed of.
 16. Records of each participant's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
 17. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
 18. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
 19. A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.
 20. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
 21. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
 22. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. [21 CFR §812.140(d)] However, if the investigator is maintaining the records, they must be maintained per Veterans Affairs Record Control Schedule (RCS) 10-1.
 23. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in 21 CFR §812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under

- 21 CFR §812.140, including the requirements of 21 CFR §812.145. [21 CFR §812.140(e)]
24. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.
 25. §812.145 Inspections.
 26. An investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept). [21 CFR §812.145(a)]
 27. An investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. [21 CFR §812.145(b)]
 28. An investigator shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [21 CFR §812.145(c)]
 29. An investigator shall prepare and submit the following complete, accurate, and timely reports: [21 CFR §812.150(a)]
 30. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
 31. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
 32. An investigator shall submit progress reports on the investigation to the sponsor, the monitor and the reviewing IRB at regular intervals, but in no event less often than yearly.
 33. An investigator shall notify the sponsor and the reviewing IRB (see 21 CFR §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with §812.35(a) also is required.
 34. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

35. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
36. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete and current information about any aspect of the investigation.
37. An Investigational Device Exemption is an FDA-approval of the application for an exemption that permits an un-marketed device to be shipped for the purpose of doing research on the device. [VHA Handbook 1200.05 3.i]
38. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR §812, other applicable FDA regulations, and applicable VHA regulations. [VHA Handbook 1200.05 15]
39. The principal investigator is responsible for compliance with all applicable FDA regulations. [VHA Handbook 1200.05 15.i]

m. Investigators involving human beings as subjects in research must obtain legally effective authorization for the use and disclosure of the subject's PHI (HIPAA Authorization or waiver from the IRB).

n. Obtaining Informed Consent. (Please see Section 7: Informed Consent for detailed requirements for Informed Consent)

(1) Investigators wishing to involve human beings as subjects in research will obtain legally effective informed consent of the subject or the subject's legally authorized representative (unless a waiver is authorized by the IRB). (No subjects with Impaired Decision Making Capacity (IDMC) may be enrolled unless prior approval has been received from the IRB.) The principal investigator must ensure the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team actually obtain and document consent. Investigators must inform the IRB of such matters as the timing of obtaining informed consent and of any waiting period (between informing the participant and obtaining the consent) that will be observed.

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

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

o. Documenting Informed Consent

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

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

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

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

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

(2) The original signed consent form must be retained in the investigator's research file under conditions of confidentiality. A copy of the consent form must be given to the subject or the subject's legally authorized representative. A copy or duplicate original of the signed consent form must also be filed in the subject's VA medical record.

p. Screening for impaired decision making capacity will be conducted during all consent interviews. At the request of the investigator, IRB or R&D, specific study related questions may be utilized to screen for understanding and ability to make an informed judgment in the subject's own best interest regarding whether or not to serve as a study volunteer. The questions are generated by the investigator with guidance with the IRB. It is first assumed that prospective subjects have decision making capacity. The Informed Consent Test of Comprehension is used as a tool for screening and is not intended as a medical assessment of decision making capacity. The person obtaining consent, trained in the consent process, will ask comprehension questions of the subject and will sign the form. The form will be maintained in the investigator's study file. Potential subjects who demonstrate impairment in decision making capacity will not be permitted to enroll as subjects unless the IRB has previously approved enrollment of subjects with impaired decision making capacity. In these cases a surrogate must provide consent. In cases where the prospective subject does not demonstrate sufficient decision making capacity, the practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

q. Signed consent forms will be reviewed for quality assurance purposes by the IRB Coordinator who will report findings to the IRB and R&D Committees at least semi-annually. A log of participants recruited during the approval period is submitted at the time of the continuing review.

r. If someone other than the investigator conducts the interview and obtains consent, the investigator must formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity. The investigator remains ultimately responsible, even when delegating the task of obtaining to another individual.

(1)The delegation of the responsibility to conduct the consent interview (and obtain consent) is by completing the Scope of Practice Form.

(a) One is by designating the individual on the VA form: Request to Review Protocol/Proposal. Licensed physicians and medical staff who are credentialed

through VetPro are not required to have a Scope of Practice. All non-licensed clinicians and research staff must be credentialed through VetPro per VHA Directive 2009-054..

(2) **Prior to adding any individuals with the delegated authority to obtain consent**, the additional staff member roles must be submitted to the IRB. The individual may not begin obtaining consent until appointment, credentialing and training have been verified.

s. It is required that research informed consent be documented in the Computerized Patient Record System (CPRS). It is required that research subjects be identified in CPRS.

(1) Researchers must use the CPRS progress note template titled "Research Patient" to document each episode of informed consent.

(a) The note template includes:

Participant in Medical Research Project

For Information, Contact :

Ext :

Date Project Initiated :

Expected Date of Completion :

Description:

(2) When the researcher has completed or ended the patient's involvement in the research, CPRS Management Team (Clinical Applications) should be contacted to have the posting changed to Past Research Patient as instructed on the template.

(3) The "Research Patient" progress notes will be flagged as Clinical Warnings in the clinical alert CPRS postings box at the top right corner of the subject's CPRS cover page.

(4) In addition, all research visits should have an entry in the Subject line of the CPRS progress note with the initial word as "Research" or "General Note

t. All amendments to, or modification of, the research proposal including the consent form must be approved by the sponsor and IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject. The investigator is to promptly report such changes in the protocol to eliminate hazards to the IRB. Any information collected without prior approval of the IRB and R&D Committee may not be used for research data analysis or publication.

u. Serious Adverse Events (SAE) and/or Unanticipated Adverse Events (UAE) must be reported to the IRB and other required entities. If a DSMB or DMC is used, all events must be reported to the DSMB or DMC and a summary of the DSMB or DMC findings must be reported to the IRB and other entities as required. Other AEs, as defined by the monitoring plan in the protocol, must be reported in accordance with the monitoring plan approved by the IRB and as defined in FDA regulations, or other applicable Federal regulations.

v. Investigators are required to report all non-compliance to the IRB Coordinator (or the AO or ACOS R&D in the absence of the IRB Coordinator). This includes noncompliance by study personnel. (Non-Compliance refers to failure to follow

medical center policies and procedures, regulatory requirements, ethical treatment of subjects, the requirements of VHA Handbook 1200.05, or the requirements or determinations of the IRB.)

w. Investigators will immediately report to the research office when a study has been terminated and complete an IRB Request for Continued Approval of Human Use form and check "project has terminated".

x. Investigators will prepare and maintain adequate and accurate study files. Among items to be maintained in the study files are: the protocol; correspondence with the IRB, R&D, Research Safety committee; correspondence with study sponsor; oversight audits and correspondence (FDA, DHHS, etc); amendments; HIPAA Authorizations; Consent forms and DMC plan and forms. A case history for each individual subject shall document that informed consent was obtained prior to participation in the study. In drug trials, case histories will record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The PI maintains records of receipt, use or description of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark, the names of all persons who received, used or disposed of each device, why and how many units of the device have been returned to the sponsor, repaired or otherwise disposed of.. Records of each participants case history and exposure to the device, documents evidencing informed consent, all relevant observations,, a record of the exposure of each participant to the device including the date and time of each use and any other therapy, deviations from protocol and any other records required by the FDA.

y. Research records and raw data shall be retained by the investigator per the Veterans Affairs Record Control Schedule 10-1. Records involving investigational drugs are not to be destroyed until approval by the sponsor has been received. [VHA Handbook, Investigational Drugs and Supplies 1108.04] For FDA regulated research, investigators will permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

z. If the investigator leaves the VA facility the original research records must be retained at the institution.

aa. The principal investigator must identify a qualified clinician to be responsible for all study-related health care decisions. The principal investigator, investigator or other individual may serve as the qualified clinician. Note: This is not required for survey research, retrospective chart review, or other research in which the subject's medical condition is not relevant to, or affected by, the study.

bb. Investigators receiving support from other Federal agencies, such as the National Institutes of Health (NIH), must meet requirements for the protection of human participants of the funding source in addition to those of VA. [VHA Handbook 1200.05 4.c]

cc. Investigators conducting clinical trials should consult with the study sponsor to determine if the clinical trial is or needs to be entered in a national registry. The VA Office of Research and Development (ORD) currently has established processes for registering the trials it sponsors. The studies that have been identified as clinical trials and some observational studies are registered in the National Library of Medicine's [clinicaltrials.gov](http://www.clinicaltrials.gov) (<http://www.clinicaltrials.gov>) registry. It should be noted that in addition to efforts by the U.S. Congress and World Health Organization to increase clinical trials registration, the International Committee of Medical Journal Editors (ICMJE) has issued a statement that it will consider a clinical trial for publication only if it has been registered in a registry that meet certain criteria (http://www.icmje.org/clin_trialup.htm).

dd. External Audits By Regulatory And Granting Agencies (such as: ORO, FDA, OHRP, NIH, NCI, DOD and VA Cooperative Studies Program). This does not include routine monitoring visits from pharmaceutical clinical trial monitors conducted by Clinical Research Associates (CRA's). Before the audit takes place, investigators are to notify the ACOS R&D when external audits by regulatory and granting agencies are scheduled. Reports of audit findings are to be provided to the IRB in a timely manner, but no later than 30 days after the investigator receives the report.

ee. When a human subject becomes a prisoner after the research has commenced, the Principal Investigator shall notify the IRB and local institutional officials to determine the appropriate course of action.

Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB will promptly re-review the protocol in accordance with the requirements of 45 CFR §46, subpart C if the principal investigator wishes to have the prisoner subject continue to participate in the research.

All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of 45 CFR §46, subpart C have been satisfied with respect to the relevant protocol.

In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of 45 CFR §46, subpart C are satisfied.

In order to permit continuation of medications when discontinuing a research medication that might be harmful to a subject who is imprisoned, the investigator should bring the issues to the Chair of the IRB in order to do what is in the best interest of the subject.”

SURROGATE CONSENT FOR PERSON WHO IS INCOMPETENT OR HAS AN IMPAIRED DECISION-MAKING CAPACITY (IDMC)

1. Before an incompetent person or persons with impaired decision-making capacity may be considered for participation in any VA research, the IRB must find that the following conditions are met: IRB composition (IRB composition is an institutional responsibility, provided here for information only)
 - (1) The IRB must include at least one member who is an expert in the area of the research
 - (2) Consider adding a member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population
- b. Research involving persons with impaired decision-making capability (IDMC) may only be approved when the following conditions apply
 - (1) Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. This item [1. b. (1)] comes from VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research. This item is applied at the PVAMC as follows:
 - (a) This means that persons with IDMC must be necessary to the research. If the research can produce valid results without them, then persons with IDMC should not be included. The following sentence in criteria one permits both subjects with IDMC and those who do not have IDMC to be included in the study if there is a compelling reason to do so for the scientific validity of the research. “The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects.”
 - (b) The notification to the IRB for any protocols that may need to include subjects with IDMC must attest to the fact that subjects with IDMC are needed in order to have a representative sample of subjects with the condition/characteristic being studied. (This can include studies with just those with IDMC or both those with IDMC and those who do not have IDMC.)
 - (2) The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant

- (3) Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. The representative must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest
- c. The IRB must make a determination in writing of each of the criteria listed in (1), (2) and (3) of b. above.
- d. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives. Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.
- f. Such consent (from surrogate) may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a **signed and dated progress note**.
- (1) The **practitioner**, in **consultation with the chief of service**, or COS, may determine after appropriate **medical evaluation** that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
- (2) Consultation with a **psychiatrist or licensed psychologist** must be obtained when the determination that the prospective research subject lacks decision-making capacity is **based on a diagnosis of mental illness**.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 10. Quality Assurance

October 19, 2011

Quality Assurance

1. Compliance Activities

1. The Research Compliance Officer conducts compliance audits throughout the year including, but not limited to, the annual informed consent audits and triennial regulatory audits. Other audits may be requested as needed.
2. The goal of the annual informed consent audit is 100% compliance with obtaining all required signatures and dates as required by the IRB policies and procedures. The goals of the triennial regulatory audits include, but are not limited to, 100% compliance with the following: study personnel training, study procedures, including study changes, started after IRB approval, unanticipated problems involving risk to participants or others reported to the IRB according to IRB policies and procedures, and of all study documentation is maintained. Other compliance audits will have goals based upon the nature and type of audit.
3. Compliance audits are reported to the investigator (if applicable), IRB, R&D, ACOS, and other leadership as appropriate (i.e., Medical Center Director). Each party is able to comment and dispute any compliance findings.

2. IRB Quality Assurance Activities

1. The HRPP completes several QA/QI activities throughout the year. These activities are submitted annually to the QM Committee as part of the Research Service Performance Improvement Plan and may change yearly based on need. QA/QI activities include but are not limited to:

Measure	Goal
The percentage of studies tabled by a convened upon its initial review	To identify common issues in order to better educate investigators in protocol submission
Number of protocols assigned per reviewer	To ensure equitable workload amongst members
Percentage of studies conditionally approved by a convened IRB	To identify common issues in order to better educate investigators in protocol submission
Number of continuing reviews and modifications reviewed by a convened IRB compared to those reviewed by expedited review,	To assess workload efficiencies

2. The reports are reviewed by the Medical Center Quality Management Committee, semi-annually.

3. The IRB monitors ongoing staff and subject complaints. All complaints are presented to the IRB and R&D Committee meetings.

4. The IRB monitors the informed consent process by direct observation.

3. Review and Evaluation of Quality Assurance Activities

A. The R&D committee reviews Human Subject Protection Program QA/QI reports for the following:

1. To monitor and measure the effectiveness of the Human Research Protection Program
2. To plan improvements based upon measures of effectiveness
3. To implement planned improvements
4. To monitor and measure the effectiveness of improvements.

B. The QA/QI reports are submitted to the R&D Committee by the IRB Coordinator at the next convened meeting after the QA/QI report is completed.

C. The R&D will document in the minutes acceptance of the reports, request for continuation of the monitoring, or revision of the monitoring plan. The minutes will also document planned improvements and the plan to monitor and measure the effectiveness of improvements.

D. The R&D will communicate its findings, including planned improvements, and the plan to monitor and measure the effectiveness of the improvements in writing to the IRB, with notification to the ACOS and AO for Research.

4. Additional QA/QI Activities

A. The R&D Committee

The R&D Committee may request a QA/QI report during the course of the year. This request is communicated through the IRB in writing.

5. Reports to other PVAMC Committees

Research service submits an annual Performance Plan to the Quality Management office. This plan details the measures that will occur across the research service during the year.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 11: HIPAA Compliance

October 19, 2011

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) HUMAN SUBJECTS RESEARCH POLICIES AND PROCEDURES

1. PURPOSE: To establish a service level policy for conducting research at the Providence VA Medical Center (PVAMC) in accordance with the Health Insurance Portability and Accounting Act (HIPAA) of 1996, also known as the Privacy Rule. The Privacy Rule, while not intended to regulate the conduct of research, does have implications for the use of protected health information in the conduct of research. This policy along with VHA Handbook 1605.1 (Privacy and Release of Information), will help to ensure the proper use and disclosure of VA patients' protected health information (PHI) in research that is conducted at the PVAMC.

2. POLICY: The HIPAA Privacy Rule was effective on April 14, 2003. The final modification to this rule by the Department of Health and Human Services (HHS) was published on August 14, 2002 in the Federal Register (Vol. 67, No. 157, pages 53182-53273).

3. DEFINITIONS:

- a. **Access-** Access is the obtaining or using of information, electronically or on paper or other medium, for the purpose of performing an official function.
- b. **Business Associate** - A business associate is an individual, entity, company or organization who, on behalf of the Veterans Health Administration (VHA), performs or assists in the performance of functions or activities involving the use or disclosure of PHI, or who provides certain services to VHA that involve the disclosure of PHI by VHA. Per Patricia Watts, Office of Research and Development, sponsors are generally not considered business associates because they do not perform or assist in the performance of functions
- c. **Covered Entity** – The VHA is a single covered entity for the purpose of complying with the Privacy Rule. This covered entity includes all VHA hospitals and health care systems.
- d. **De-identified Information** - De-identified information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual.
- e. **Designated Record Set** – A group of records maintained by or for VHA that includes any of the following: medical records; billing records; enrollment, payment, claims, adjudication, and case or medical management records; or information that is used, in whole or part, to make decisions regarding individuals.

- f. **Disclosure** - Disclosure is the release of, transfer of, provision of access to, or divulging in any other manner of information outside VHA. The exception to this definition is when the term is used in the phrase “accounting of disclosures.”
 - g. **Health Information** - Health information includes any information that is: created or received by a health care provider or health plan that relates to the past, present, or future physical or mental health or condition of an individual; part of the provision of health care to an individual; or related to payment for the provision of health care to an individual. This encompasses information pertaining to examination, medical history, diagnosis, findings or treatment, including such information as laboratory examinations, X-rays, microscopic slides, photographs, prescriptions, etc.
 - h. **Individually-identifiable Information** – Individually-identifiable information is any information, including health information maintained by VHA, pertaining to an individual that also identifies the individual and, except for individually-identifiable health information, is retrieved by the individual’s name or other unique identifier. Individual-identifiable health information is covered regardless of whether or not the information is retrieved by name.
 - i. **Individually-identifiable Health Information** - Individually-identifiable health information is a subset of health information, including demographic information collected from an individual, that is:
 - (1) Created or received by a health care provider, health plan, or health care clearinghouse;
 - (2) Relates to the past, present, or future condition of an individual and provision of or payment for health care; and
 - (3) Identifies the individual or a reasonable basis exists to believe the information can be used to identify the individual.
- NOTE:** Individually-identifiable health information does not have to be retrieved by name or other unique identifier to be covered by this SOP.
- j. **Limited Data Set** - A Limited Data Set is protected health information that excludes specific direct identifiers of the individual or of relatives, employers or household members of the individual. A limited data set is not de-identified data. A limited data set can only be used for the purposes of research, public health or health care operations, and can only be disclosed for the purpose of research. The use of a Limited Data Set in research requires IRB approval.
 - k. **Protected Health Information (PHI)** - PHI is individually-identifiable health information maintained in any form or medium. **NOTE:** PHI excludes employment records held by a covered entity in its role as an employer.
 - l. **Research** - For the purposes of this policy, “research” is a systematic investigation, including research development, testing and evaluation, that is designed to develop or contribute to generalized knowledge.
 - m. **VHA Investigator** – A VHA Investigator must be a VHA employee (which includes WOC employees) or contract personnel. To determine if a researcher is a VHA Investigator contact the Research Service Office.
 - n. **Without Compensation (WOC) Appointment** - A WOC appointment is a personnel appointment by which an individual contributes time to VA activities but receives no monetary compensation.

4. RESPONSIBILITIES:

- a. The **Associate Chief of Staff for Research & Development** is responsible for developing and managing policies and procedures for the creation, use and disclosure of PHI for research purposes at the PVAMC.
- b. The **Research and Development Committee (R&D)** is responsible for:
 - (1) The review and approval of policies and procedures regarding the creation, use and disclosure of PHI for research purposes at the PVAMC.
 - (2) The review and approval of all research prior to initiation of the research protocol.
- c. The **Institutional Review Board Chairperson** is responsible for reviewing and determining the appropriateness and approval for submitted requests regarding preparatory and decedent research. The IRB must also ensure the protocol and informed consent form are consistent with the HIPAA authorization.
- d. The **Privacy Officer** is responsible for reviewing and determining the appropriateness and approval for the creation, access, use and disclosure of PHI in research projects submitted to the IRB for review. The Privacy Officer, not the IRB, is responsible for approving the HIPAA authorization.
- e. **VHA Investigators** are responsible for:
 - (1) Adhering to the policies and procedures set forth in the HIPAA Privacy Rule, VA policy, and this SOP.
 - (2) Adhering to the assurances signed and agreed to with any Institutional Review Board form.
 - (3) Ensuring the confidentiality and protection of any VHA patient protected health information that is created, accessed, used and/or disclosed.
 - (4) Ensuring that any VHA patient protected health information is not disclosed to any other person or entity, except as required by law, research oversight or as deemed acceptable by the IRB.
 - (5) Use the requested data only in a manner consistent with the approved research protocol for which the information was requested.
- f. **Research Staff** are responsible for:
 - (1) Adhering to the policies and procedures set forth in the HIPAA Privacy Rule, VA policy and this SOP.
 - (2) Adhering to the assurances signed and agreed to with any Institutional Review Board form.
 - (3) Ensuring the confidentiality and protection of any VHA patient's protected health information that is created, accessed, used and/or disclosed as part of a research project conducted at the PVAMC.
 - (4) Ensuring that any VHA patient protected health information is not disclosed to any other person or entity, except as required by law or research oversight, or as deemed acceptable by the Privacy Officer and IRB.

5. PROCEDURES

a. **Scope of Policy**

This Policy covers all VA patients' PHI, which is or may be created, used or disclosed by, through or during research activities. This policy applies to all VA employees or appointees (including those serving without compensation), and contract personnel at

VA facilities and approved off-site locations who conduct research, assist in the performance of research or otherwise use or disclose PHI in connection with research activities at the PVAMC. In most cases, the prior review and approval of the IRB will be required in the implementation of this Policy.

If a research activity conducted by a Providence VA Medical Center VA Investigator includes the use or disclosure of PHI, the PVAMC Privacy Officer and IRB must approve the use of this information. All PVAMC VA investigators conducting PVAMC IRB-approved research must obtain authority to use or disclose PHI from the potential research subject in a written authorization that is separate from the research consent document unless the IRB waives the requirement for an authorization.

b. Research Use or Disclosure of PHI With Authorization

- (1) As a general rule, a researcher must obtain an Authorization from all participants in research **prior to** the internal use or external disclosure of PHI for any research-related purpose that is not otherwise permitted or required under this Policy.
- (2) Prospective Privacy Officer and IRB review is required of the HIPAA Authorization form.
- (3) An Authorization for Research must be written in plain language, and must contain **all** of the following elements:
 - (a) The identity, i.e., name and social security number, of the individual to whom the information pertains.
 - (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 and/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) or class of persons or office designation(s) authorized to make disclosures of PHI and to use the PHI for research-related purposes. Because the VHA is a single covered entity, use of "VHA" as the releasing entity is acceptable.
 - (d) The name or other specific identification of the person(s) or class of persons or office designation(s) authorized to receive disclosures of the PHI and to use the PHI for research-related purposes;
 - (e) A description of each purpose of the requested use or disclosure of the PHI;
 - (f) An expiration date or event that relates to the individual or the purpose of the use or disclosure of the PHI. Examples of appropriate expiration date language are as follows:
 - (i) The statement "end of research study" or similar language is sufficient if the authorization is for use or disclosure of individually-identifiable health information for research.
 - (ii) The statement "none" or similar language is sufficient if the authorization is for the agency to use or disclose individually identifiable health information, including for the creation and maintenance of a research database or research repository.

- (g) The dated signature of the individual, or someone with the authority to act on behalf of the individual. **Note:** if the Authorization is signed by an authorized representative, include a description of the representative's authority under Rhode Island State law to act for the individual;
- (h) A statement that the individual may revoke the authorization in writing to the Principal Investigator except to the extent that VHA has already acted in reliance on it, and a description of how the individual may revoke the authorization. However, the researcher may continue to use and disclose, for research integrity and reporting purposes, any PHI collected from the individual pursuant to such Authorization before it was revoked, in which case the authorization must include **EITHER**:
 - (i) The exceptions to this right and description of how the individual may revoke his/her authorization, **OR**
 - (ii) A reference to the VHA's notice of privacy practices, if the exception information is contained there.
- (i) A statement that treatment, payment, enrollment, or eligibility for benefits cannot be conditioned on the individual completing an authorization. Participation in a research study may be conditioned on the individual signing the authorization (see 45 CFR 164.508(b)(4(i))).
- (j) A statement that individually identifiable information that is 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. Non-VA recipients to whom VA discloses PHI under a valid Authorization may not protect the information and might re-disclose the PHI.
- (4) The individual must be provided with a copy of the signed Authorization.
- (5) The original signed authorization must be maintained in the Investigator files with the signed informed consent form.

c. Information from Research Subjects Who are Not VHA Employees

- (1) The VHA may disclose the individually-identified health information of research subjects who are not VHA employees to non-VHA investigators for research purposes provided there is a prior written authorization. (See section c above).
- (2) If there is no prior written authorization, VHA may disclose individually-identifiable health information, excluding 38 U.S.C. 7332-protected information, to Federal investigators (e.g., Department of Defense) if the Under Secretary for Health, or designee, has approved the research, and the IRB has waived the authorization requirement in accordance with 45 CFR 164.512(i) prior to PHI.
- (3) If there is no prior written authorization, VHA may disclose individually-identifiable health information, excluding 38 U.S.C. 7332-protected information and names and addresses of individual participants to non-Federal investigators if the Under Secretary for Health, or designee, has approved the research, and the IRB has waived the authorization requirement in accordance with 45 CFR 164.512(i) prior to PHI.
- (3) If there is no prior written authorization, VHA may disclose individually-identifiable health information, including names and addresses of individual participant, but excluding 38 U.S.C. 7332-protected information to non-Federal

investigators if: the non-Federal Investigators provide the names and addresses of the individual participants; there is VHA approval by both the Under Secretary for Health, or designee; and there is PVAMC IRB waiver of authorization.

- (3.) All requests for release of information with authorization must be forwarded from the investigator to the ACOS for R&D. The ACOS for R&D will generate the request to be submitted to the Under Secretary of Health.
- (4) Title 38 U.S.C. 7332-protected information may be disclosed without written authorization, if in addition to the requirements of VHA Handbook 1605.1 subparagraph 13b(1)(b), or subparagraph 13b(1)(c), the requirements of 38 CFR 1.488 are met. Specifically, the research protocol must indicate:
 - (a). The information must be maintained in accordance with the security requirements of 38 CFR Section 1.466 or more stringent requirements;
 - (b) The information will not be re-disclosed except back to VA; and
 - (c) The information will not identify any individual patient in any report of the research or otherwise disclose patient identities.
- (5) The Privacy Officer must approve all disclosure requests prior to initiation.

d. Information from Research Subjects in Their Capacity as VHA Employees

- (1) VHA may disclose the individually-identifiable information of research subjects in their capacity as VHA employees, excluding health information, to non-VHA Investigators for research purposes without written authorization, and only in accordance with the Privacy Act and applicable VA privacy policy.
- (2) VHA employee health information is to be disclosed using the same privacy process as veteran health information.
- (3) The Privacy Officer must approve all disclosure requests prior to initiation.

e. Procedure for Signing an Authorization

- (1) Written authorization for release of information is valid when signed by:
 - (a) the participant.
 - (b) if the patient is not conscious, coherent or not competent for whatever reason, a legally recognized proxy must sign the Authorization. Rhode Island state laws recognize the following order of individuals capable to serve as proxies.
 - (i) Court appointed Guardian, or Proxy designated by Durable Power of Attorney.

f. Waiver of Authorization by IRB

- (1) A request from an investigator for the IRB to waive the HIPAA authorization must be accompanied by sufficient information to allow the IRB to make the required determination. The waiver request must include the following information:
 - (a) The use or disclosure of the requested PHI involves no more than a *minimal risk to the privacy* of individuals, based on the presence of at least the following elements:
 - (i) An adequate written plan to protect the identifiers from improper use and disclosure;

- (ii) An adequate written plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or unless such retention is otherwise required by law (Note- Until a specific Record Control Schedule is developed for research records, all records must be kept indefinitely); and
- (iii) Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by the HIPAA Privacy Rule;
- (b) The request for waiver of HIPAA authorization explains why the research could not practicably be conducted without the waiver; and
- (c) The request for waiver of HIPAA authorization explains why the research could not practicably be conducted without access to and use of the requested PHI.
- (d) The request for waiver of HIPAA authorization includes a brief description of the protected health information.
- (e) If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), there is assurance in writing that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))
- (2) In order to request a waiver of HIPAA authorization, a researcher must complete and submit the appropriate form to the IRB for review. The IRB will review and determine whether or not the waiver of authorization is acceptable and appropriate.
- (3) If the waiver is approved, the IRB will document its findings in the approval letter and HIPAA waiver reviewer checklist, both of which will be filed in the protocol file. The documentation in the approval letter and reviewer checklist will include the following required information:
 - (a) Elements included in e.(1) above.
 - (b) A statement identifying the IRB of record and the date on which the alteration or waiver of authorization was approved;
 - (c) A statement that the alteration or waiver of authorization satisfies the following criteria:
 - (i) The use or disclosure of the requested information involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
 1. An adequate plan to protect the identifiers from improper use and disclosure;
 2. 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 mandated by applicable VA or other Federal

requirements (Note- Until a specific Record Control Schedule is developed for research records, all records must be kept indefinitely); and

3. 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. (ii)

The research could not practicably be conducted without the waiver;
and

- (iii) The research could not practicably be conducted without access to and use of the requested information.

- (d) A brief description of the PHI for which use or access has been determined to be necessary by the IRB (*Note: For all in (3) (c) and (d) above, a simple statement as to compliance with criteria by the IRB is not sufficient. Each criterion must be addressed in the approval letter or other document in the protocol file. The IRB must state its determination for each criterion*);

- (e) The specific findings on which the IRB based its decision to grant the waiver of HIPAA authorization.

- (f) Identification of the IRB review procedure used to approve the waiver or alteration of HIPAA authorization (either convened IRB review procedures (see VHA Handbook 1200.05, par. 13 and 38 CFR 16.108(b) or expedited review procedures (see VHA Handbook 1200.05, par. 21 and 38 CFR 16.110).

- (g) Signature of Chair of the IRB, or qualified voting member of the IRB designated by the Chair, on the HIPAA authorization waiver checklist and approval letter. *Note: The documentation of the IRB's findings in the form of the approval letter and HIPAA Waiver Reviewer Checklist, will be filed in the IRB protocol file. If the IRB does not document the waiver of authorization as required, the waiver will not be considered valid.*

- (4) Uses and/or disclosures of PHI made pursuant to a Waiver are subject to the Minimum Necessary rules as noted in section m below.

g. Recruitment of Research Subjects

The following methods of recruitment are acceptable options for subject recruitment.

These recruitment activities require prospective IRB review and approval.

- (1) A PVAMC investigator may speak directly with his/her patients, who may qualify for and be interested in a particular research project, without an Authorization.

- (2) A PVAMC investigator may publish an IRB-approved advertisement and have potential subjects call a designated research staff member directly. If any PHI will be collected during the conversation, the process must receive a waiver of authorization from the IRB. The PHI collected in such a situation must be only the minimum necessary for recruitment for the specific research project. In these situations, an investigator should submit a completed Partial Waiver of Authorization for Screening/Recruitment Purposes form to the IRB for review and approval, prior to collecting any PHI without obtaining authorization.

- (3) All other uses and disclosures of PHI for the purpose of contacting and/or recruiting potential research participants may require a waiver of authorization. An investigator may be required to submit a completed Partial Waiver of Authorization for Screening/Recruitment Purposes form to the IRB for review and approval, prior to collecting any PHI without obtaining authorization.

h. Reviews Preparatory to Research

- (1) In preparatory to research activities, access to PHI can be granted to VHA researchers without a waiver of HIPAA authorization, provided they are recording data in the aggregate and that individually identifiable data is not recorded (e.g. to design a research study or to assess the feasibility of conducting a study). However, prospective approval from the IRB or IRB Chair is needed.
- (2) Prior to accessing any PHI for this purpose, the VA researcher must submit a formal request including complete protocol to the IRB for review.
- (3) The researcher certifies in the formal request that all of the following criteria are satisfied:
 - (a) The use of PHI is sought **solely** to prepare a research protocol;
 - (b) The researcher shall not record or remove the PHI from the Providence VA Medical Center in the course of the review; and
 - (c) The PHI for which access is sought is the minimum necessary for the preparation of the research.
- (4) Non-VHA Researchers may not access VHA data for reviews preparatory to research.

i. Research on Protected Health Information of Decedents

- (1) VHA researchers may use and disclose a decedent's PHI for research without an authorization from the subject(s) only when prospective IRB approval has been obtained.
- (2) Prior to accessing any PHI for this purpose, the VHA researcher must submit a completed formal request including complete protocol to the IRB for review.
- (3) The researcher certifies in the formal request that all of the following criteria are satisfied:
 - (a) The use or disclosure is sought **solely** for research on the PHI of decedent(s);
 - (b) The researcher has documentation, at the request of the VHA, of the death of such individuals; and
 - (c) The PHI for which use or disclosure is sought is the minimum necessary for the purposes of the research.
- (4) Uses and/or disclosures of PHI of decedents are subject to the Minimum Necessary Standard.

j. Use or Disclosure of "De-Identified" Health Information

- (1) The use of de-identified health information does not apply under the HIPAA Privacy Rule and may be used or disclosed for research purposes without a HIPAA Authorization or waiver.

- (2) Researchers must provide documentation to the IRB, prior to the disclosure of PHI, that the health information has been de-identified by the following method:
 - (a) **Removal of All Identifiers (“Safe Harbor” Method).** The IRB may determine that health information is de-identified for purposes of this Policy, if the Principal Investigator completes and submits the PVAMC Plan for addressing HIPAA Privacy Regulations form and the HIPAA Worksheet. The list of 18 identifiers concerning the individual and the individual’s employer, relatives and household members that **must** not be contained in the data presented to be de-identified include: names; geographic subdivisions smaller than a state; zip codes; dates directly related to an individual; telephone numbers; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary identifiers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; web universal resource locators (URL); internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images; and any other number, characteristic or code that could be used to identify the individual.

(3) Re-identification

- (a) A VHA investigator may assign a code, or other means of record identification, in order to allow information, which has been de-identified under subparagraph i(2) (a) and (b), to be re-identified by VHA, provided that:
 - i. The code or other means of record identification is not derived from, or related to, information about the individual and that the code is not otherwise capable of being translated so as to identify the individual;
 - ii. The code, or other means of re-identification, is not used or disclosed by VHA for any other purpose; and
 - iii. VHA does not disclose the mechanism (e.g., algorithm or other tool) for re-identification.
- (b) The code or other means of record identification is not considered one of the identifiers that must be excluded for de-identification. **NOTE:** *When disclosing de-identified data to non-VA entities this code needs to be removed.*

k. Limited Data Set

- (1) A researcher may use or disclose a Limited Data Set for research purposes without an Authorization or Waiver of Authorization.
- (2) A “Limited Data Set” is defined as PHI that **may include** any of the following *direct identifiers*:
 - (a) Town, city, state and zip code;
 - (b) All elements of dates directly related to an individual, including birth date, admission date, discharge date, and date of death.
- (3) A Limited Data Set must **exclude all** of the following *direct identifiers* of the Individual or of the individual’s relatives, employers, or household members of the individual: names; postal address information *other than town or city, State, and zip code*; telephone numbers; fax numbers; electronic mail

addresses; social security numbers; medical record numbers; health plan beneficiary identifiers; other account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; web universal resource locators (URL); internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images and any comparable images.

- (4) A Limited Data Set may be used or disclosed only if there is a **Data Use Agreement** between the VHA and the recipient of the limited data set. The Data Use Agreement is intended to provide assurance of the limited use or disclosure of the information in the limited data set. (5) The Data use Agreement must specify the following:
 - (a) The permitted uses and disclosures of information by the recipient, consistent with the purposes of the research;
 - (b) The limits on who can use or receive the data;
 - (c) That the recipient will not re-identify the data or contact the individuals; and
 - (d) That the recipient will use appropriate safeguards to prevent use or disclosure of the limited data set other than as permitted by the Privacy Rule and Data Use Agreement or as required by law.
- (6) A VHA investigator may not release a limited data set from the VHA entity without the prior approval of the IRB. The VHA investigator must submit a Data Use Agreement to the Privacy Officer and IRB for review and approval, prior to releasing the limited data set from the VHA.

I. Minimum Necessary – The Privacy Rule restricts use and disclosure of PHI. However, it does contain exceptions which grant access in certain circumstances. Underlying all the exceptions, however, is the principle that any access should be limited to the minimum amount of information necessary to accomplish the intended purpose of the use or disclosure. For VHA research purposes, this standard requires a VHA researcher to evaluate the needs of his or her study and to request access only to those pieces of information that are necessary for the complete and accurate development of the research. This is advisable even if a research subject permits more information to be used or disclosed.

m. Individual's Right to Access and Amend PHI

- (1) As a general rule, individuals who participate in research have a right to access their own PHI that is maintained in a Designated Record Set (DRS).
- (2) However, individuals participating in research protocols that include treatment (ex: clinical trials) may be denied access to their PHI obtained in connection with that research protocol, **provided that**:
 - (a) The PHI was obtained in the course of the research;
 - (b) The individual agreed to the denial of access in the Research Authorization;
 - (c) The research remains in process; and
 - (d) The individual's rights to access such PHI are re-instated once the research study has ended and the Research Authorization has expired.

n. Individual's Revocation of Research Authorization

- (1) As a general rule, an individual may revoke his/her Authorization, in writing to the Principal Investigator, at any time.
- (2) The revocation will be applicable to the protocol or protocols specified by the individual.
If the individual revokes his/her authorization, he/she may not be able to continue participation in the research project(s), which he/she specifies. The revocation of authorization will not affect the individual's right as a VHA patient, if he/she is a VHA patient.
- (3) However, the researcher may continue to use and disclose, for research integrity and reporting purposes, any PHI collected about the individual in good faith pursuant to receipt of the revocation of Authorization. If the individual's information has already been combined with other subjects information in the study, such as when numbers are averaged, or if the individual's information has been sent to the study sponsor, the investigator may continue to use it, but no further information about the individual will be collected after he/she revokes his/her authorization.
- (4) The Principal Investigator shall keep copies of all revocations of Authorizations for a specific protocol, and report them to the IRB at the time of continuing review.

o. Business Associates

- (1) Business Associates who will receive VA patients' PHI must enter a Business Associate Agreement with the VHA, prior to the release of the VA patients' PHI.
- (2) VHA Investigators with questions regarding whether or not a business associate agreement should be entered into with an entity should contact the Research Service Office.
- (3) The VHA Contracting Office will process Business Associate Agreements.

p. Accounting of Disclosures

- (1) As a general rule, a VHA patient has a right to receive an accounting of disclosures of their PHI for research purposes that have been made over the six years prior to the request unless such disclosure was made pursuant to an Authorization or is part of a Limited Data Set.
However, this does not include disclosures prior to April 14, 2003.
- (2) The Principal Investigator must keep records of all disclosures of PHI in the following circumstances:
 - (a) Disclosures pursuant to an IRB waiver;
 - (b) Disclosures of PHI used in preparation of a research protocol; and
 - (c) Disclosure of a decedent's PHI used for research.
- (3) If the research involves disclosure of PHI involving <50 individuals and an authorization from the subject has not been obtained, the Principal Investigator must keep an accounting of the disclosure that contains the following:
 - (a) Date of the disclosure
 - (b) Description of PHI disclosed
 - (c) Statement of purpose and basis of the disclosure

- (d) Frequency, periodicity or number of disclosures made during the accounting period
 - (e) Date of last disclosure during the accounting period
 - (f) Name of research or person who received the PHI and address of that individual.
- (4) If the research involves disclosure of PHI involving >50 individuals and an authorization from the subject has not been obtained, the individual should be provided a list of research protocols in which the individual's PHI *may have been used*.

The Principal Investigator must keep an accounting of the disclosure that contains the following:

- (a) The name of the protocol or other research activity;
- (b) A description of the purpose of the study;
- (c) The type of PHI disclosed;
- (d) The timeframe during which such disclosures occurred and
- (e) The name, address and telephone number of:
 - ii. The Entity sponsoring the research, and
 - iii. The researcher(s) or others to whom the data/information was disclosed.

q. Notice of Privacy Practices

All VHA and non-veteran/DOD research participants must receive a Notice of Privacy Practices (NPP). Many of the VHA patients will probably receive this Notice of Privacy Practice prior to participating in a research study. If a VHA or non-veteran/DOD participant has not received a copy of the NPP, one must be provided to them and they must acknowledge receipt of the NPP by signing VA form 10-0483 (Receipt of Notice of Privacy Practices). A copy of this form should be provided to the participant and a copy must be sent to the PVAMC Privacy Officer.

r. Transition Provision

- (1) Researchers may continue to use and disclose PHI created or received before and after April 13, 2003, if the researcher has obtained any one of the following prior to that date:
 - (a) An authorization or other express legal permission from an individual to use or disclose the PHI for research;
 - (b) The individual's informed consent to participate in the research; or
 - (c) IRB approval of a waiver of informed consent for the research.

NOTE: A researcher must obtain an Authorization in the event informed consent is sought after April 13, 2003, even if a waiver of informed consent was obtained prior to April 13, 2003.
- (2) The PVAMC IRB has approved the use of the PVAMC HIPAA Authorization Form template for use by investigators with PVAMC IRB-approved research projects during this transition period. Individual IRB approval of the PVAMC HIPAA Authorization Form is not required, unless a research study sponsor requires specific language to be added. At that time, IRB approval of the modified HIPAA Authorization Form is required.
- (3) At the time of continuing review the following should occur:

- (a) Research projects using an informed consent form, must maintain the informed consent form and HIPAA Authorization as separate documents.
- (b) Research projects for which the IRB has approved a waiver of informed consent should complete the Waiver of Informed Consent/Authorization form.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 12: Research Misconduct

October 19, 2011

Standard Operating Procedure for Investigating Research Misconduct

1. **PURPOSE:** To set policy and procedures for the reporting, investigating, and resolving of complaints alleging research misconduct at the Providence VA Medical Center (PVAMC) consistent with VA Handbook 1058.2.
2. **POLICY:** It is the policy of the PVAMC to sustain public trust in the research enterprise, which requires confidence in the research record and in the processes involved in its ongoing development. To this end allegations of or apparent misconduct in scientific research will be investigated and appropriate action taken against individuals if it is determined that research misconduct has occurred. This policy applies to research and related activities conducted by VA investigators regardless of source of funding (or even if unfunded). This policy does not deal with other research improprieties that fall outside the definition of research misconduct (see below). Separate VA policies and procedures exist which deal with conflicts of interest, sexual harassment, and violations of federal rules that govern protection of human subjects in research and the welfare of laboratory animals.
3. **DEFINITIONS:**
 - A. Research Misconduct
 - (1) Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
 - (a) Fabrication. Fabrication is making up data or results and recording or reporting them.
 - (b) Falsification. 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.
 - (c) Plagiarism. Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

- (2) Misrepresentation of one's qualifications or the misrepresentation of one's ability to perform research proposed in applications or similar submissions falls within the definition of research misconduct.
- (3) Research misconduct does not include:
 - (a) Honest error or differences of opinion.
 - (b) Authorship disputes other than plagiarism.
 - (c) Research Impropriety. Research impropriety includes ethical lapses that do not fall within the definition of research misconduct. Examples of such improprieties include: conflicts of interest, misallocation of funds, sexual harassment, discrimination, and breaches of human subjects protections and animal welfare requirements. These improprieties are subject to other VA regulations, policies, and procedures, and in some cases, other laws and regulations.
- (4) To constitute research misconduct, the behavior must:
 - (a) Represent a significant departure from accepted practices of the relevant research community.
 - (b) Be committed intentionally, knowingly, or with reckless disregard for the integrity of the research.
- (5) To establish a finding of research misconduct, the allegation must be proven by a preponderance of the evidence; i.e., the allegation is more likely than not to be true.

c. Investigation of Allegations of Research Misconduct

- (1) VA employees include paid staff, "without compensation" (WOC) employees, contractors, and Intergovernmental Personnel Agreement (IPA) personnel engaged in or requesting support for VA research. This includes, but is not limited to: scientists, trainees, technicians and other staff members, students, fellows, guest researchers, and collaborators who fall within these specified categories.
- (2) An informant is a person who makes an allegation of research misconduct (whistleblower).
- (3) Respondent(s) are the person(s) against whom an allegation of research misconduct is directed or whose actions are the subject of an Inquiry or Investigation. Use of this term does not imply that the person(s) are, or will be, the subject of a disciplinary proceeding.
- (4) Research Integrity Officer (RIO). The RIO is the appointed official who is responsible for receiving and coordinating reviews of formal allegations of research misconduct.

- (5) An allegation is a written statement that research misconduct may have occurred, submitted to the potential Respondent's supervisor, Associate Chief of Staff or Coordinator/Research and Development (ACOS-Coordinator/R&D), or the RIO.
- (6) Inquiry is a process in which initial information is gathered solely to determine whether the readily available evidence warrants a formal investigation of research misconduct.
- (7) Investigation is a formal process whereby a properly constituted Investigation Committee evaluates all the relevant facts, determines whether the evidence supports a finding of research misconduct, identifies the responsible individual(s), and assesses the seriousness of the misconduct.
- (8) Retaliation is taking or threatening to take an adverse action against an informant or other individual in response to a good faith and reasonable allegation or cooperation with an Inquiry or Investigation of research misconduct. An adverse action may include an intentional failure to take a warranted action.
- (9) Joint Jurisdiction. VA Research may be funded by entities such as PHS, private foundations, or commercial sponsors. VA employees may be affiliated with other entities such as OSRI, or other institutions. These non-VA entities may be allowed to lead Inquiries and Investigations (if approved by the Director), to participate in VA Inquiry and Investigation Committees, or to be informed of the results of Inquiries and Investigations.

4. RESPONSIBILITIES:

a. Informants

- (1) VA employees have a responsibility to report suspicions of misconduct in VA research if, after a careful assessment of the readily available facts, they honestly and reasonably believe there is credible evidence of misconduct.
- (2) VA employees also have a responsibility to cooperate in good faith with research misconduct investigations whether led by PVAMC or by an agency/entity with joint jurisdiction (see VA Handbook 0700, and 38 CFR Sec. 0.735-12[b]).
- (3) VA employees, former VA employees, and applicants for VA employment who make allegations of research misconduct or cooperate with an Inquiry or Investigation consistent with the Whistleblower Protection Act of 1989, may seek redress for retaliation as provided under that Act (see Title 5 of the United States Code [U.S.C.] Section 1201 Notes, et seq.).

- (4) Informants' requests to protect their identities are to be honored as far as possible. In order to complete most Investigations, however, an Informant's identity and testimony may ultimately be required.
- (5) Informants may consult privately with the RIO before making a formal, written allegation.
- (6) Informants who make good faith and reasonable allegations of research misconduct must be given an opportunity to provide testimony during the Inquiry, to review portions of the Investigation Report pertinent to their own testimony, and to be informed of the general outcome of the Inquiry and Investigation as it relates to their allegations. Informants do not otherwise have a right to participate in the review or determination of the alleged misconduct case.
- (7) VA employees whose research misconduct allegation or cooperation with an Inquiry or Investigation is not in good faith may be subject to disciplinary measures.

b. Respondents

Primary responsibility for ensuring the authenticity of reported data rests with the principal investigator. In addition, all investigators identified as authors of a report assume responsibility for the authenticity of the portion of the report to which they contributed.

- (1) Respondents must be given timely, written notification of the allegations made against them, a description of all such allegations, and reasonable access to the data and other evidence supporting the allegations.
- (2) Respondents will be given the opportunity to respond to allegations of research misconduct, the supporting evidence, proposed findings of research misconduct, and proposed corrective actions, if any. They must be promptly notified of final findings and actions.
- (3) Respondents must have the opportunity to be interviewed and present evidence during the Inquiry and Investigation and to provide comments on the Investigation Report. Respondents are required to cooperate in good faith with any Inquiry or Investigation conducted.
- (4) Respondents may obtain the advice of legal counsel or a personal advisor who is not otherwise involved with the case. The counsel or advisor may be present at interviews with the Respondent, but may not speak for, or on behalf of, the Respondent during the Inquiry or Investigation.

- (5) Respondents are prohibited from retaliating against Informants who make good faith and reasonable allegations of research misconduct, even if such allegations are ultimately not substantiated.
- (6) Respondents against whom a finding of research misconduct is made under these procedures must be afforded an opportunity to appeal that finding and proposed corrective action.
- (7) If another agency or entity has joint jurisdiction over a misconduct case, additional sanctions within the authority of that agency or entity may also apply.
- (8) Respondents who are not found guilty of committing research misconduct must be afforded reasonable assistance in restoring their reputations to the extent that the PVAMC administration deems appropriate, and within the scope of the PVAMC authority.

c. VA Administration

The PVAMC administration must make diligent efforts within the scope of their authority to protect from retaliation Informants who make good faith and reasonable allegations of research misconduct or who cooperate with an Inquiry or Investigation in good faith.

- (1) The PVAMC Director is responsible for appointing Committee members, convening Inquiry and Investigations in a timely manner, defining the scope authority of the Committees, reviewing Reports, and communicating with the VISN 1 Director and Office of Research Oversight (ORO).
- (2) The Chief of Staff (COS) and ACOS/R&D (or Coordinator/R&D) are kept informed of the progress of the Inquiry and Investigation, and may serve on the Inquiry and Investigation Committees.
- (3) The RIO is appointed by the Director. The RIO:
 - (a) May be consulted by Informant(s) prior to submitting a written allegation. The RIO will explain the procedures for making an allegation and their responsibilities and safeguards under these procedures, and review the allegation with the informants.
 - (b) Determines whether the alleged activities meet the definition of research misconduct and threshold for formal inquiry.
 - (c) Has the responsibility to inspect and sequester all research records related to a misconduct allegation without notice.
 - (d) Oversees Inquiries and Investigations, maintaining files of all documents and evidence, ensuring the confidentiality and security of those files, forwarding all information to the appropriate offices or persons as required

by these procedures, and otherwise acting as a liaison between the VA facility and ORO.

(e) Maintains appropriate safeguards for Respondents and Informants.

5. PROCEDURES:

a. Allegations

- (1) Anyone may make an allegation of research misconduct. VA employees have a responsibility to report suspicious activities. Before submitting a written allegation, potential informants are encouraged to contact the RIO (email: Christine.Fitzgerald2@va.gov or telephone: 401-457-3066), the ACOS/R&D if different than the RIO, or the Respondent's supervisor. Allegations must be made in "good faith", meaning that the Informant has reason to believe the allegation to be true and is in a position to know.
- (2) The written allegation should include as much relevant detail as possible, and be submitted to the RIO. Informants and allegations will be held confidential to the extent possible. Anonymous allegations may be considered, but a full Investigation may lead to identification of the Informant.
- (3) The RIO will determine whether the allegation contains all of the threshold requirements for opening an Inquiry.
- (4) The PVAMC Director, COS, and ACOS/R&D (or Coordinator/R&D if one exists) will be informed of all allegations, whether or not they reach the threshold for initiating a formal Inquiry.
- (5) Within 5 working days the Informant will be informed whether the allegation will lead to a formal Inquiry. If not, the Informant will have the opportunity to revise the allegation.
- (6) The RIO, in consultation with PVAMC leadership, will determine whether the alleged misconduct involves other entities such as funding agencies (e.g. VA Merit Review, PHS, NSF, American Heart Association, American Diabetes Association), pharmaceutical companies, the Ocean State Research Institute (OSRI), or affiliated institutions. Entities with joint jurisdiction over the research will be consulted, and may participate in or lead subsequent Inquiry and Investigation.
- (7) Between the time that a research misconduct allegation is filed and when it is fully resolved, VA may take interim action(s) to minimize harm or threatened harm to research subjects, serious violations of animal welfare requirements, research safety compromises, harm or threatened harm to those involved in the investigation, risks to public health or safety, loss or destruction of VA funds or property, or possible violations of civil or criminal law associated with

the alleged research misconduct. All interim administrative actions taken to minimize damage must be reported to ORO.

b. Inquiry

- (1) The Director must convene an Inquiry within 5 working days after a research misconduct allegation is received if the allegation meets the threshold requirements and it has been determined that the PVAMC will lead.
- (2) As soon as possible the RIO must sequester all physical materials that might serve as evidence in determining the merits of the research misconduct allegation.
- (3) The following persons will be provided written notification of the misconduct allegation and the opening of an Inquiry.
 - (a) The named Respondent(s) and Informant(s)
 - (b) The VISN 1 Director and ORO Central Office
 - (c) Entities with joint jurisdiction, if any. For PHS-funded studies the Office of Research Integrity will be notified.
 - (d) The Respondent's supervisor
- (4) Inquiries may be conducted by either the RIO or an Inquiry Committee appointed by the PVAMC Director
- (5) Both the Respondent and the Informant must be interviewed, if available. Additional individuals who can provide relevant information may also be interviewed. Written transcripts of these interviews must be prepared, provided to the respective interviewees for correction, and included in the record
- (6) The Inquiry must be complete within 30 working days of receipt of the written allegation. A written Inquiry report will be prepared by the RIO or Inquiry Committee and sent to the Director.
 - (a) If the Report finds insufficient evidence for Research Misconduct, and the Director agrees, the case will be terminated.
 - (b) If the Report finds sufficient evidence for Research Misconduct, or the Director disagrees with a recommendation to terminate the case, an Investigation must be opened.
 - (c) All individuals and entities notified of the allegation will be notified of the result of the Inquiry.

c. Investigation

- (1) The Director must convene an Investigation within 10 working days of the recommendation to open an Investigation, and appoint an Investigation Committee.
- (2) The RIO must notify the Respondent and Informant of the Committee's membership. Within 5 working days of receiving such notification, the Respondent and the Informant may each submit written objections to the selection on the basis of conflict of interest. The final decision to retain or replace Committee members belongs to the Director.
- (3) The Investigation Committee is to conduct a thorough review of the research misconduct allegation. They may consider other potential instances of related research misconduct not specified in the allegation; the Inquiry Report; sequestered and submitted materials; interviews with the Informant, Respondent, and other witnesses; and any other relevant evidence that can be obtained. The Committee must reach a decision as to whether and to what extent research misconduct has occurred, the type and extent of misconduct, who is responsible, and what corrective actions are appropriate. VA Counsel may be consulted.
- (4) The Investigation Committee will produce a draft Investigation Report. The draft Investigation Report will be provided to the Respondent, and relevant sections will be provided to the Informant. Written comments must be submitted to the Committee within 5 working days after receipt. The Investigation Committee makes any necessary revisions to the report and attaches the Respondent and Informant comments, if any, to the final Investigation Report.
- (5) The final Investigation Report is submitted to the Director within 90 calendar days of the start of the Investigation.

d. Outcome

- (1) The Director sends the final Investigation Report, with comments if any, to the Director of VISN 1, ORO, and entities with joint jurisdiction. The report is reviewed by the Director of VISN 1 and by ORO. The final outcome, which may include sanctions, is determined by ORO. ORO notifies the Under Secretary for Health, VISN 1 Director, PVAMC Director, heads of entities with joint jurisdiction, the Informant, and the Respondent.
 - (a) If the outcome does not result in a finding of Research Misconduct, the Director will notify other entities and individuals involved and will assist in restoring the Respondent's reputation.
 - (b) If the outcome results in a finding of Research Misconduct, the Respondent has 30 calendar days to appeal the finding to the Under Secretary of Health.

(2) After completion of a case and all ensuing related actions, the RIO will prepare a complete file, including the records of any inquiry or investigation and copies of all documents and other materials furnished to the RIO or committees. The RIO will keep the file for at least seven years after completion of the case to permit later assessment of the case. VACO or other authorized personnel will be given access to the records upon request.

6. REFERENCES:

- a. Federal Policy on Research Misconduct. 65 Fed. Reg. 76260 (December 6, 2000).
- b. VA Handbook 1058.2. Research Misconduct.
- c. VA Handbook 0700, VA Administrative Investigations Handbook.
- d. VA Handbook 5021, Employee/Management Relations.
- e. Title 5 U.S.C. Section 1201 Notes, et seq. Whistleblower Protection Act of 1989.
- f. Title 38 CFR Part 44, Government Wide Debarment and Suspension (Nonprocurement).
- g. Title 38 CFR §§ 1.200 through 1.205. Referrals of Information Regarding Criminal Violations.
- h. Title 42 CFR Parts 50 and 93. PHS Policies on Research Misconduct.
- i. Title 38 CFR Part 0. Standards of Ethical Conduct and other Responsibilities

STEP	ACTION	TIMELINE	<input type="checkbox"/>	DATE	REFERENCE
1	Convening the Investigation	Within 10 work days of recommendation to open			1058.2 15c
a	Committee members selected by the Director	Investigation convention			1058.2 15c, 15e(4)
	i. Three to five Committee members				1058.2 15e
	ii. VAMC employees with relevant research experience				1058.2 15e(4)
	iii. Committee Chair is $\geq 5/8$ ths VAMC employee, actively involved with VA research				1058.2 15e(5)
b	Agencies/entities with concurrent jurisdiction, if any, designate a representative	Investigation convention			1058.2 15e(6)
c	Actual or apparent conflicts of interest				
	i. Document any objection by Respondent or Informant to Committee member selection based on conflict	5 days after notification of Committee selection			1058.2 15e(8)
	ii. The Director makes final decision to retain or replace				
	iii. The Director replaces any Investigation Committee member who has actual or apparent conflict of interest	Any time during the case			1058.2 ¶15e(7)
2	Investigation Committee Charge				
a	Receive Charge Letter from the Director	Investigation convention			1058.2 ¶15c
	i. Purpose is to determine whether and to what extent research misconduct has occurred, who is responsible, and what corrective actions are appropriate				1058.2 ¶15f(2), ¶15b
	ii. Review any other potential instances of <i>related</i> research misconduct not specified in the allegation				1058.2 ¶15f
b	Carefully review procedures in Handbooks 1058.2 and 0700	First meeting			1058.2 ¶15f(2)
c	Understand the scope of the Investigation	Prior to review			1058.2 15f(2)
3	(Interim Actions)	Any time during the case			
a	<i>If discover significant information outside scope of Investigation that may merit some action: Notify Director</i>	Promptly			0700 Ch.4, §B8
b	<i>If discover evidence of criminal activity</i>	Immediately			0700 Ch.1, §E(3)(a)(2)
	i. Suspend Investigation				
Step	ACTION	TIMELINE	<input type="checkbox"/>	Date	REFERENCE

	ii. Report discovery to the RIO and the Director			
	iii. Resume Investigation only when instructed by Director			
	c If receive outside request for information about the Investigation: Forward the request to the Director	Upon receiving request		0700 Ch.4, §C
4	Investigation Review	Complete within 90 days of Investigation initiation		1058.2 15f(1)
	a Thoroughly review the following materials:	Within 90 days		1058.2 15f
	i. The research misconduct allegation			
	ii. The Inquiry Report			
	iii. Materials sequestered by the RIO			
	iv. Materials submitted by the Informant, Respondent, witnesses, and others			
	v. Any other relevant evidence that can be obtained			
	b Interview the following individuals:	Within 90 days		1058.2 15f(4)
	i. Respondent			
	ii. Informant			
	iii. Other individuals with relevant information			
	c Suggested Interviewing Steps	Prior to/During Interview		0700 Ch. 5
	i. Follow Witness Testimony Checklist			0700 App. H, §§4-7
	ii. Review Witness Interview Tips			0700 App. D, §4
	iii. Prepare Witness Planning Worksheet for each witness			0700 App. G
	iv. Review Summary of Witness Obligations and Rights			0700 App. I
	d If Respondent obtains legal counsel or personal advisor	When informed thereof		1058.2 9d
	i. Provide Designation Form			0700 Ch.5, §C; App.K
	e Provide written Notice of Witness Rights and Obligations	Prior to each interview		0700 Ch.5, §B(3)
	i. Sample Notice			0700 App. J
	ii. Signed by witness			0700 Ch.5, §B(3)
	f. Administer oath or affirmation (subject to witness' consent)	Start of each interview		0700 Ch.5, §A(1-2), and App. H, §5
	g Interview Transcription	After each interview		1058.2 15f(4); 0700 Ch.5, §A(1)(b)
	i. Prepare written transcripts of all interviews			
	ii. Provide transcripts to interviewees for correction			
	h Optional: Consult subject-matter experts	During Investigation		1058.2 15f(5)
	i. Optional: Consult Regional Counsel on legal matters	During		1058.2 15f(5)

		Investigation		
	j. Protect the privacy of all participants and confidentiality of information gathered to the extent possible	Throughout Investigation		1058.2 10
5	(For Extensions of Investigation Review Period)			
	a. Notify the Director of need to extend Investigation review period	> 5 working days prior to end of review period		1058.2 15f(1)
6	(Admissions of Misconduct)			
	a. If the Respondent admits to research misconduct	Any time during the case		1058.2 12f
	i. The admission must be in writing			
	ii. The admission must be signed by the Respondent			
	iii. The admission must be signed by a witness			
	b. Are all the elements of a research misconduct finding evident in the Respondent's admission? »	At time of admission		
	i. YES (<i>Continue to Step 6c</i>);			
	ii. NO (<i>Continue Investigation</i>)			
	c. Is further investigation needed to discover the full extent of the Respondent's misconduct or others' roles? »	At time of admission		
	i. YES (<i>Continue Investigation</i>);			
	ii. NO (<i>Go to Step 7</i>)			
7	Decision	Within 90 days of Investigation initiation		
	a. Did research misconduct occur? »			1058.2 15f(6)
	i. YES (<i>Continue to Step 7b</i>);			
	ii. NO (<i>Go to Step 7c</i>)			
	b. Make a decision on each of the following issues:			
	i. What type(s) of research misconduct are involved			
	· Fabrication			
	· Falsification			
	· Plagiarism			
	ii. What is the extent of the misconduct			
	iii. Who is responsible for the research misconduct			
	iv. What are appropriate corrective actions			
	· Consider the criteria set forth in Handbook 1058.2			1058.2 18a
	c. Were decisions reached by consensus?			1058.2 15f(6)
	i. YES;			
	ii. NO			

	<ul style="list-style-type: none"> · Note the areas of disagreement · Note the arguments supporting/opposing each view · Note the majority opinion 				
Step	ACTION	TIMELINE	<input type="checkbox"/>	Date	REFERENCE
8	Investigation Report	Within 90 days of Investigation initiation			1058.2 15f(1)
a	Use Standard Format				0700 Ch.6, §A(2), §B, and App. N
b	Summarize				1058.2 15g(1)
i.	The allegation				
ii.	The evidence reviewed				
iii.	The Committee's recommendations regarding				
	· whether research misconduct occurred				
	· the type of research misconduct involved				
	· the extent of the misconduct				
	· who is responsible				
	· appropriate corrective actions				
c	Provide the Investigation Report to the Respondent; request response	Receive written comments within 7 days			1058.2 15g(2)
d	Provide the portions of Investigation Report related to the Informant's role/testimony to Informant; request response	Receive written comments within 7 days			
e	Make any necessary revisions to the Investigation Report	Within 90 day period			
i.	Attach comments to the final Investigation Report				
f	Forward Investigation Report to the Director	Within 90 day period			0700 Ch.6, §D(1)

References: VHA Handbook 1058.2 ("Research Misconduct")
VA Handbook 0700 ("Administrative Investigations")

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Providence, Rhode Island**

Section 13: Informed Consent Monitor

October 19, 2011

INFORMED CONSENT PROCESS MONITOR

1. **PURPOSE:**
 - a. To define the procedures utilized in the informed consent (observation) compliance process.
 - b. To define the procedures for reporting informed consent process compliance.

2. **RESPONSIBILITY:** The Research Compliance Officer (RCO) is responsible through the Medical Center Director for administering quality assurance monitors in order to maintain high standards of compliance to human subject protection.

3. **PROCEDURE:**
 - a. The RCO or designee will randomly select five investigators with actively recruiting protocols annually. From the list of chosen investigators, one protocol will be randomly selected for the informed consent process observation. The RCO may also choose to observe the consent process for new research coordinators or assistants for training purposes with concurrence from the investigator or at the request of the IRB.
 - b. The RCO will notify the Principal Investigator in writing the following information: 1) time period that the monitoring will occur (to be determined on frequency of recruitment but within 10 business days of notification); 2) name of the selected protocol; and 3) description of the monitoring process.
 - c. The Principal Investigator (PI) is responsible for contacting the RCO and informing him/her of the time and location of the scheduled consent at least 48 hours in advance.
 - d. The RCO may designate (with their concurrence) an appropriately trained (GCP and Human Subject) member of the research community to observe the consent process
 - e. The RCO or designee will observe the consent process, completing the Informed Consent Process Monitor Checklist.
 - f. The RCO or designee will provide immediate feedback to the investigator or person obtaining consent at the conclusion of the monitor.
 - g. Written results of the monitor will be reported to the PI within 5 business days and at the next scheduled IRB and R&D and recorded in the respective Committee meeting minutes. It will also be reported in the annual QM Research PI Plan.
 - h. The PI is given an opportunity to respond to the report and present a plan of action if deficiencies are noted.

- i. The response from the PI will be shared with the committees. The response may be accepted or require further action. Actions may include:
 - Additional human subject protection training
 - Amend the Informed Consent document
 - Suspension or termination of project
- j. All actions of the committees will be noted in the minutes.
- k. The PI will retain a copy of all correspondence and reports in the Investigator file.

Providence VA Medical Center

Informed Consent Process Monitor

Study Title:

Investigator:

Observer:

Date: **Initial**

Except as provided elsewhere, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative 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.

Required Elements of Informed Consent 38 CFR § 16.116 (a)	Yes	No
Statement that study involves research		
Explanation of the purposes of the research		
Expected duration of the subject's participation		
Description of the procedures to be followed		
Identification of any procedures that are experimental		
Description of any reasonably foreseeable risks or discomforts to the subject		
Description of any unforeseeable risks or costs to the subject		
Description of any benefits to the subjects or to others that may reasonably be expected from the research		
Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject		
Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained		
For more than minimal risk, an explanation as to whether any compensation is available if injury occurs, and if so what they consist of or where further information may be obtained.		
For more than minimal risk, 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		
An explanation of whom to contact for answers to pertinent questions about the research		

An explanation of whom to contact to questions about the research subject's rights		
Whom to contact in the event of a research related injury to the subject		
A statement that participation is voluntary		
Statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled		
Statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled		
Statement that in the event of research-related injury the VA had to provide necessary medical treatment to a participant injured by participation.		
ADDITIONAL ELEMENTS		
38 CFR § 16.116. (b)		
Statement that particular treatment or procedure may involve risks to subject (or to embryo or fetus, if subject is or may become pregnant), which is currently unforeseeable		
Any anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to subject's consent		
Any additional costs to subject that may result from participation in the research		
Consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by subject		
Statement that significant new findings developed during the course of research which may relate to subject's willingness to continue participation will be provided to the subject		
The approximate number of subjects involved in the study.		

Assessment of Understandability of information:

Eighth grade (or lower) reading level		
Words and sentences are short and simple		
One or two ideas/subjects discussed per paragraph		
Medical or scientific terms are defined and/or completely explained		
Quantities are given in familiar amounts (e.g. tablespoons instead of mls.		
Second person (you) is used in information section		
Translated consent forms are available when study involves recruitment of non-English speaking subjects in the native language(s) of those subjects		

Process Review

- latest approved version of ICF		
- all signatures dated		
- each page has subject name, title of study, PI name, date, and name of VAMC?		
- page 1, has subjects last four		
- did the investigator/designee encourage questions?		
- did the subject ask questions?		
- did the investigator/designee answer questions?		
- did the investigator/designee read the ICF?		
- Pre-test questions conducted (if applicable)		
Comments:		

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Section 14: Contacts from Participants or Others

October 19, 2011

This section describes the mechanism to solicit and respond to contacts from participants and others, including past participants, prospective participants or designated representative. The PVAMC Research Office strives to establish a confidential and responsive process.

A. Request for Contacts from Participants or Others

1. Current, prospective or past research participants are encouraged to contact the PVAMC Research Office to discuss any problems, concerns, and questions; to obtain information; or to offer input at any time.
2. The informed consent form lists the Individuals whom subjects are instructed to contact if they have an issue related to their research participation. In addition, participating in research informational posters and brochures are distributed throughout the Research buildings and displayed in prominent patient areas. These documents include contact information of the Research Office for further information if they have questions, concerns, problems, or suggestions.

B. Receiving Contacts from Participants and Others

1. Anyone in the Research office may receive a contact regarding problems, concerns, questions, requests for additional information. The recipient of the call should take care to record all relevant information in a thorough manner and request that the caller provide a contact number for follow-up calls, unless the caller desires to remain anonymous. The report of contact will be forwarded to the IRB Coordinator for triage.
2. The caller will be reassured that all inquiries are important, and that all efforts will be taken to investigate the circumstances, and that appropriate measures will be taken to address the issue. The caller will be informed that he/she will receive a response in a timely manner (provided contact information is given). Questions and requests for information will be directed to other research persons, as appropriate.
3. All complaints, concerns, questions, etc. involving research will be logged into a database by the IRB Coordinator who will route and/or track the issues until resolution and follow ups are complete. Simple inquiries or concerns will be handled by the IRB Coordinator as appropriate and reported to the appropriate committees and or administrative persons. The IRB Coordinator will conduct an

initial review to obtain as many facts as available to relay to the appropriate persons. During this review, every effort will be exercised to maintain the confidentiality of all parties involved. The ACOS will be notified of all substantiated allegations or trending of improprieties, serious subject and/or staff issues, or investigational misconduct and the procedures outlined in Section 4.8 Non-Compliance with Human Research Protection Program will be followed. If the concern involves research misconduct the procedures outlined in Section 12: Research Misconduct of this document will be followed.

4. Contacts that involve a complaint will be managed according to the procedures described in Section 4.8, Non-Compliance with Human Research Protection Program of this document.

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Section 15: Central IRB

October 19, 2011

PURPOSE

A Memorandum of Understanding (MOU) was developed between the Providence VA Medical Center and the Veterans Health Administration (VHA) Central Office, operating the VA Central Institutional Review Board (IRB) that sets forth the agreed upon respective authorities, roles, and responsibilities of the VA Central IRB, and the Providence VA Medical Center, for the initial and continuing review, as well as review of amendments, monitoring, reporting, and other relevant requirements, for select multi-site research projects involving human subjects.

This MOU does not preclude Providence VA Medical Center from continuing to participate in any existing agreements the Providence VA Medical Center may have with other VA or non-VA entities. This MOU is between the signatories only and does not include any other entities that are independently operating under their own Federalwide Assurances (FWAs), and it specifically excludes other entities with which Providence VA Medical Center may have a separate MOU for IRB and/or Research and Development (R&D) Committee services.

GENERAL PROVISIONS

1. Both signatory institutions will be guided by the “Ethical Principles and Guidelines for the Protection of Human Subjects of Research” as set forth in The Belmont Report, published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in April 1979.
2. Like all VA employees, VHA employees conducting or reviewing research are subject to the Federal Criminal Code and the Standards of Ethical Conduct for Executive Branch Employees. The obligation to act in accordance with ethics laws and regulations applies to all individuals while acting under a VA appointment, including full and part-time employees, without compensation (WOC) employees, and employees under the Intergovernmental Personnel Act (IPA) of 1970. Ethics officials in the Office of General Counsel in VA Central Office and VA Regional Counsel Offices are available to provide guidance on dealing with actual or potential conflicts of interest. Both VA Central IRB and the Providence VA Medical Center will evaluate any potential conflict of interest issues of all members of the local research team in accordance with their respective policies and standard operating procedures (SOPs).
3. Both signatory institutions will adhere to 38 CFR 16 and 17, 45 CFR 46 Subpart A, and 21 CFR 50 and 56; and other pertinent VA and Federal requirements applicable to human subjects research. If the Chief Research and Development Officer (CRADO)

approves research involving children or prisoners in accordance with VHA Handbook 1200.05, investigators must comply with 45 CFR 46, Subparts D or B, respectively. VA Central IRB or the Providence VA Medical Center will not approve a research project if it does not meet all these requirements. VHA Handbook 1200.05 will serve as the reference source for the definitions of all terms used in this MOU.

4. In accordance with the Health Insurance Portability and Accountability Act (HIPAA), 45 CFR 164.512(i), and VHA Handbook 1605.1, Privacy and Release of Information, VA Central IRB may grant a HIPAA Waiver of Authorization for use or disclosure of protected health information (PHI) for research reviewed by VA Central IRB, if justified and if all criteria for a waiver of authorization are met.

5. The VHA Central Office and the Providence VA Medical Center will each maintain a current Federalwide Assurance (FWA) through VA Office of Research Oversight (ORO) and the Department of Health and Human Services Office for Human Research Protections (OHRP) listing VA Central IRB as an IRB of record. The Principal Deputy Under Secretary for Health serves as the Institutional Official and the CRADO serves as the Human Protections Administrator (HPA) for the VHA Central Office Human Research Protections Program (HRPP). Any change or modification in the FWA status of either Institution will be reported to the other immediately in writing (within 1 working day).

6. Both the VHA Central Office and the Providence VA Medical Center will secure and maintain accreditation of their HRPPs through VA-designated accrediting organization as appropriate and per VA requirements.

7. There will be no charge to the Providence VA Medical Center or to investigators for the use of VA Central IRB.

RESPONSIBILITIES OF THE VHA CENTRAL OFFICE HRPP AND VA CENTRAL IRB

The VHA Central Office HRPP assures Providence VA Medical Center that the VHA Central Office HRPP and VA Central IRB will carry out the following functions and responsibilities in accordance with all applicable requirements:

1. The Institutional Official will ensure that VA Central IRB is provided, through the Chief Research and Development Officer (CRADO), with sufficient resources to support VA Central IRB operations. These resources will include, but not be limited to, adequate meeting space, equipment, financial support, and staff.

2. VA Central IRB will maintain current OHRP IRB registration in accordance with the requirements specified in VHA Handbook 1200.05. It will submit updates to the registration as its membership changes in accordance with the requirements in VHA Handbook 1058.03.

a. All VA Central IRB members and staff will receive appropriate initial and ongoing training with regard to VA and other Federal requirements for the protection of human subjects.

b. VA Central IRB will manage any conflicts of interest of IRB members in accordance with 38 CFR 16 and other applicable Federal and VA requirements. VA Central IRB members will recuse themselves from any discussion on any protocol or protocol-related matter in which those members have a conflict of interest. Members may provide information concerning proposals if asked by the presiding VA Central IRB Chair, but will leave the room prior to any further discussion and/or vote.

3. The VHA Central Office HRPP will maintain policies and Standard Operating Procedures (SOPs) that incorporate, whether by inclusion or reference, Federal statutes and regulations, as well as VA, VHA, and other policies, procedures, and requirements applicable to reviewing human subjects research.

a. The SOPs will include processes for compliance monitoring, audits, and reporting to appropriate regulatory authorities by VA Central IRB and its administrative staff, as well as by the participating local VA facilities as appropriate.

b. The SOPs will also include processes for reporting results of any external monitoring or audits (e.g., Food and Drug Administration (FDA), OHRP) of VA Central IRB research oversight activity that impacts the research being conducted at the Providence VA Medical Center to the Providence VA Medical Center's Institutional Official. This includes visits by sponsors and regulatory or compliance entities.

c. All VA Central IRB SOPs will be reviewed at least annually for compliance with all pertinent VA and other Federal requirements.

4. VA Central IRB will meet a minimum of once a month, and can meet more often if determined necessary by VA Central IRB Co-Chairs and VA Central IRB administrative staff. Members will attend in-person or via audio or video conference. If the Co-Chairs and administrative staff determine there are no agenda items that require action by the convened IRB, the scheduled meeting may be cancelled.

5. VA Central IRB will perform initial review of selected multi-site research projects.

a. VA Central IRB will evaluate local context for each protocol submitted using one or more of the following methods:

i. Reviewing the Providence VA Medical Center's Local Site Application (VA Central IRB Form 104), and any additional information submitted by the Local Site Investigator or the Providence VA Medical Center.

ii. Knowledge of the local research context by one or more of VA Central IRB members or staff. Such knowledge may have been obtained through direct experience with the Providence VA Medical Center, its subject populations, and/or the local community.

iii. Obtaining relevant information from an appropriate ad hoc advisor(s) who has had direct experience with the Providence VA Medical Center, its subject populations, and/or the local community.

iv. Systematic, reciprocal, and documented communication between VA Central IRB and Providence VA Medical Center. This communication will include regular interactions with one or more designated site liaisons by one or more VA Central IRB members or administrative staff and/or periodic visits to the Providence VA Medical Center as prescribed by VA Central IRB and Providence VA Medical Center's SOPs.

b. VA Central IRB will require the use of an informed consent document for all research involving human subjects unless this requirement is waived by VA Central IRB. The informed consent document and process, waiver of documentation of informed consent, or waiver of informed consent, must meet all requirements in VHA Handbook 1200.05.

c. VA Central IRB will provide a timely written notice (usually within 10 working days of a VA Central IRB action) to the Providence VA Medical Center of any action requiring the Providence VA Medical Center's response. Such actions include VA Central IRB's initial review considerations and its final approval or disapproval of a project.

6. VA Central IRB will conduct meaningful and substantive continuing review of approved projects at a minimum of once per year or more often if determined appropriate to the degree of risk to subjects. The continuing review will evaluate information submitted by the Principal Investigator (PI) including, but not limited to, the continuing review application containing all the elements required by VHA Handbook 1200.05 and all interim reports.

a. VA Central IRB will remain cognizant of local issues throughout the duration of the project and may request additional information from local sources or ad hoc advisors to supplement its review.

b. VA Central IRB will provide a timely (within 10 working days), written notice of the results of the continuing review to the Providence VA Medical Center, including any lapses of approval, in accordance with VA Central IRB SOPs.

7. VA Central IRB will evaluate any requests to amend or modify a previously approved protocol. VA Central IRB will notify all participating local sites in writing within 10 working days after it approves any amendment or modification to a protocol. VA Central IRB will provide a copy of the approval and the amendment or modification to all participating local sites.

8. VA Central IRB oversight of approved projects will include, but not be limited to:

a. Requiring all VA Central IRB-approved projects that present greater than minimal risk to contain a specific data safety monitoring plan that includes a means of communication between the PI and local site investigators to ensure adherence to the plan.

b. Working closely with the Providence VA Medical Center to investigate any complaints from subjects or others, incidents of investigator noncompliance or unanticipated problems, and to coordinate required reporting to regulatory agencies in

accordance with VA Central IRB SOPs, local site SOPs, and all VA and other Federal requirements.

c. Sending any of its members or administrative staff to a participating local site if determined necessary to complete any investigation or if requested by the Providence VA Medical Center.

9. If VA Central IRB determines that a given project does not constitute research, or does not constitute human research, it will provide a written letter with its decision to the PI who will be responsible for providing the letter to participating local VA facilities.

10. If VA Central IRB determines that a given project is exempt from IRB review, it will provide a written letter with its decision to the PI who will be responsible for providing the letter to all Local Site Investigators to share with their respective participating local VA facilities.

11. VA Central IRB will review the PI's Initial Application for each protocol to determine which sites are engaged and, therefore, require a Local Site Investigator and a Local Site Application.

12. VA Central IRB will maintain a website that will contain VA Central IRB SOPs, application forms, instructions, deadlines, reviewer checklists, a list of VA Central IRB-approved projects, local VA facilities that use VA Central IRB, and other relevant information about the VHA Central Office HRPP and VA Central IRB.

13. The VHA Central Office HRPP will seek feedback from the PI, Local Site Investigators, participating local VA facilities, and regulatory officials on the efficiency and effectiveness of VA Central IRB operations as part of the continuous quality improvement process.

14. VA Central IRB will maintain all applications, membership documents, and other relevant records in accordance with VA Central IRB SOPs, and all VA and other Federal requirements. VA Central IRB will provide Providence VA Medical Center ready access to pertinent VA Central IRB records for review and/or copying as needed in conjunction with any HRPP accreditation review, regulatory requirement, or in any matter concerned with the rights and welfare of any subject.

RESPONSIBILITIES OF Providence VA Medical Center

The Providence VA Medical Center's Institutional Official assures the VHA Central Office HRPP and VA Central IRB that Providence VA Medical Center will assume the following responsibilities in accordance with all applicable VA and other Federal requirements. Providence VA Medical Center will:

1. Retain ultimate responsibility for oversight of its local HRPP that includes:

a. Ensuring that all research approved or determined exempt by the VA Central IRB is submitted to the local site R&D Committee for review.

b. Safeguarding the rights and welfare of human subjects of all research approved by its R&D Committee.

c. Educating the members of its research community to establish and maintain a culture of compliance with all VA and other Federal requirements, as well as all Providence VA Medical Center requirements relevant to the protection of human subjects.

d. Instituting appropriate local oversight mechanisms to ensure compliance with the determinations of VA Central IRB. This includes performing routine audits and monitoring of locally conducted VA Central IRB-approved projects and reporting results of these activities to VA Central IRB.

e. Promptly informing VA Central IRB of any complaints from subjects or others; unanticipated problems involving risks to subjects or others; serious adverse events that are unanticipated and related to the research; suspension or termination of research activities; or serious or continuing noncompliance encountered in VA human subjects research projects approved by VA Central IRB. The Providence VA Medical Center will work with VA Central IRB to ensure all VA and other Federal reporting requirements are met including, but not limited to, those specified in VHA Handbook 1058.1, Reporting Adverse Events in Research to the Office of Research Oversight (ORO).

2. Modify its existing FWA, through ORO per VHA Handbook 1058.03, to designate VA Central IRB as an IRB of record.

a. If the Providence VA Medical Center uses one or more of its local academic affiliate's IRBs as an IRB of record, the Providence VA Medical Center will review the relevant MOU Providence VA Medical Center holds with its academic affiliate and, if necessary, modify the MOU between Providence VA Medical Center and its academic affiliate to permit the Providence VA Medical Center to use VA Central IRB.

b. If the Providence VA Medical Center uses the services of another VA facility's R&D Committee, then Providence VA Medical Center will review the relevant MOU with the other VA facility and, if necessary, modify the MOU to permit Providence VA Medical Center to use VA Central IRB.

3. Maintain documentation that all required training, credentialing and privileging is up to date for all local HRPP staff and for all local research team members of VA Central IRB-approved projects.

4. Work with the Local Site Investigator in preparing the Local Site Application to participate in any research project that has been designated for review by VA Central IRB. The Local Site Investigator will submit the Local Site Application to the PI and VA Central IRB through the local Associate Chief of Staff (ACOS) for R&D (or equivalent).

5. Provide comments and/or suggestions to VA Central IRB about VA Central IRB's initial review considerations in a timely manner, not to exceed 30 calendar days, from the date of receipt of the initial review considerations.
6. Notify the Local Site Investigator and VA Central IRB in a timely manner, not to exceed 10 calendar days after receipt of VA Central IRB's final approval of a project, whether or not the local site chooses to participate or declines to participate in the project.
7. Ensure the project is reviewed at the next regularly scheduled meeting of its R&D Committee after it agrees to participate in a given VA Central IRB-approved project.
8. Ensure that the project is not started until it has been approved by **both** VA Central IRB and the local R&D Committee.
9. Forward any Freedom of Information Act (FOIA) requests received by Providence VA Medical Center for any records concerning VA Central IRB documents to the VHA Central Office FOIA Officer for review and release as applicable.
10. Agree not to independently modify any VA Central IRB-approved protocol except where necessary to eliminate apparent immediate hazards to the human subjects in accordance with 21 CFR 56.108(a) and 38 CFR 16.103(b)(4).
 - a. VA Central IRB must be notified within 5 working days if such an action is taken.
 - b. VA Central IRB will not review emergency use of test articles. Such use must be reviewed at the local level in accordance with the Providence VA Medical Center's policies and procedures.
11. Notify VA Central IRB immediately of potential research impropriety, misconduct, suspension, debarment, or restriction of any local research team member associated with a VA Central IRB-approved project.
12. Provide VA Central IRB access to the research subjects' clinical records and/or case files if required as part of any VA Central IRB oversight or monitoring activity. This includes providing access to any VA Central IRB member, administrative staff, or designee.
13. Participate in the annual review of the VHA Central Office HRPP, including an evaluation of VA Central IRB composition and operations, in accordance with VA Central IRB SOPs and as required by VHA Handbook 1200.1, the R&D Committee Handbook.
14. Maintain compliance with any additional state, local, or institutional requirements related to the protection of human subjects. Providence VA Medical Center should consult its VA Regional Counsel Office or Office of General Counsel as needed.

15. Promptly notify VA Central IRB and the PI of any changes in the local study team on active projects.
16. Provide procedures for coordinating approval of local committees, including but not limited to the R&D Committee, Radiation Safety Committee, Biosafety Committee, Institutional Animal Care and Use Committee (IACUC), and/or any other relevant local committees in accordance with local SOPs. Copies of such approvals must be submitted to VA Central IRB.
17. Conduct routine compliance audits and monitoring and report findings to appropriate regulatory authorities and VA Central IRB. This includes any audits or monitoring plan included in VA Central IRB final approval of the project.
18. Maintain a file on each VA Central IRB-approved project that will include the PI's Initial Application, the Providence VA Medical Center's Local Site Application, VA Central IRB-approved consent form that will be used locally, other documents associated with the initial application, VA Central IRB final approval documents, Providence VA Medical Center R&D Committee approvals, local audits and monitoring reports, and any subsequent correspondence, amendments, continuing review reports and approvals, and any other pertinent documents.
19. Provide information as requested to the Providence VA Medical Center Local Site Investigator and the project's PI as part of the continuing review process.
20. Maintain current written SOPs that incorporate Providence VA Medical Center's specific responsibilities as outlined in this MOU.
21. Comply with all VA Central IRB SOPs as applicable.
22. The Providence VA Medical Center will not:
 - a. Submit a Local Site Application for a specific project to VA Central IRB if another IRB of record for Providence VA Medical Center has already disapproved that VA facility's participation in the project.
 - b. Submit an application to another IRB of record for review if VA Central IRB has determined that the Providence VA Medical Center should not participate in a specific project.
23. Upon approval of this agreement by both parties and the addition of VA Central IRB as an IRB of record on the Providence VA Medical Center's FWA, the Providence VA Medical Center's Institutional Official will provide a letter to VA Central IRB designating in writing which local official (e.g., Associate Chief of Staff for Research and Development (ACOS for R&D), Administrative Officer for R&D, R&D Committee Chair, local IRB Chair) is authorized to perform each of the following three functions on behalf of Providence VA Medical Center (NOTE: One local official may have authority to perform all three functions, or each of the functions may be delegated to different local officials). The appointment letter must also include the names and contact information

for each designated local official, including what function each official is performing if more than one is appointed.

- a. Providing comments and/or suggestions to VA Central IRB in response to VA Central IRB initial review considerations. **This duty has been delegated to the Administrative Officer.**
- b. Responding to VA Central IRB's final approval of the project on behalf of Providence VA Medical Center as to whether the Providence VA Medical Center chooses to participate or declines to participate in the project. **The local ACOS will sign the response from this facility.**
- c. Serving as the liaison among VA Central IRB, the Local Site Investigator, and the Providence VA Medical Center for oversight, compliance, and monitoring purposes. **The duty has been delegated to the IRB Coordinator.**

TERMINATION PROVISIONS

1. This MOU may be terminated by either the Providence VA Medical Center or the VHA Central Office HRPP without cause by giving a 60 day advance written notice of termination to the other Institution and to ORO. The 60 day notice period will not start until receipt of the written notice by the other party. The agreement may be terminated for cause only under the direction and guidance of ORO.
2. All current and active protocols will continue to be monitored under the provisions of the agreement until all VA Central IRB-approved projects active at the Providence VA Medical Center have been closed or safely moved to another site. The Providence VA Medical Center will maintain all documentation regarding the site's participation in the project in accordance with the time frames specified in VA and other Federal requirements.
3. This agreement went into effect on August 7, 2008, and will remain in effect until terminated as above or the agreement is amended and/or revised per mutual agreement of both Institutions. As required by VHA Handbook 1058.03, this agreement will be reviewed every 3 years by each institution at the time of renewal of that institution's FWA to determine if any conditions have changed that will require revision of the agreement.

Standard Operating Procedures for Research Involving Human Subjects

Research Service
Providence VA Medical Center
Providence, Rhode Island

Section 16: Institutional Conflict of Interest

October 19, 2011

INSTITUTIONAL CONFLICT OF INTEREST

1. PURPOSE

This policy describes the relationships that may produce a real or perceived institutional conflict of interest (COI) for the research being conducted at the Providence Veterans Affairs (VA) Medical Center.

2. SCOPE

This policy applies to all human subject research conducted in the Providence VAMC. This policy applies to investigators, IRB members and staff, R&D members, R&D staff, and institutional officials

3. POLICY

The policy of the VA is to ensure that the welfare of human subjects and the integrity of research will not be compromised, or appear to be compromised, by competing institutional interests or obligations. Although the Department of Veterans Affairs (VA) has separated technology transfer functions (see VHA Handbook 1200.18) from research administration, circumstances may exist in which separation of function is not sufficient to avoid the appearance of institutional conflict of interest. This policy applies to all human subject research conducted in the Providence VAMC. This policy applies to investigators, project staff members, IRB members and staff, R&D members, R&D staff, and institutional officials.

4. DEFINITIONS

a. Disclosure. Disclosure is the formal written process of documenting all aspects relating to the development of potential intellectual property for the purpose of determining and assigning ownership.

b. Equity. The money value of a property or of an interest in a property in excess of claims or liens against it.

c. Institutional Conflict of Interest. An institutional conflict of interest may occur when the institution, or any of its senior management or an affiliate foundation or organization, has an external relationship or financial interest in a company or organization that itself has a financial interest in a VA investigator's research project.

d. Intellectual Property (Invention). Intellectual property is any art, machine, manufacture, design, or composition of matter, or any variety of plant, which is or may be patentable under the patent laws of the United States.

e. Inventor. The inventor is the individual responsible for the conception or reduction to practice of a device or process.

f. Patent. A patent is an official written document securing to an inventor for a term of years the exclusive right to make, use, or sell an invention.

g. Re-disclosure. Re-disclosure is the formal written process of documenting all aspects relating to any improvement of a previously disclosed invention for the purpose of issuing a new determination on the improved invention.

h. Royalty. A royalty is compensation for an invention.

i. Significant financial interest . Any equity interest, royalties, compensation valued (when valued in reference to current public prices, or where applicable, using accepted valuation methods) at equal or greater than \$10,000.

5. RESPONSIBILITIES

The ACOS/R&D, R&D Committee, and IRB Committee will be responsible for evaluating potential institutional conflict of interest and will take actions as required to avoid, or to appropriately manage, apparent institutional COI.

6. PROCEDURES

6.1 Process for Identifying Conflict of Interest for Investigators or Research Personnel. (See IRB SOP for the management of IRB member conflict of interests)

- a. All investigators and project staff are required to complete the Conflict of Interest Disclosure Form.
- b. The IRB Coordinator will conduct an initial review all Conflict of Interest Disclosure forms. He/she will inform the ACOS for Research of any potential conflicts of interest and provide him/her the complete protocol, informed consent document (if applicable), conflict of interest disclosure form and any other appropriate documents. If there is no COI, no further action needs to be taken.
- c. The ACOS will transmit to the IRB whether or not a COI appears to exist. If a declared financial interest is identified, the ACOS will (1) notify the R&D Committee, and (2) notify the IRB that the application must be tabled until an appropriate management plan has been incorporated into the protocol. The IRB may review the protocol to assist the development of the management plan so that the financial interest will not affect the protection of participants, or the design, conduct, or reporting of the research, but may not approve the research without the management plan.
- d. The ACOS will present a review of COI issues to the R&D Committee in the context of protocol deliberations.

- e. The IRB and R&D Committee may initiate remedies to manage or eliminate conflict of interest (see section 6:3.b below for possible actions). R&D initiated remedies must be reviewed by the convened IRB.
- f. Once the evaluation of the COI has occurred, the convened IRB will review the protocol, the financial interest, and the management plan, if any.
- g. . When a significant COI exists and is not remedied by the process described above, a non-biased third party may be authorized to obtain informed consent if a potential or actual COI could influence the tone, presentation, or type of information discussed during the consent process. Independent monitoring may be necessary in this instance. As stated in f, the IRB must review the management plan.
- h. The IRB has the final authority to decide whether the interest and its management, if any, allowed the research to be approved. The IRB may add to the management plan as needed.

6.2 Assessment of Institutional Potential Conflict of Interest (COI)

a. Invention/Intellectual Property Disclosure: In the case of an invention (to include improvement of an invention) or believed invention, the inventor must complete a VA certification page and prepare a statement for submission to the inventor's supervisor. These documents are available at the Technology Transfer Program (TTP) website www.vard.org. The inventor's supervisor must review the employee inventor's statement. The file is then submitted via the Research and Development (R&D) Office for review and approval by the ACOS/R&D. It is then sent to the Director, R&D Technology Transfer Section in VA Central Office. The Technology Transfer Section provides one of three outcomes. They are that the Government:

- (1) Maintains right, title, and interest in, and to, any invention of a Government employee;
- (2) Is entitled to a royalty free license with ownership remaining with the inventor; or
- (3) Claims no interest or license; i.e., all rights remain with the inventor.

6.3 Management of Conflict of Interest

a. Notification of IRB and R&D Committees: The ACOS/R&D is notified of the outcome from R&D Technology Transfer Section in VA Central Office. It is the responsibility of the ACOS/R&D to notify the IRB and R&D Committee by written correspondence when a protocol involves an invention that may involve royalties and patents so that when the IRB reviews (initial, continuing, or review of a modification), the institutional financial conflict of interest is known to the IRB. The R&D Committee will review any actions taken by the IRB through review of IRB minutes. The IRB has the final authority to determine whether the research is approvable.

b. Potential actions: Potential actions to be considered to better protect subjects are any (or a combination) of the following:

- (1) Disclosure of the financial interest to potential subjects;
- (2) Not conducting the proposed research, or halting it if it has commenced;
- (3) Reducing or otherwise modifying the financial (equity or royalty) stake involved;
- (4) Increasing the segregation between the decision-making regarding the financial and research activities;
- (5) Requiring an independent data and safety monitoring committee or similar monitoring body;
- (6) Modifying of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change in investigator; or
- (7) Establishing a research monitoring process, so that the research can be closely scrutinized to ensure that potential conflicts do not undermine the integrity of the work and/or of the PVAMC.

7. REFERENCES

- a. VHA Handbook 1200.5 paragraph 7.A (9)
- b. VHA Handbook 1200.18
- c. OHRP Final Guidance Document. *Financial relationships and interests in research involving human subjects: Guidance for human subject protection*. May 5, 2004.
- d. Association of American Medical Colleges. *Protecting subjects, preserving trust, promoting progress II: Principles and recommendations for oversight of an institution's financial interests in human subjects research*. October 2002.

Appendix A

ACTIVITIES APPROPRIATE FOR EXPEDITED REVIEW

Research activities included in paragraph 2 may be reviewed by an expedited review process, unless otherwise required by the Institutional Review Board (IRB). (Authority: Title 45 Code of Federal Regulations (CFR) 46.110, 38 CFR 16.110, and 21 CFR 56.110.) The following is extracted from 63 FR 60364-60367, November 9, 1998, "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure." NOTE: 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 forth in 38 CFR 16.110.

1. Applicability

a. The following research activities are appropriate for expedited review:

- (1) Research that presents no more than minimal risk to human subjects, and
- (2) Research that involves only procedures described in paragraph 2. The research activities should not be considered of minimal risk merely because of their inclusion in paragraph 2. Inclusion on this list of research activities 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 expedited review process may not be used when identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability; or be damaging to the subject's financial standing, employability, insurability, and/or reputation; or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are minimal.

c. The expedited review process may not be used for classified research involving human subjects.

d. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply to expedited review.

e. The research categories appropriate for expedited review pertain to both initial and continuing IRB review.

2. Research Categories

a. Clinical studies of drugs and medical devices, only when one of the following conditions is met.

- (1) 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.

(2) Research on medical devices for which an investigational device exemption application (21 CFR Part 812) is not required; or the medical device is cleared and/or approved for marketing and the medical device is being used in accordance with its cleared and/or approved labeling.

b. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(1) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 milliliters (ml) in an 8-week period and collection may not occur more frequently than 2 times per week; or

(2) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than two times per week. NOTE: 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" see 45 CFR 46.402(a). Source: 63 Federal Register (FR) 60364-60367, November 9, 1998. VA does not conduct research-involving children as subjects unless a waiver has been obtained from the CRADO.

c. Prospective collection of biological specimens for research purposes by noninvasive means. Examples are as follows:

(1) Hair and nail clippings in a non-disfiguring manner.

(2) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

(3) Permanent teeth if routine patient care indicates a need for extraction.

(4) Excreta and external secretions (including sweat).

(5) 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.

(6) Placenta removed at delivery.

(7) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

(8) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(9) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

(10) Sputum collected after saline mist nebulization.

d. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. NOTE: For VA approved research, the term x-rays as used in this Appendix means ionizing radiation as defined in paragraph 3 of this Handbook. Where medical devices are employed, they must be cleared and/or approved for marketing. NOTE: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications. Examples of procedures eligible for expedited review are:

(1) 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.

(2) Weighing or testing sensory acuity.

(3) Magnetic resonance imaging.

(4) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.

(5) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

e. 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 VA regulations for the protection of human subjects (38 CFR 16.101(b)(4)). This listing refers only to research that is not exempt.

f. Collection of data from voice, video, digital, or image recordings made for research purposes.

g. 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 VA regulations for the protection of human subject (38 CFR 16.101(b)(2) and (b)(3)). This listing refers only to research that is not exempt.

h. Continuing review of research previously approved by the convened IRB as follows:

(1) Research in which the enrollment of new subjects is permanently closed; all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or

(2) Research in which no subjects have been enrolled and no additional risks have been identified; or

(3) Research in which the remaining research activities are limited to data analysis.

i. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (listed in subpars. 2b

through 2h of this App.) 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.