

Portland Veterans Affairs Medical Center

Institutional Review Board Policies & Procedures

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Substantive changes in this revision:

1. Revised Title
2. Revised order of items throughout the document
3. Revised protocol deviation reporting and review policy
4. Revised policy regarding required review for change in PI
5. Revised policy regarding attendance of PI at meetings for mentored studies
6. Clarified language regarding requirements for safety monitoring
7. Removed language regarding FDA-regulated test articles, as it will be captured in the "Investigational Device and/or Drug Usage in Research & Development Service" policy

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I. INTRODUCTION

The Portland VA Medical Center (PVAMC) Institutional Review Boards' (IRB) Policies & Procedures (P&P) for the protection of human subjects in research is a reference for IRB members, IRB analysts, investigators, and other individuals associated with the Human Research Protection Program (HRPP). This P&P details the policies and procedures based on the regulations and policies governing human research and the requirements for submitting research proposals for review by the IRB. All references to IRB in this document refer to all IRBs functioning under the PVAMC's signed Federalwide Assurance (FWA) governed by the Office for Human Research Protections (OHRP). Each IRB shall adhere to the policies and procedures outlined in this P&P document. Other policies and procedures not included in this document are referenced by title, and are available on the PVAMC R&D & Development Web page.

Questions regarding the PVAMC IRB P&P may be directed to the IRB analysts and/or the Research Assurance Officer.

Additional information about the Research Program and the Human Research Protection Program may be accessed on the PVAMC Research & Development Home Page at <http://www.portland.va.gov/research/index.asp>.

II. ABBREVIATIONS

ACOS	Associate Chief of Staff
AE	Adverse Event
AO	Administrative Officer
CFR	Code of Federal Regulations
COS	Chief of Staff
CRF	Case Report Form
CRQ	Continuing Review Questionnaire
CRADO	Chief Research and Development Officer
DHHS	Department of Health & Human Services
DOD	Department of Defense
DPAHC	Durable Powers of Attorney for Health Care
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FWA	Federalwide Assurance
HIPAA	Health Insurance Portability & Accountability Act
HRPP	Human Research Protection Program
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
IRQ	Initial Review Questionnaire
ISO	Information Security Officer
MIRB	Manage Your Institutional Review Board
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Sciences University
ORD	Office of Research and Development, VA Central Office
ORO	Office of Research Oversight
P&P	Policies & Procedures
PHI	Protected Health Information
PI	Principal Investigator
PO	Privacy Officer
PVAMC	Portland VA Medical Center
R&D	Research & Development
RAO	Research Assurance Officer
RCO	Research Compliance Officer
RSO	Radiation Safety Officer
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
UAE	Unanticipated Adverse Event/Experience
UPR	Unanticipated Problem Involving Risks to Subjects or Others

III. DEFINITIONS

- **Adverse event (AE) or problem:** any untoward physical or psychological 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 the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research.
 - 1) **Serious Adverse Event:** an AE that results in death, a life-threatening experience, inpatient hospitalization or prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes; or death.
 - 2) **A local or internal AE** in the context of a multi-site study is one occurring in a human subject, research staff or others participating in a PVAMC IRB-approved research project conducted at PVAMC or by PVAMC staff with participants who are enrolled at PVAMC or by PVAMC staff.
 - 3) **Serious Problem:** a problem that may reasonably be regarded as
 - 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.
 - 4) **Related AE or Problem:** one that may reasonably be regarded as caused by or probably caused by the research.
 - 5) **Unanticipated Problem involving Risk (UPR):** event or problem in VA research that is new or greater in nature, severity, or frequency than previously known given the procedures described in protocol-related documents and the characteristics of the study population.
- **Administrative Hold:** voluntary interruption of research enrollments and/or ongoing research activities by an appropriate facility official, research investigator, or sponsor (including the VHA Office of Research and Development (ORD) when ORD is the sponsor). The term does not apply to interruptions of VA research related to concerns regarding safety, rights, or welfare of human research subjects, research investigators and staff, or others.
- **Administrative Termination:** projects for which the approval period has expired and the Principal Investigator (PI) has failed to complete the continuing review paperwork (provided there are no subjects currently enrolled) may be administratively terminated at the discretion of the IRB. In such a case the PI will be notified of the termination and a new submission will be required if the project is to resume.
- **Administrative Withdrawal:** a new proposal that has received contingent approval or was tabled at the IRB initial review may be administratively withdrawn if the PI fails to meet the contingencies the IRB has specified. Please see Section VII, T, for more information. In such a case the PI will be notified of the withdrawal and a new submission will be required if the approval process of the project is to resume.
- **Anonymous:** de-identified information, i.e. the identity of an individual who has provided a sample, or from whom genetic information has been obtained, or the identity of the individual's blood relatives cannot readily be determined or associated with the information. "Anonymous" does not mean coded, i.e. using an encryption key or other means of linking the information to a specific individual. (Also see definition of De-Identified.)
- **Blinded:** a study design comparing two or more interventions in which the investigators, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects; it is sometimes called a masked study design.

- **Conflict of Interest:** a conflict of interest exists when an individual's financial interests or other obligations interfere, or appear to interfere, with the individual's obligations to act in the best interests of the human research participants and the PVAMC and without improper bias. This may include both financial and non-financial conflicts of interest. The mere appearance of a conflict may be as serious and potentially damaging to the public trust as an actual conflict. Therefore, potential conflicts must be disclosed, evaluated, and managed with the same thoroughness as actual conflicts. Please see the HRPP Policy "Conflict of Interest in Research" at <http://www.portland.va.gov/portland/research/documents/hrpp/coi-policy.pdf>.
- **De-Identified:** 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. In order to be considered de-identified, the following 18 elements must be removed: name; address; names of relatives; names of employers; birth date; telephone number; fax number; e-mail addresses; social security number; medical record number; health plan beneficiary number; account number; certificate/license number; any vehicle or device serial number; web URL; Internet Protocol Address; Finger or voice prints; Photographic images (e.g. full facial photographs); and any other unique identifying number, characteristic, or code. Information may also be statistically de-identified. This is typically performed by an experienced statistician who analyzes the data and affirms that the risk is "very small" that a particular person could be identified from the information collected. (Also see definition of anonymous.)
- **Exempt Research:** research determined by the Institutional Review Board (IRB) to involve human subjects only in one or more categories as determined by OHRP. **NOTE:** Categories of exemption are listed on the Certification of Exemption form at http://www.portland.va.gov/portland/research/piservices/rd_forms.asp#alphabetical.
- **Experimental Subject:** as defined by the DOD, human subject involved in research under a DOD Addendum that involves an intervention or interaction with the subject for the primary purpose of obtaining data regarding the effect of either.
- **Federal-wide Assurance (FWA):** a written commitment by an institution to protect human subjects participating in research. Under federal regulations, any institution conducting or engaged in federally supported research involving human subjects must obtain an FWA in accordance with 38 CFR 16.103. *NOTE: All research conducted under VA auspices is considered to be Federally-supported.* This requirement also applies to any collaborating "performance site" institutions. Under 38 CFR 16.102(f), an institution is engaged in human subject research whenever its employees or agents: intervene or interact with living individuals for research purposes; or obtain, release, or access individually-identifiable private information for research purposes. FWAs are filed through the VA Office of Research Oversight (ORO) with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP).
 - **FWA: Department of Defense (DOD) Addendum:** Addendum to FWA that must be filed by the central Office of Research and Development (ORD) when a study is sponsored by the Department of Defense and the DOD requires. Such an addendum describes specific DOD responsibilities for the study.
- **Fetus:** is the product of conception from the time of implantation until delivery.
 - **Viable fetus:** is now termed a "viable neonate."
 - **Nonviable fetus:** is a fetus *ex utero* that, although living, is not able to survive to the point of independently maintaining heart and respiration. *NOTE: In 45 CFR 46 Subpart B, this definition is used as the definition of a non-viable neonate.*
 - **Dead fetus:** is a fetus which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.
- **Human Biological Specimens:** defined in VHA Directive 2000-043 as "any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or

fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures.”

- **Human Research Protection Program (HRPP):** a comprehensive system to ensure the protection of human subjects participating in research. The ethical conduct of research is a shared responsibility among all individuals involved in the HRPP. It requires cooperation, collaboration, and trust among the institution, investigators and their staff, the subjects who enroll in the research, Institutional Review Board members, R&D Committee members, and R&D Service staff.
- **Human Subjects:** defined by federal regulations 45 CFR 46 and 38 CFR 16.102 (f)] as "living individual(s) about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects." The VA regulations further define human subjects to include investigators, technicians, and other assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled.
 - **Human subjects per FDA regulations:** an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. In addition, 21 CFR 812.3 states a "*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."
 - **Human subjects per DOD regulations:** a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information. *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.
- **Individually-identifiable Information:** 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. Individually-identifiable health information is covered by the Health Insurance Portability and Accountability Act of 1996 (HIPAA), regardless of whether or not the information is retrieved by name. This includes information about the individual which is or may be readily ascertained by the investigator or associated with the information, even through the use of a codebook. "Individually identifiable information" is considered to be information attached to one or more of the 18 unique

identifiers defined in the HIPAA Human Subjects Research Policy and Procedure (<http://www.portland.va.gov/Research/hrpp/index.asp#policies>).

— Although coded information is generally considered individually identifiable, the following situations would render information not individually identifiable in a research project: (a) the investigators and the holder of the code-key enter into a written agreement prohibiting the release of the code-key to the investigators under any circumstances; or (b) there are written policies and operating procedures approved by the Institutional Review Board (IRB) for a repository or data management center that prohibit the release of the code-key to the investigators under any circumstances; or (c) there are other legal requirements prohibiting the release of the code-key to the investigators. Human subjects are discussed in Title 38 Code of Federal Regulations Part 16 (38 CFR 16) and VHA Handbook 1200.05. Guidance regarding use of biological specimens in research may be found on the ORD Web site at http://www.research.va.gov/programs/tissue_banking/default.cfm.

- **Individually-identifiable Health Information:** 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.
- **Institutional Review Board (IRB):** a formally established subcommittee of the Research and Development (R&D) Committee with and for the purposes expressed in the Common Rule. The IRB is an appropriately constituted group that the VA has formally designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. The IRB also provides oversight and monitoring of such protections. In accordance with the Common Rule, VA and FDA regulations, the IRB has responsibility for approving, requiring modification (to secure approval), or disapproving research.
- **Investigational Device:** as defined by the FDA, a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device. Investigational devices include transitional devices that are objects of investigations.
- **Investigational Drug:** a chemical or biological drug that is used in a clinical investigation. The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug. However, for purposes of this IRB P&P, an Investigational Drug may be 1) an approved drug that is being studied for an unapproved or approved use, dose, dosage form, administration schedule, or under an IND application in a controlled, randomized, or blinded clinical trial or 2) a new chemical compound not yet released by the FDA for general use. Concurrent medications, comparators, or rescue medications used in the clinical trial that are not the drug(s) being studied are not defined as investigational drugs unless they are not commercially approved or not available through commercial channels. Prescription drugs, over-the-counter drugs, nutritional supplements, herbal preparations, and legend items used for diagnosis or treatment and meeting the definition of "investigational drug" are considered investigational drugs.
- **Investigational Device Exemption (IDE):** an application to the FDA that allows an investigational significant risk device to be used in a clinical investigation to collect safety and effectiveness data. If the device is determined by the IRB to be a non-significant risk device, it is considered to have an approved application for IDE after IRB approval is obtained.
- **Investigational New Drug (IND Application):** an application to the FDA that allows an investigational drug or biological product to be studied in humans. An IND must be in effect prior to shipment and administration of investigational drug or biological products. IND is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." **NOTE:** See 21 CFR 312.2(a)-(b) at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312> for applicability and exemptions. See definition of Investigational Drug above.

- **Investigator**: an individual under the direction of a Principal Investigator (PI) who is involved in some or all aspects of the research project, including the design and conduct of the study, analysis and interpretation of the collected data, and writing of resulting manuscripts. An investigator must be compensated by VA, be appointed to work without compensation (WOC), or be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970. The FDA considers an investigator and a PI to be synonymous.
- **Ionizing Radiation**: particles or rays with sufficient energy to cause the ejection of orbital electrons from absorber atoms. Ionizing radiation should be addressed within the protocol and the informed consent when used in a research study. Ionizing radiation includes diagnostic and therapeutic procedures done for research purposes. Sources of radiation include nuclear medicine, radiation therapy, and radiology.
- **Legally Authorized Representative (LAR)**:
 - 1) For purposes of signing an informed consent, a legally authorized representative is defined as an individual, or judicial or other body, authorized under applicable Federal law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. An LAR includes not only persons appointed as healthcare agents under Durable Powers of Attorney for Health Care (DPAHC), but also the following in descending order of priority:
 - a. Health Care agent (i.e. an individual named by the individual in a Durable Power of Attorney for Health Care) (38 CFR 17.32(e))
 - b. Court appointed guardians of the person
 - c. Spouse
 - d. Adult children (18 years of age or older)
 - e. Parent
 - f. Adult siblings (18 years of age or older)
 - g. Grandparent
 - h. Adult grandchild (18 years of age or older)
 - i. Close friend

Note: The list above contains the only surrogate entities allowed to provide consent for research purposes. Refusal to consent by a person who is a higher priority surrogate shall not be superseded by the consent of a person who is a lower priority surrogate. Additionally, if there are two or more individuals in the same class and the decision is not unanimous among all available members of the class, then no person under this section may provide informed consent. Surrogates may not receive financial compensation for providing consent.
 - 2) For purposes of signing a HIPAA Authorization, a legally authorized representative is defined as follows:
 - a. A court-appointed legal guardian (Note: *A VA Federal fiduciary administratively appointed by VBA to administer a beneficiary's VA monetary benefits is not empowered to exercise privacy rights of the VA beneficiary who is the subject of that appointment including granting authorization, i.e. Power of Attorney.*)
 - b. A person legally authorized in writing by the individual (or the individual's legal guardian) to act on behalf of the individual.
 - c. If the individual is deceased, then Executor of Estate, next-of-kin, or other person who has authority to act on behalf of the individual.
- **Minimal Risk**: when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- **Minors (Children)**: persons who have not attained the legal age of 18 for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

- **Neonate**: newborn.
 - 1) **Viable neonate**: newborn that is able, after delivery, to survive to the point of independently maintaining heart and respiration (given the benefit of available medical therapy).
 - 2) **Non-viable neonate**: see under “fetus”.
- **Non-Compliance**: Failure to adhere to federal regulations or the requirements or determinations of the IRB.
 - 1) Serious non-compliance
 - a. involves substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
 - b. substantively compromises the effectiveness of a facility’s human research protection or human research oversight programs.
 - 2) Continuing non-compliance is a persistent failure to adhere to the laws, regulations, or policies governing human research.
- **Office of Research and Development (ORD)**: the office within VHA Central Office responsible for the overall policy, planning, coordination, and direction of research activities within VHA. **NOTE**: The Program for Research Integrity Development and Education Program (PRIDE) is the program within ORD responsible for training, education, and policy development related to human subjects protection.
- **Office of Research Oversight (ORO)**: the primary VHA office for advising the Under Secretary for Health on all matters of compliance and assurance regarding human subject protections, animal welfare, research safety and security, research information protection, and research misconduct. **NOTE**: *ORD and ORO are two separate offices within VHA. The CRADO reports to the Principal Deputy Under Secretary for Health. The Chief Officer of ORO reports to the Under Secretary for Health.*
- **Pregnancy**: period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test) until expulsion or extraction of the fetus.
- **Principal Investigator (PI)**: within VA, an individual who conducts a research investigation, i.e. under whose immediate direction research is conducted, or, in the event of an investigation conducted by a team of individuals, the responsible leader of that team. The FDA considers a PI and an investigator to be synonymous.
- **Prisoner**: any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- **Private Information**: information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. Private information is information about a patient and/or study participant that is “individually identifiable” (see definition above).
- **Qualified Designee**: for the IRB Chair, either the IRB Alternate Chair or other voting IRB member with commensurate experience.
- **Quorum**: more than half of the voting members of a committee being present and including
 - 1) at least one member whose primary concerns are in non-scientific areas,
 - 2) at least one non-affiliated member,
 - 3) for FDA-regulated studies, at least one member is a licensed physician,
 - 4) for research that involves participants likely to be vulnerable to coercion or undue influence, at least one IRB member knowledgeable about or experienced in working with such participants, and

5) at least one member representing the general perspective of participants.

At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.

- **Research:** defined by the VA regulations as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
 - 1) Systematic - designed to answer a question or test a hypothesis that addresses a research intent by an organized method.
 - 2) Generalizable – knowledge that may be applied to populations or settings different from the ones used in the investigation
 - 3) FDA regulations define research as “any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i)” (i.e. any use of a drug other than the use of an approved drug in the course of medical practice, “or 520(g),” (i.e. any activity that evaluates the safety or effectiveness of a device), “of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.”
“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. In summary, an activity is FDA-regulated research (clinical investigation) when 1) it involves the use of a drug other than the use of an approved drug in the course of medical practice; and/or 2) involves evaluating the safety or effectiveness of a device and/or 3) data will be submitted to or held for inspection by FDA.
 - 4) The FDA regulations further state that “...the terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.”
 - 5) Any prospective or retrospective collection of clinical data with the intent to contribute to generalizable knowledge constitutes research as defined by VA regulations. Examples of such clinical data collection include research seminars, posters, abstracts, manuscripts, and pilot data. Case Reports (published reviews of three or fewer clinical records by one or more members of the care team) are not considered research, but do require submission of an Application for Case Report Review application to an IRB analyst. Clinical reviews (reviews of four or more clinical records whether or not care team members are involved) are considered human research and must have IRB and Research & Development Committee approval.
 - 7) Research involving human subjects means any activity that either:
 - a. Meets the VA definition of research” and involves human subjects as defined by VA; or
 - b. Meets the FDA definition of research and involves human subjects as defined by FDA.
- **Research Records:** Research records include, but are not limited to, IRB and R&D Committee records, records of all observations, other data relevant to the investigation, progress notes, research study forms, surveys, questionnaires, and other documentation regarding the study.
 - 1) **IRB Records:** IRB records include, but are not limited to, copies of all research proposals and amendments reviewed; scientific evaluations, if any, that accompany the proposals; approved informed consent documents; progress reports submitted by investigators; reports of injuries to subjects; reports of complaints from subjects; minutes of IRB meetings; reports of expedited review activities; records of continuing review activities; copies of all correspondence between IRB and the investigators; reports of deviations from IRB-approved protocol; a list of IRB members; written procedures for IRB in the same detail as described in 38 CFR 16.103(b)(4) and (5); and statements of significant new findings provided to subjects as required by 38 CFR 16.116(b)(5).

- 2) **Investigators' Research Records:** all relevant research documents including copies of all IRB-approved versions of the protocol and amendments; case report forms and supporting data (including but not limited to signed and dated informed consent forms and HIPAA authorization forms); documentation for each subject including signed informed consent, interactions with subjects by telephone or in person, observations, interventions, and other data relevant to the research study; reports of adverse events; data analyses; codes and keys used to de-identify and re-identify subjects' PHI; reports (including, but not limited to abstracts and other publications); all correspondence (including, but not limited to, that with the funding source or sponsor) and with applicable oversight entities (including, but not limited to, IRB, R&D Committee, ORO, and FDA); and a master list of all subjects for whom informed consent has been obtained in the study, regardless of whether the IRB approved a waiver of informed consent documentation.
- **Suspension of Research:** a temporary interruption of some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. NOTE: This does not include interruptions resulting solely from the expiration of the IRB approval period.
 - **Termination of Research:** a permanent halt of all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review. **Termination of approval** occurs when the IRB determines that the research study must cease or when the investigator has completed all work and requests to close the study.
 - **Test Article:** a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.
 - **VA Research:** research approved by the R&D Committee, conducted by VA investigators with a VA appointment (Compensated, Without Compensation –WOC, or Intergovernmental Personnel Agreement – IPA) while on VA time, using VA resources (e.g., equipment), and/or on VA property (including space leased or used by VA). The research may be funded by VA or other sponsors or may be unfunded.
 - **VA Facility:** any entity operated by the VA, including but not limited to VA hospitals, medical centers, and healthcare systems; space owned, leased, or rented by VA; and space shared with a non-VA entity (unless the VA space is leased to a non-VA entity and specifically designated in writing not to be used by VA or VA employees for research).

IV. PURPOSE AND ETHICAL FRAMEWORK

A. Purpose of the IRB

The PVAMC IRBs' primary responsibility is to ensure that the rights and welfare of subjects are protected in the VAMC human research program. In doing so, the IRBs must ensure that human research is conducted ethically, and in compliance with VA other federal regulations, applicable Oregon and Washington state laws (applicable if determined by Regional Counsel to be more stringent than federal law), the signed FWA, and the PVAMC's institutional policies and procedures.

B. Ethical Principles Governing the IRB

VA Research must be carried out in an ethical manner. The basic ethical principles governing research involving human subjects are provided in the Nuremberg Code (<http://ohsr.od.nih.gov/guidelines/nuremberg.html>), the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/index.html>), and the Belmont Report (<http://ohsr.od.nih.gov/guidelines/belmont.html>).

1. The Nuremberg Code

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

2. The Declaration of Helsinki

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

3. The Belmont Report

The Belmont Report contains three basic ethical principles central to human research that guide the IRB in assuring protection of the rights and welfare of subjects. These three principles are:

- i. **Respect for persons** recognizes individual autonomy and is applied by obtaining informed consent, consideration of privacy and confidentiality, and assuring additional protections for vulnerable populations.
- ii. **Beneficence** requires that possible benefits are maximized and possible risks minimized for research subjects.
- iii. **Justice** is evidenced in the equitable selection of subjects with regard to distribution of burdens and benefits.

C. The Regulatory Mandate to Protect Human Subjects

The Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects:

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

In January 1991, the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VA at 38CFR16, the Common Rule is also codified by the Department of Health and

Human Services (DHHS) as Subpart A of the DHHS regulations at 45CFR46. DHHS has three additional Subparts in the regulations, as well, that are not in 38CFR16. **All** human subject research conducted at the PVAMC must adhere to the regulations at 45CFR46 and 38CFR16.

2. **VA regulations and the Federal Policy (Common Rule) for the Protection of Human Subjects**

1. 38 CFR 16 – Protection of Human Subjects
2. 38 CFR 17.33 - Patients' rights
3. 38 CFR 17.85 - Treatment of research related injuries to human subjects
4. 38 CFR 17.45 - Hospital care in research studies
5. 38 CFR 17.92 - Outpatient care for research studies

Codified by the VA at 38 CFR 16, the Common Rule is identical to Subpart A of the DHHS regulations, but does not include the additional DHHS Subparts B, C, and D.

3. **Food and Drug Administration (FDA) Regulations**

The following FDA regulations must also be adhered to when appropriate:

1. 21 CFR 50 – Protection of Human Subjects
2. 21 CFR 56 – Institutional Review Boards
3. 21 CFR 54 – Financial Disclosure by Clinical Investigators
4. 21 CFR 312 - Investigational New Drugs (IND)
5. 21 CFR 812 – Investigational Device Exemptions (IDE)

4. **DHHS Office for Human Research Protections (OHRP) – Federalwide Assurance**

DHHS mandates that every institution conducting human research with federal funds register itself with OHRP and obtain an assurance of compliance approved by the OHRP. Under this OHRP-issued Federalwide Assurance (FWA), the IRB that reviews the human research projects is responsible for adhering to and fulfilling the requirements of the Federal regulations of 45CFR46.

The PVAMC IRB Assurance number is FWA00000517.

The IRBs that the PVAMC utilizes, and their registration numbers, are as follows:

- The VA Med Ctr, Portland, OR IRB#1. The registration number is IRB00001976.
- The VA Med Ctr, Portland, OR IRB#2. The registration number is IRB00003313.
- Veterans Health Administration Central Office, IRB #1. The registration number is IRB00006332.
- Oregon Health & Science University IRB-3. The registration number is 0000471.

All Community Based Outpatient Clinics over which the PVAMC has legal authority are listed by name in the FWA. Information regarding the FWA may be found by accessing the U.S. Department of Human Services Office for Human Research Protections web site <http://ohrp.cit.nih.gov/search/> and entering the FWA number. The Portland VAMC IRBs abide by the terms in the FWA.

The use of a commercial IRB is not permitted.

5. **Department of Defense (DOD) Regulations at 32 CFR 219**

DOD regulations must also be followed when appropriate, i.e. research funding is granted by the DOD for research approved by the PVAMC IRB. Under such circumstances, if the DOD requests, a DOD addendum will be added to the FWA for the PVAMC. R&D office staff will determine at initial review if a DOD addendum is required. The responsible staff member will add the addendum to the FWA and then notify IRB analysts, IRB chair and members, investigators and research staff of any special requirements.

D. Authority of the IRB

1. Authority of the PVAMC IRBs

The PVAMC IRBs, designated by the PVAMC Director and the R&D Committee (VHA Handbook 1200.05), and named in the FWA must prospectively review and make a decision concerning all human subject research conducted at the PVAMC or by PVAMC employees or agents, or otherwise under the auspices of the VA. Further, these IRBs have statutory authority to

1. take any action necessary to protect the rights and welfare of human subjects in the research program;
2. approve, require modifications in, or disapprove the facility's human research, based on its consideration of the risks and potential benefits of the research, and whether or not the rights and welfare of human subjects are adequately protected;
3. conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (38 CFR 16.109);
4. suspend or terminate the enrollment and/or ongoing involvement of human subjects in each facility's research as it determines necessary for the protection of those subjects (38 CFR 16.113); and
5. observe and/or monitor the PVAMC's conduct of human research, including the informed consent process, to whatever extent it considers necessary to protect human subjects.

2. Review of Research at Other Institutions

The IRB is responsible for the protection of the rights and welfare of human research subjects at the PVAMC and for research conducted under PVAMC auspices.

The IRB may be designated for review of research under another institution's assurance only with the written agreement of the Medical Center Director and in accordance with applicable ORD, ORO, and OHRP requirements. Such designation must be accompanied by a written agreement specifying the responsibilities of the facility and its IRB under the other institution's assurance. IRBs operated by the PVAMC have no authority over or responsibility for research conducted at other institutions in the absence of such a written agreement.

E. Review of Policies and Procedures

This Standard Operating Procedure of the IRB must remain current and in compliance with all applicable regulations. To remain current, this P&P must be reviewed and periodically updated. The Research Assurance Officer (RAO) with the assistance of the IRB Chairs, IRB analysts, ACOS/R&D, and AO/R&D will update these policies and procedures to comply with the most recent VA and federal regulations. Proposed changes will be presented to each IRB for input. Revisions will be implemented upon review and approval of a majority of each IRB. The revised version will then be forwarded to the R&D Committee for approval. Notifications of changes and an updated IRB P&P will be made available electronically to all members, and distributed in hard copy to those who request it.

Other documents used by the IRB for its day-to-day functions, including but not limited to investigator submission forms, investigators' manual, guidance documents, reviewer forms, checklists, etc., will also be reviewed and revised as needed.

V. Shared Responsibilities of the Institution in Protecting Human Subjects

A. Medical Center Director

The Medical Center Director is the FWA Signatory Official. The Signatory Official is the official legally authorized to represent the institution under the Department of Health & Human Services approved FWA. The Medical Center Director is responsible for the research program:

1. Fostering an institutional culture that supports the ethical conduct of all human research;
2. Completing assurance training prior to signing FWA and every 3 years thereafter;
3. Ensuring compliance with all Federal and VA regulations governing research including ensuring that any IRB(s) of record are established in accordance with the requirements of applicable handbooks and regulations, registered with OHRP and, if appropriate, FDA, and listed as an IRB of record on the PVAMC FWA;
4. Accountable for the HRPP within the facility including but not limited to
 - overseeing the IRBs, R&D Committee, research office, and all researchers, ensuring they are appropriately knowledgeable to conduct research in compliance with ethical standards and all applicable regulations,
 - assuring the development and implementation of an educational plan for IRB members, staff, and researchers.
5. Appointing the voting members, including chairs, alternate chairs, members, and alternate members of the R&D Committee and all of its subcommittees and reviewing and approving all R&D Committee meeting minutes;
6. Suspending or terminating the IRB membership of any individuals not fulfilling their responsibilities or obligations;
7. Assuring the independence of the IRBs and offering direct access to chairs, alternate chairs, and members if they experience undue influence or have concerns about the IRB;
8. Assuring adequate resources including but not limited to administrative space for meetings (with privacy) other sensitive duties, for offices, and for secure storage of records; appropriately knowledgeable personnel, equipment, and educational opportunities;
9. Acting as point of contact for correspondence addressing human research with OHRP, FDA, and VHA Central Office;
10. Ensuring the HRPP is appropriately accredited;
11. Certifying that all personnel involved in research have appropriate credentials and, if applicable, privileges;
12. Ensuring a local Research Subject Outreach Program that includes
 - communication about individual studies,
 - information about volunteering in research,
 - venues for information and input, and
 - educational activities, when appropriate;
13. Ensuring that no recruiting documents, flyers, or advertisements for non-VA research are posted within or on the premises of the PVAMC;
14. Appointing a Research Compliance Officer who reports directly to the Director and is responsible for developing and implementing a research compliance program;
15. Ensuring appropriate audits of studies and informed consents;
16. Approving requests for permission to conduct international research and ensuring CRADO approval prior to its initiation at PVAMC; and
17. Assuring an annual evaluation of the HRPP.
18. When an external IRB (e.g., Oregon Health and Science University – OHSU, with whom PVAMC has an affiliate MOU) other than the VA Central IRB is an IRB of record, the Director is responsible for

- signing a separate MOU that delineates the respective roles, responsibilities, and authorities of the VA facility and the external organization providing the IRB, including, but not limited to, the external organization's providing unredacted IRB minutes and other relevant documents to PVAMC with the organization providing the IRB;
 - ensuring compliance with all VA and other federal regulations by the external IRB;
 - appointing two or more VA employees with a minimum of 5/8th VA-compensated appointments (no without-compensation or Inter-agency Personnel Agreement - IPA - appointments) as voting members unless a waiver for such representation is obtained from the CRADO;
 - at least one VA member must have scientific expertise and
 - at least one must be present during review of PVAMC research at a convened meeting,;
19. When the VA Central IRB is an IRB of record, the Director is also responsible for
- signing and adhering to the MOU between VHA Central Office and PVAMC; and
 - delegating authority for commenting and responding to VA Central IRB review in response to initial review considerations, whether PVAMC chooses or declines to participate in a study, and serving as liaison between PVAMC as well as the Local Site Investigator (LSI) with VA Central IRB.

The Director delegates the authority for all respective roles and responsibilities within the HRPP, providing organizational structure and ensuring accountable leadership for oversight activities for all human research at PVAMC to the Associate Chief of Staff/R&D.

B. Associate Chief of Staff/Research & Development (ACOS/R&D)

The Associate Chief of Staff for Research & Development reports to the Director through the COS and is responsible for the following:

1. Developing, managing and evaluating policies and procedures that ensure compliance with all federal regulations and any applicable state statutes (as determined by Regional Counsel to be more stringent than federal law) governing research. This includes monitoring changes in state, VA and other federal regulations and policies related to human research protection and overseeing all aspects of the HRPP program established for human research protections.
2. Acting as liaison between the VHA Office of Research and Development and the institution's R&D Committee, as well as advising the Director and VISN 20 leadership on key matters regarding research.
3. Implementing the institution's HRPP policy.
4. Assuring that principal investigators and other researchers are informed via targeted email when HRPP policies are changed.
5. Submitting, implementing, and maintaining an approved FWA through the Medical Center Director and the Office of Research Oversight (ORO) and to the Office of Human Research Protections (OHRP).
6. Administering the facility's R&D programs, including the R&D Committee and applicable subcommittees.
7. Managing the finances of the facility's R&D Program.
8. Assisting investigators in their efforts to carry out the VA's research mission by providing educational opportunities and informing investigators of all changes in federal and applicable state regulations and local policies governing human research.
9. Developing and implementing needed improvements and ensuring follow-up of actions as appropriate for the purpose of managing risk in the research program.
10. Developing training requirements and ensuring that these training requirements, including those for human, animal, and bio-safety research for investigators and members of the applicable subcommittees and staff are completed.

11. Reviewing, or designating a reviewer for, all sponsor agreements to assure ethical standards and practices in research are upheld.
12. Developing plans and methods, implementing, and evaluating programs for outreach to research participants, potential participants and their communities.
13. Suspending or terminating research on an urgent basis if it is not being conducted in accordance with the IRB's requirements.
14. Assure research policies prevent billing of research subjects for research visits.
15. Fulfilling all other responsibilities delegated by the Director and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.

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

The Privacy Officer and Information Security Officer are responsible for ensuring proposed human research complies with all applicable requirements for privacy, confidentiality, and information security. They do not have responsibility for approving or disapproving a study, nor the authority to prevent or delay IRB approval of a study. However, to ensure compliance and streamline communication with PIs, any privacy, confidentiality and information security concerns identified by the PO and/or ISO are included with the IRB contingencies and communicated to the PI by the IRB analysts. The PO and ISO are responsible for the following:

1. reviewing all proposed study protocols and any other relevant materials submitted with the IRB application;
2. identifying any deficiencies and make recommendations for correction;
3. follow-up with the PI in a timely manner to ensure research is in compliance with relevant privacy, confidentiality, and information security requirements before the study is initiated;
4. providing summary reports clearly indicating that all applicable requirements have been met or identifying specific deficiencies and suggesting available options for correcting those deficiencies to the IRB analysts or, in the case of exempt research, to the ACOS/R&D, within a time frame that does not prolong the approval process;
5. assuring all studies are in compliance before research initiation; and
6. generating monthly reports in the Computerized Patient Record System (CPRS) to identify subjects whose participation in research has been completed or terminated.

D. Deputy Associate Chief of Staff/ Research & Development

At the PVAMC, the Deputy ACOS/R&D fulfills all duties and responsibilities delegated by the ACOS/R&D.

E. Research & Development Committee

The Research & Development Committee serves in an advisory capacity to the Medical Center Director through the COS on the professional and administrative aspects of the research program. For specific responsibilities, see Standard Operating Procedures for the Research & Development Committee at <http://www.portland.va.gov/research/documents/rd-sop.pdf>.

F. The Principal Investigators (including local site investigators in multi-site studies)

The IRB recognizes one Principal Investigator (PI) or two co-PIs for each project. Anyone with a research appointment, either VA-paid or WOC, may be designated as PI, unless they are in training. Those in training, e.g., residents, fellows, students serving internships or externships, even if they have a license or certification, may not be designated as PI. Such investigators must be mentored and the mentor must serve as PI.

The PI has ultimate responsibility for his/her research project and must act in accordance with the policies of the HRPP and the IRB and report to the IRB as required.

Principal Investigators conducting human research at the PVAMC are responsible for adhering to the responsibilities, policies and procedures outlined in the MCM No. 151-01, IRB P&P and HRPP policies and procedures. Specific responsibilities include:

1. Ensuring research is scientifically sound and minimizing risk to subjects or others.
2. Ensuring compliance with all applicable local, VA, and other Federal requirements.
3. Ensuring adequate resources to carry out the research safely, including but not limited to sufficient investigator time, appropriately qualified research team members, equipment, and space.
4. Submitting all required reports by the due date(s) specified by the R&D Service administrative office to comply with federal, VHA and local requirements.
5. Completing all required education in the protection of human research participants, as well as other required training for research.
6. Overseeing research staff, assure all education and training requirements are met, assure the research study is implemented in accordance with the approved protocol, and that all staff meet all VHA, federal, and local requirements.
7. Maintaining credentials and, as appropriate, privileges at the PVAMC for performing all procedures proposed in all research protocols involving human subjects submitted by the principal investigator. If an investigator lacks the requisite credentials and/or privileges, a collaborating VA clinician who is appropriately credentialed and/or privileged must be listed on the application as the responsible clinician. The collaborating clinician assumes responsibility for the specific procedures in question and for all study-related health care decisions and will be listed on the IRQ as the responsible clinician.
8. Initiating the study only **after** receiving written final approval from the IRB and the ACOS/R&D.
9. Adhering to all assurances given to the IRB at the time the project was approved and ensuring that the study is implemented as approved by the IRB and in accordance with all applicable requirements.
10. For studies involving drugs, devices, or other FDA-regulated test articles, adhering to all requirements in the "Investigational Device and/or Drug Usage in Research & Development Service" policy.
11. Distributing the "Volunteering in Research" brochures received from the R&D Office at the time of approval of the research study to all participants.
12. Giving a copy of the signed consent form to each subject and assure the subject initials the original signed consent form acknowledging receipt of the copy. For studies which involve the Research Pharmacy, a copy must also be provided to the Research Pharmacy.
13. Forwarding the original signed HIPAA Authorization, the signed informed consent form (VA Form 10-1086) and, if applicable, Consent for Use of Picture and/or Voice (VHA Form 10-3203) for each participant enrolled in the research project to the R&D Service for scanning into the participant's electronic medical record or a study folder (for subjects not requiring a CPRS record). After auditing and scanning, the R&D Service will return the original signed consent form to the principal investigator (or designated coordinator) for inclusion in the case history files.
14. Creating progress notes for participants in the Computerized Patient Record System (CPRS), when appropriate (see section XVIII, O & P of this P&P).
15. Maintaining a master list of all consented subjects and securing it appropriately in compliance with VA confidentiality and information security requirements in the investigator's files.
16. Maintaining an Accounting of Disclosures of PHI to all non-VA entities.
17. Submitting all original unanticipated adverse events, problems involving risk and other required reports outlined in section XVI occurring in the study to the IRB in a timely manner consistent with PVAMC policy.

18. Completing and submit in a timely manner to avoid lapse of approval annual review forms for continuing approval of ongoing research.
19. Submitting publications resulting from research to the R&D Committee for approval prior to publication. The publication must include the PVAMC in the address of authors, and VA support must be mentioned in a footnote or acknowledgment.
20. Citing PVAMC IRB approval in the methods section of all manuscripts involving human studies.
21. Informing the Chief of Pharmacy Service when a study involving investigational drugs has been terminated.
22. Maintaining research files based on standards of good clinical practice (see Definitions in this P&P, Investigator research records).
23. Fulfilling all other responsibilities and adhere to the policies and procedures outlined in the appropriate institutional, HRPP, and R&D Service committees' policies and procedures.

G. All Investigators/Research Staff/Employees/Students

All investigators and research staff, including students involved in the conduct of research, and employees are responsible for the following:

1. Completing all credentialing and training requirements.
2. Ensuring that all unanticipated SAEs and all serious unanticipated problems involving risks to subjects or others in VA research are reporting in writing to the IRB.
3. Reporting any apparent serious or continuing non-compliance to the IRB.
4. Adhering to all federal regulations and local policies governing human research.

H. IRB Analysts and Other Designated R&D Office Staff

Full- and part-time IRB analysts report to the IRB Chair, the AO/R&D, and ACOS/R&D. The analysts act as a liaison between the investigators and the IRB. Space for the IRB analysts and IRB files is under the purview of the Research Service. Contact information for the IRB analysts is located on the IRB Committee web site at <http://www.portland.va.gov/portland/research/Committees/irb/index.asp>.

The IRB analysts are responsible for adhering to the responsibilities for the Research Service Administrative Staff outlined in the MCM No. 151-01:

1. Reviewing research proposal submissions and advising principal investigators about federal, VA, state, and local requirements for conducting research.
2. Maintaining IRB meeting calendars, minutes, membership information, membership education, study documentation and records in accordance with regulatory requirements and reporting change in IRB membership to OHRP.
3. Tracking the progress of submitted research protocols.
4. Generating correspondence to the PI and/or study contact regarding the results of reviews conducted by the IRB and reviews conducted by the Privacy Officer and Information Security Officer.
5. Determining whether a proposal is ready to be reviewed by the convened board, if applicable.
6. Placing research proposals on the IRB agenda.
7. Creating IRB meeting agendas.
8. Generating IRB minutes.
9. Maintaining databases related to IRB study tracking.
10. Documenting completion of all required training for all research investigators before IRB approval is given.
11. Tracking annual completion of required training, including:
 - notifying PIs and research staff when annual training is due;
 - informing ACOS or Deputy ACOS/R&D if training is not completed within one month of expiration;
 - sending a memo from ACOS informing the PI and employee that s/he is no longer approved to

work on the research study and require the PI to submit a Research Personnel Change Form to the IRB to remove the employee from the study.

- If a PI fails to complete training, sending a memo from the ACOS administratively suspending the conduct of his/her studies until the training is completed and informing the IRB of the non-compliance.
12. Responding to requests for consultation, (i.e. questions regarding IRB policies and procedures, e.g., questions involving whether or not a project is considered human research and whether it should be submitted to the IRB for review and approval) from investigators, research staff, clinicians, etc., received directly from the individual(s) or from the IRB members and/or chairs. IRB analysts may consult with IRB members and chairs and/or the RAO if necessary to address an individual's questions.
 13. Responding to calls from research participants and other to answer questions about research in general and about PVAMC HRPP policies, and, when appropriate forward them to others within R&D Service or to specific investigators.
 14. Providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts convened in accordance with Subpart D.
 15. Assigning the primary and, if applicable, *ad hoc* reviewers to review material submitted to the IRB. The IRB Chairs will assist the IRB analysts, as necessary, in completing this responsibility.
 16. Evaluating each protocol to determine whether a consultant is needed.
 17. Obtaining an outside consultant to conduct an in-depth review of a protocol if there is not at least one person on the IRBs with appropriate scientific expertise.
 18. Fulfilling all other responsibilities and adhere to the policies and procedures outlined in the appropriate institutional, HRPP, and R&D Service committees' policies and procedures.

Additionally, the IRB analysts or other designated R&D Service administrative personnel shall carry out the following responsibilities:

1. Scanning original informed consent forms into the participant's electronic medical record or, if no CPRS record is required, into a separate file behind the VA firewall, and ensuring that the original informed consent form is returned to the Principal Investigator.
2. Distributing educational brochures about VA research obtained from the VA Office of Research (ORD) and Development to investigators to give to potential research participants.
3. Creating a research flag to be activated on patient's medical records, when applicable.
4. Distributing educational research posters and brochures obtained from ORD around the medical center in waiting and clinic areas.

I. Research Assurance Officer (RAO)

The Research Assurance Officer, a member of the Research Service Office, is responsible for the following:

1. Attending IRB and R&D Committee meetings as *ex officio* non-voting member.
2. Serving as independent contact for research participants to discuss and address problems, concerns, and questions and explain rights.
3. Serving as lead contact for accreditation of HRPP.
4. Writing, reviewing, and revising HRPP policies and procedures to assure compliance with all federal regulations and policies as well as accreditation standards.
5. Providing human research protection education to investigators, IRB members, and IRB analysts.
6. Receiving and addressing complaints about research at the PVAMC. (See [Complaints and Allegations of Non-Compliance](#).)
7. Fulfilling other responsibilities as directed by the ACOS/R&D and the IRBs.

J. Research Compliance Officer

The Research Compliance Officer may act as a consultant to the facility's IRB, but may not serve as a member (voting or non-voting) of the IRB. Individuals from the RCO office may attend IRB meetings to provide the results of RCO-conducted audits or other information which may be useful to the IRB. The RCO is responsible for the following:

1. Conduct regulatory and informed consent audits of all human research per VHA Handbook 1058.01.
2. Report audit findings to the IRBs and the R&D Committee in a timely fashion.
3. Meet all human research protection requirements of the Office of Research Oversight.

VI. IRB MEMBERSHIP & RESPONSIBILITIES

A. IRB Membership Composition

The IRB membership is selected to assure appropriate diversity, including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes, as well as representation by multiple professions, knowledge and experience with vulnerable subjects and inclusion of both scientific and non-scientific members. The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and possess the professional competence necessary to review specific research activities. Officials in Research and Development administration are prohibited from serving as voting members of the IRBs. A member of the IRB may fill multiple membership position requirements for the IRB.

In addition to the diversity of membership based on consideration of race, gender and cultural background, each IRB will have at least

1. five members;
2. one member whose primary area of interest is scientific;
3. one member whose primary area of interest is non-scientific;
4. one member who is not affiliated with the Portland VA Medical Center or any of its components or other community-based clinics such as Bend, Camp Rilea, etc., and who is not part of the immediate family of a person affiliated with the medical center;¹ (Volunteers without a WOC or veterans whose only relationship is receiving care at the PVAMC or benefits from the Veterans Benefits Administration are not considered to be affiliated.)
5. one or more members of more than one profession;
6. one member from the Research & Development Committee; and
7. a chair with a VA appointment.

B. IRB Chair

1. **Appointment** – The ACOS/R&D nominates one Chair for each IRB by submitting a resume of the individual to the R&D Committee. The R&D Committee reviews the nomination, and recommends the individual for formal appointment by the PVAMC Director. The chair must hold a paid VA appointment.
2. **Voting Status** – The Chair is a full voting member of the IRB, and is counted in the quorum of the committee.
3. **Length of Service** - The chair serves a one-year term and may be re-appointed indefinitely.
4. **Responsibilities**
 - a. Conduct IRB meetings.
 - b. Call special meetings when necessary.
 - c. Consult the IRB analysts to ensure operation of the IRB is within all applicable regulatory requirements.
 - d. Review and sign IRB minutes that summarize the actions and reasons for these actions of each presented item reviewed by the IRB.
 - e. Review and act on requests for exemption from IRB review, i.e. determining if studies qualify for exemption from IRB review.
 - f. Review requests for expedited review and if the expedited process is appropriate, either review and approve the study on behalf of the IRB, or assign a reviewer to advise the chair

¹ Affiliated: any individual with a WOC appointment UNLESS the WOC is only for IRB membership; individuals who have retired from VA and receive VA retirement benefits; employees of institutions that have a formal academic affiliation agreement with VA; and employees of the VA non-profit foundation (PVARF).

so that the chair can then act on the request on behalf of the IRB. Requests that do not meet the criteria for expedited review will be considered by a fully convened IRB. A reviewer may not disapprove a study by expedited review.

- g. Initially review reports of unanticipated problems/adverse events and determine whether immediate action is necessary to assure participant safety.
- h. Work with IRB members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are adequately protected.
- i. Sign final initial IRB approvals, unless the Alternate Chair is presiding, for protocols or actions approved by the IRB.
- j. Notify the RAO of any research-related complaints and allegations of non-compliance with HRPP institutional policies raised by any individual, review research-related complaints and allegations of non-compliance with HRPP and IRB policies brought forward from the RAO and determine if a special meeting of the IRB must be convened to address an immediate participant safety issue or if the issue can be held until the next scheduled meeting.
- k. Report any attempts by investigators or research staff of undue influence toward approval of research to the RAO.
- l. Report to appropriate regulatory bodies consistent with VHA policies and procedures.
- m. Assist the IRB analysts, as necessary, in assigning primary and *ad hoc* reviewers to review material submitted to the IRB.

C. IRB Alternate Chair

1. **Appointment** - The ACOS/R&D nominates one Alternate Chair for each IRB by submitting a resume of the individual to the R&D Committee. The R&D Committee reviews the nomination, and recommends the individual for formal appointment by the PVAMC Director. The Alternate Chair must hold a paid VA appointment.
5. **Voting Status** – The Alternate Chair is a full voting member of the IRB, and is counted in the quorum of the committee. The alternate chair may be present, and vote, at the same time as the chair, and only takes on the duties of alternate chair when the Chair is absent.
2. **Length of Service**
The Alternate Chair serves a one-year term and may be re-appointed indefinitely.
3. **Responsibilities**
 - a. Performs responsibilities of the Chair in his/her absence.
 - b. Assists the Chair as needed.

D. IRB Members

1. **Appointment:** IRB members are nominated by the ACOS/R&D when the ACOS/R&D submits resumes for member(s) to the R&D Committee. The R&D Committee reviews the nomination(s), and recommends the individual(s) for formal appointment by the PVAMC Director.
2. **Length of Service:** Members serve 3-year terms and may be re-appointed indefinitely. Each year on July 1, one-third of member terms will expire and new members will be appointed or current members re-appointed. Regular attendance at IRB meetings is expected, and a member may be removed from the IRB on the basis of repeated unexcused absences or non-attention to the functions and responsibilities of the IRB. The R&D Committee reviews IRB membership annually.
3. **Responsibilities**
 - a. Review all human research, assessing the scientific and scholarly validity, and ensure the rights and welfare of research subjects are protected. Such review will assess whether the procedures are consistent with sound research design such that it is likely to yield the expected knowledge.

- b. Learn about and remain current on ethical, legal and regulatory issues related to IRB business.
- c. Complete appropriate IRB reviewer forms.
- d. Verify that all changes required by the IRB were made for research projects contingently approved by the IRB.
- e. Maintain the integrity of the IRB review process. In particular, avoid discussing IRB protocols with investigators outside of a convened IRB meeting in a manner that might suggest possible IRB determinations.
- f. Maintain confidentiality regarding any information contained in any review.
- g. Serve as primary reviewers when assigned, generally within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings.
- h. Conduct expedited reviews on behalf of the IRB when so designated by the IRB chair.
- i. Participate in other subcommittees, audits, and education, so long as there is no conflict of interest with IRB responsibilities.
- j. In addition to completing the education requirements set forth by the IRB Chair, also successfully complete the education requirement in the protection of human research participants as indicated in the HRPP policy "Education for the Protection of Human Research Subjects Policy and Procedure" at <http://www.portland.va.gov/Research/hrpp/index.asp>.
- k. Report any attempts by investigators or research staff of undue influence toward approval of research to the RAO.

E. Alternate IRB Members

1. **Identification:** Alternate members are identified and invited to be IRB members based on their professional specialty, qualifications, and experience, which must be comparable to those of the primary member for whom they will serve as alternate. The IRB Roster identifies for which primary member each alternate may serve.
2. **Appointment:** Alternate members may be nominated by the ACOS/R&D, voted on by the R&D Committee and appointed by the Medical Center Director. These alternates are nominated with the same criteria of selection as IRB members.
3. **Length of Service:** An alternate IRB member's length of service may be based upon one of the following:
 - a. the individual's term as an IRB member, if already a full time IRB member;
 - b. the term of the individual s/he is representing; or
 - c. a three-year term, if the individual serves as an alternate for multiple full time IRB members.
4. **Responsibilities:** An alternate IRB member has the same responsibilities as a full time IRB member.

F. Ex-Officio Members

Ex-officio members, appointed due to their position at the PVAMC, may not vote, deliberate, nor contribute to a quorum. These members must adhere to the same conflict of interest policies and procedures as voting IRB members. Ex-officio members are not nominated and appointed by the Medical Center Director. They may include the Administrative Officer (AO) R&D, Information Security Officer, Privacy Officer, and Research Assurance Officer.

G. Individuals with Special Expertise (Ad Hoc Members/Use of Consultants)

On an as-needed basis, the IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of any issues requiring expertise beyond or in addition to that available on the IRB. This may include the review of a study involving a clinical procedure or specialty not represented on the IRB. The IRB members and/or chair may determine that the IRB needs additional technical assistance.

Recommendations for consultants may come from the ACOS/R&D, R&D Committee members, IRB members, and/or medical staff. The *ad hoc* reviewer will be invited to review the research project and will be provided with documented expectations. The IRB chair and/or analysts will make the arrangements for such a review. The *ad hoc* reviewer must adhere to the same conflict-of-interest policies and procedures as the IRB members. The *ad hoc* reviewers may attend the IRB meeting when the study is reviewed, however, their presence or absence will not be used in establishing a quorum for an IRB meeting. An *ad hoc* reviewer may not serve as the primary reviewer, nor vote with the IRB. An *ad hoc* reviewer may provide guidance and expertise either in person or through written comment. The qualifications and comments of the *ad hoc* reviewer will become part of the minutes supporting the IRB deliberations.

H. Compensation for IRB Service

IRB members are not compensated for serving on the IRB, but may receive reimbursement for travel costs.

I. Conflict of Interest of IRB Members

As indicated in the “Conflict of Interest in Research Policy and Procedure” located on the R&D web site at <http://www.portland.va.gov/research/documents/hrpp/coi-policy.pdf>, all IRB members must aim to avoid real or perceived conflicts of interest and follow the conflict of interest policy. Members of the IRB may not work for or hold equity in any outside business interest with which the VA might do business, e.g., pharmaceutical companies or medical device manufacturers. (See Conflict of Interest in Research Policy”.) The IRB chairs and members may find themselves in any of the following potential conflicts of interest:

- 1) The IRB Chair or member is listed as an investigator on the research.
- 2) An investigator must report to or is under the supervision of an IRB chair or member.
- 3) An IRB chair or member competes for research grants or contracts in the same or similar field as an investigator whose research is scheduled for review.
- 4) An IRB member is a family member of an investigator whose research is scheduled for review.

In cases where a conflict of interest exists, the member must step out of the room during the review of the study. If they are attending by video- or teleconference, the call must be terminated during that portion of the discussion (rather than placed on “hold”), and then re-established when the discussion and vote are complete. Conflicts of interest of IRB members will be noted in the minutes, and the individual is identified as “recused” during the vote.

J. Training of IRB Chairs and Members and Ongoing Evaluation

As a condition of the FWA, IRB members are provided education about human research protection. The IRB chairs and members shall meet the educational requirements set forth in HRPP policy “Education for the Protection of Human Research Participants in the Research & Development Service” (<http://www.portland.va.gov/Research/hrpp/index.asp>).

1. New IRB Member Training

The chairs of each IRB and the RAO and/or a designated IRB analyst shall provide members with an initial orientation to their committee activities and appropriate continuing education related to the IRB. Each new IRB member’s training consists of the following:

- a. The RAO or an IRB analyst shall schedule a training session with each new member to review their responsibilities, the IRB P&P and other HRPP policies and procedures, and offer the opportunity for questions and discussion.
- b. The IRB Chair shall discuss with the member(s) the parameters of IRB decision-making and answer any questions the new IRB member(s) may have regarding their responsibilities as

IRB member(s) and the functioning of the IRB. The IRB Chair may also assign a mentor to work with the new member.

- c. All IRB members are informed of the website link to the PVAMC IRB P&P (<http://www.portland.va.gov/portland/research/Committees/irb/index.asp#policies>) and all other PVAMC HRPP policies and procedures prior to their first meeting with the IRB. They are also given a hard copy of the IRB P&P or any policy if they so request.
- d. Once a new member has completed all educational requirements and attended enough meetings to feel competent to carry out his/her duties and responsibilities, s/he will be assigned studies to review based on his/her unique expertise, i.e. strengths, education, and experience levels.

2. Continuing IRB Education

The IRB members, including the non-scientist members, are responsible for completing the annual educational requirements as set forth in the HRPP policy "Education for the Protection of Human Research Participants in the Research & Development Service."

(<http://www.portland.va.gov/Research/hrpp/index.asp>)

K. IRB Evaluations

Each year, the RAO sends evaluation forms to each IRB member and chair offering the opportunity for self-evaluation. A separate section of the evaluation form addresses the additional responsibilities of the chairs. IRB analysts as a group also evaluate each member and chair using the same form. The RAO reviews and adds comments, then meets with the ACOS/R&D and the chair of the R&D Committee for final review. In addition, each chair also evaluates how the IRB functions as well as the level of service, quality and efficiency of the IRB analysts and submits a report to the ACOS/R&D. All evaluations are then included in a report to the R&D Committee by the RAO through the ACOS/R&D. Individual members will be given direct feedback if evaluations indicate a need for further training or when determining if a member should be re-nominated for another term at the end of their current term. Results of the evaluations also assist in determining what areas of regulation and ethics may require further education for all.

VII. IRB Recordkeeping and Required Documentation

A. Record Retention

The IRB shall keep all records indefinitely (until VA Records Control issues guidance for scheduled storage and destruction). Records include electronic and written data as well as voice and video recordings. All IRB records collected over the course of the protocol will be maintained by the IRB analysts in the PVAMC Research Service space. If a study does not receive funding and the PI decides not to conduct the research without funding, but the IRB has conducted a review of the study, the records will also be kept indefinitely. If an investigator leaves the PVAMC facility, the original research records must be retained at the PVAMC.

B. IRB Records

IRB records include the following:

1. IRB membership information
2. Education/training records
3. Credentialing files
4. Standard Operating Procedure
5. Convened IRB meeting minutes
6. Research project files (see item H. below)
7. Federalwide Assurance (FWA)

C. Access to IRB Records

IRB records are the property and the responsibility of the PVAMC Research Service office. These records are stored by the Research Service at the PVAMC either in the Research Service office, in storage areas in locked file cabinets behind magnetic security doors in order to maintain the privacy and confidentiality of research subjects' information, or archived at a National Archives and Record Administration facility. Electronic records are kept on a password-protected computer maintained by the Research Service staff as part of their official employment duties.

IRB records are accessible to the Research Service staff, IRB chairs and members, as well as the R&D Committee chair and members for committee purposes only. Research investigators shall be provided reasonable access to files related to their research. Other authorized individuals, such as accrediting officials and officials of federal and state regulatory agencies, including the Office of Research Oversight (ORO), the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA), will have access to IRB records for inspection and copying upon determination of appropriateness and necessity at reasonable times and in a reasonable manner. Appropriate accreditation bodies shall be provided access and may recommend additional procedures for maintaining security of IRB records.

IRB analysts and/or Research Service staff will maintain a log of individuals who access the IRB records, excluding the IRB members who review the IRB records for committee purposes only and Research Service staff.

D. IRB Membership Roster

The IRB analysts maintain the current IRB membership rosters and report any changes to the OHRP with a copy to the VA Office of Research Oversight (ORO). See IRB roster at <http://www.portland.va.gov/portland/research/Committees/irb/index.asp> for the current composition of each IRB. The IRB rosters will include the following information:

1. names
2. degrees

3. voting and alternate status and representative capacity
4. representative capacities regarding vulnerable populations, if any, each member was knowledgeable about or experienced in working with
5. affiliation status (whether the member or an immediate family member of the member was affiliated with the organization)
6. indications of experience sufficient to describe each IRB member's chief anticipated contributions; and
7. employment or other relationship between each IRB member and the organization
8. scientific/non-scientific status
9. the primary members or class of primary members for whom each alternate member may substitute.

The IRB Membership Information binder contains copies of the IRB members' curriculum vitae/resume or equivalent and appointment letters.

E. Written Standard Operating Procedures

IRB members are provided links to the electronic copy of the PVAMC IRB Policies and Procedures document at the time they join the IRB and each time it is updated. Hard copies are provided upon request, or if a member cannot access electronic copies.

F. IRB Research Project Files

The IRB shall maintain a separate file for each research project. Protocols are assigned a unique number from the Manage your Institutional Review Board (MIRB) Database for tracking and administration purposes. The IRB application shall include the IRB forms, as applicable to the protocol. Protocol files shall include all documentation related to the protocol, i.e. submissions, IRB and investigator correspondence, audit reports, IRB forms, etc. The following information must be present when applicable:

1. Protocols
2. Investigator Brochure
3. Scientific evaluations, when provided by an entity other than the IRB.
4. Recruitment materials
5. Consent documents
6. HIPAA Authorization Documents (or documentation of waiver of HIPAA authorization)
7. Progress reports submitted by researchers
8. Reports of injuries to participants
9. Records of continuing review activities
10. Data and safety monitoring reports
11. Amendments
12. Unanticipated problems involving risks to participants or others
13. Documentation of non-compliance
14. Significant new findings
15. Determinations required by the regulations and protocol-specific findings supporting determinations for waiver or alteration of the consent process.
16. For each protocol's initial and continuing review, the frequency interval for the next continuing review.
17. Protocol violations submitted to the IRBs.
18. Audit results and documentation of compliance with remediation requirements, when audits are conducted by the RAO.
19. Subject complaints, unless complaints are filed anonymously.
20. Communications with the investigator
21. Documentation of relevant approvals
22. Documentation of waiver of informed consent or waiver of documentation of consent

G. Research Tracking System

The IRB uses a reliable computerized tracking system, the MIRB computer program maintained by the IRB analysts and Research Service staff. IRB analysts enter specific documents received, date received, date reviewed, and results of review into the MIRB database. MIRB is used to track IRB stipulations from contingent approvals, when those changes are received and approved, and the date of continuing review for research projects reviewed by the IRB. MIRB is also used to track IRB membership and generate IRB agendas, correspondence and minutes.

H. IRB Use of Checklists

The IRB members shall use the "Initial/Continuing Review Checklist" in reviewing protocols at the time of initial and continuing review. Checklists are available from IRB analysts and on the PVAMC website. IRB determinations regarding the following are documented in the IRB minutes and/or correspondence:

1. The level of risk of the research.
2. The approval period for the research, including identification of research that warrants review more often than (at least) annually.
3. Whether the medical record of each participant must be flagged to protect the participant's safety by indicating participation in the study and the source of more information about the study.
4. Justification for waiver or alteration of informed consent and/or HIPAA Authorization, addressing each of the four (4) criteria at 38 CFR 16.116(d) or, if applicable, the criteria for emergency use in 21 CFR 50.24.
5. Justification for waiver of the requirement for written documentation of informed consent in accordance with the criteria at 38 CFR 16.117(c) and 21CFR56.109.
6. For DHHS-supported research, justification for approval of research involving pregnant women, human fetuses, and human in vitro fertilization, addressing each of the criteria specified under 45 CFR 46 Subpart B of the DHHS human subject regulations. **Note:** The PVAMC does not review or conduct research directly involving human fetuses or human in vitro fertilization.
7. For DHHS-supported research, justification for approval of research involving prisoners, addressing each of the categories and criteria specified under 45 CFR 46 Subpart C of the DHHS human subject regulations. Generally, the IRB analyst is responsible for providing certification of the IRB's findings to OHRP. **Note:** The PVAMC does not review or conduct research with prisoners. However, if a human participant involved in ongoing research becomes a prisoner during the course of the study, the investigator must promptly notify the IRB and sponsor (if applicable). All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-participant must be stopped immediately. If immediate cessation of study-related interventions would place the prisoner-participant at risk, the investigator must notify the IRB Chair for additional guidance and communication with VA Central Office.
8. For DHHS and VA supported and FDA-regulated research, justification for approval of research involving children, addressing each of the categories and criteria specified under 45 CFR 46 Subpart D of the DHHS and FDA human subject regulations. VA policy specifies that a waiver for research involving children must be obtained from the Chief Research and Development Officer, Office of Research & Development (VHA Directive 2001-028, April 27, 2001). For FDA-regulated research documentation of the IRB findings is required. Notification shall go to the Commissioner of the FDA. **Note:** The PVAMC does not review or conduct research with minors except when a waiver is received from the CRADO.
9. The IRB's consideration of the additional safeguards to protect the rights and welfare of vulnerable subjects. For example, the special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children,

prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.

10. Justification for approval of emergency use of an investigative or unlicensed article, with specific reference to the criteria specified by DHHS and FDA (see the policy titled "Investigational Device and/or Drug Usage in Research & Development Service"). (Note: Please refer to VHA Handbook 1200.05 14.h. and i.)
11. Rationale for significant or non-significant risk device determinations.

I. Documentation of Expedited Reviews

The review and decision will be documented in the research project file and the next meeting agenda and minutes of the IRB based on the requirements referenced in Section X.

J. IRB Minutes

IRB analysts complete IRB minutes in MIRB. Minutes shall include the following:

1. Attendance by name, also showing when an alternate takes the place of a regular member
2. Call to order, documenting the required quorum was present for each vote, including a non-scientific member, and for review of FDA-regulated studies, a licensed physician
3. Approval of prior meeting minutes
4. New and Old Business
5. Actions taken by the IRB concerning initial or continuing review of research including the approval period; specific measures taken to protect vulnerable populations; justification for including non-veterans as subjects if applicable; a summary of discussion when real, scrambled, or partial Social Security Numbers will be used other than on the informed consent or HIPAA authorization or to write progress notes in CPRS; review of protocol or informed consent modifications or amendments; unanticipated problems involving risks to subjects or others; serious adverse event reports; reports from sponsors, cooperative groups, or Data and Safety Monitoring Boards (DSMBs); reports of continuing non-compliance with regulations by investigators and other staff or IRB determinations; waiver or alteration of elements of informed consent and justification; suspensions or terminations of research, protocol violations, and other actions as appropriate.
6. The basis for requiring changes in or disapproving research and justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the consent document or, if applicable, the DHHS-approved sample consent document.
7. Summary of controverted issues, i.e. there is a lack of consensus, and their resolutions. Discussions of controverted issues are recorded, whether or not there is a split vote.
8. Research protocols approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of each;
9. Approvals authorized utilizing expedited review procedures and the specific citation for the category of expedited review;
10. When following DHHS regulations or guidance, justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document when that document exists.
11. Stipulations met since the last IRB meeting for items contingently approved at a previous IRB meeting, i.e. requested changes submitted and reviewed and verified by the designated IRB primary reviewer and final approval letters issued by the IRB Chair;
12. Determination of the frequency of continuing review of each research project based upon the degree of risk and risk:potential benefit ratio.

Minutes shall be available for review within three weeks of the meeting. Once approved by the members at a subsequent IRB meeting and signed by the IRB chair, the minutes may not be altered by anyone, including a higher authority, and should be reviewed and acted upon by the R&D Committee at the next convened R&D Committee meeting.

K. Attendance at IRB Meetings in IRB Minutes

IRB minutes shall list attendance as follows:

1. Names of members present, according to their voting status including members or alternate members who participate through videoconference or teleconference. In cases where members participate through video- or teleconference, the minutes shall also include documentation that those members received all pertinent material before the meeting and were able to actively and equally participate in all discussions.;
2. Names of any absent/excused members, according to their voting status;
Excused applies when a member notifies an IRB analyst in advance that s/he will be absent.
Absent applies when a member has not notified an IRB analyst in advance of the meeting that s/he will be absent.
3. Names of any alternates attending in lieu of specified (named) excused/absent members. Alternates may substitute for specific excused/absent members only as designated on the official IRB membership roster;
4. Names of any *ad hoc* reviewers present;
5. Names of *ex officio* members present;
6. Names of any Research Service staff present and/or excused/absent; and
7. Names of any guests present.

L. Quorum Requirements

The IRB observes the following rules:

1. A quorum consisting of a majority of the IRB members (or their designated alternates), including at least one member whose primary expertise is non-scientific (community members) and for FDA-regulated studies, one member who is a licensed physician, must be present to conduct a convened meeting. Research must be approved by a majority of those present at the meeting.
2. Members absenting themselves due to conflicts of interest will be documented as "recused" during the vote. Recusals may not be counted toward quorum requirements.
3. The following individuals will not be considered as part of the quorum and will not vote with the IRB:
 - a. Any individual not listed on the official IRB membership roster;
 - b. Any ex-officio member of the IRB;
 - c. *Ad hoc* reviewers;
 - d. Consultants;
 - e. Guests; and
 - f. Research and Development Service Staff or Administrators.
4. When a member and his/her alternate both attend a meeting, only one may vote.
5. If a quorum is lost during a meeting, a quorum must be restored before any discussion of, or action on, issues requiring a vote may occur.

M. Documentation of Votes by the Convened IRB

Votes and deliberations on each action reviewed by the convened IRB, including the number of members voting and the names of members who excused themselves during the review of a protocol and when a member leaves the meeting because of conflict of interest. Votes are categorized as “for”, “against”, “abstained”, “recused”, and “excused.”

1. **For** means that the member(s) are voting in favor of the motion to approve, contingently approve, table or disapprove.
2. **Against** means that the member(s) are voting in opposition to the proposed motion to approve, contingently approve, table, or disapprove.
3. **Abstained** means a member states that s/he refrains from the vote voluntarily. For example, a member may refrain from a vote if s/he was only present for a portion of the discussion of a particular item.
4. **Recused** applies if a member has a conflict of interest. The member leaves the room and does not participate in the deliberations or vote.
5. **Excused** applies when a member is out of the room for the vote, i.e. restroom, emergency, etc.

N. IRB Deferral Documentation

A deferral may be documented in the IRB minutes when the IRB did not take an action on an item scheduled for review because, e.g., a quorum was lost or the IRB primary reviewer(s) was not present at the meeting. The review of the item will be postponed until the next scheduled meeting, as appropriate.

O. The Basis for Requiring Changes in or Disapproving Research

The minutes of IRB meetings shall include the basis for requiring changes in or disapproving research. In addition, the IRB will include in its written notification to the investigator, a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing (or both).

P. IRB Correspondence

Accurate records are maintained of all communications to and from the IRB, including correspondence with investigators, consultants if applicable, and the R&D Committee. IRB correspondence is signed by an IRB analyst or, in the case of initial approval, IRB chair, or voting member who reviewed, at the meeting or at such time as the text of such correspondence is confirmed with the IRB Chair or primary reviewer. At the time of any disapproval (initial, continuing, amendment, etc.), correspondence is signed by the IRB Chair or voting member. Copies of all correspondence are filed in the appropriate investigator research project file located in the PVAMC Research Service office or a designated storage area.

The IRB reserves the right to request more information or a change in research procedures. In these cases, the IRB staff will generate a separate memorandum noting whether or not any further action or required changes are needed on the part of the principal investigator or research coordinator in order to approve the continuing review, amendment, etc.

In cases in which a project at the PVAMC has multiple investigators, correspondence will be sent to the principal investigator or to the study coordinator or co-investigator designated to receive such correspondence, as noted on the IRQ or PPQ. If the study coordinator or co-investigator is designated to receive such correspondence as noted on the IRQ or PPQ, the study coordinator will be responsible for communicating the results of the review to the principal investigators. The principal

investigator is ultimately responsible for the research project and assuring that the research project and staff comply with IRB requirements. In cases where communication is electronic, upon resolution of the topic of the communication, a hard copy will be generated and filed with the project file by the IRB analysts and/or other R&D staff.

The PI is notified in writing of all IRB decisions regarding each protocol and regulatory criteria upon which decisions are based. All official IRB correspondence is addressed to the PI, but may be sent to a study coordinator as designated by the PI on the Initial Review Questionnaire.

Along with written notification of IRB approval, when relevant IRB analysts send the investigator a copy of the IRB-approved informed consent form.

1. **Initial review:** if the project receives final approval, an IRB analyst will give the IRB approval signed by the IRB chair or the voting member who was primary reviewer to the R&D Committee coordinator, and the project will be included in a list for approval at the next convened R&D Committee meeting. A letter will be sent from the ACOS/R&D as soon as possible and no later than 10 business days after the R&D Committee meeting notifying the principal investigator and/or designated study contact that the research has approval to begin.

In cases of contingent approval, or a tabled decision, an IRB analyst will notify the PI within three weeks. Response to tabled decisions will be reviewed at a convened IRB meeting. If further clarifications or changes are needed as determined by the IRB reviewer or convened IRB after response is received, an IRB analyst will inform the PI or study contact.

In the case of contingent approval, once the reviewer or convened IRB has approved the PI's response to contingencies, an IRB analyst will send the final approval letter signed by the IRB chair to the R&D Committee coordinator for inclusion on the list of studies for approval at the next R&D C meeting. An IRB analyst will also notify the PI or study coordinator within a reasonable time frame if further clarifications/stipulations are needed.

2. **Continuing Review:** Investigators will be notified within three weeks of final, tabled, or contingent approval of continuing review or modifications. Once final approval has been approved by the IRB, the signed IRB approval will be given to the ACOS/R&D. The ACOS/R&D will send the final approval with the IRB approval to the PI/study contact that the project may continue.

The IRB shall notify the principal investigator in writing of lapsed approvals, suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of a suspension or termination must be explicit.

Q. Responses to IRB Correspondence

Any required response to the notifications will be reviewed by the primary reviewer(s), unless they note that the changes are of a nature that they could be reviewed by an IRB analyst. The IRB Chair, IRB voting member, or in some cases the IRB analyst, may use expedited review procedures to verify that specific minor changes have been addressed by the PI, and authorize approval of material that was contingently approved. If research was tabled, the response will be reviewed by both the primary reviewer(s) and the convened IRB. Also see "Appeal of IRB Determinations".

The investigator shall be provided with an opportunity to respond in person or in writing to all determinations by the IRB.

Responses should come from the PI or the study coordinator. In cases where a lapse in time could potentially harm human subjects (such as a delay in reporting of an adverse event), co-investigators may communicate directly with the IRB.

R. Time Allowed for Submission of Modifications to Secure Initial Approval

In cases where research projects are approved pending minor modification at the time of initial review, investigators are given a three-month deadline to submit the required modifications to the IRB.

If the PI has not replied to the contingencies after three months, the IRB analysts will contact the PI to remind them about their contingencies and to determine whether or not the PI will be submitting the contingencies or withdrawing the study.

This deadline may be extended up to another three months for a total of six months, provided the investigator keeps the Research Service office informed of the status of the protocol. After the six-month period, the investigator will receive a warning that if the requested modifications are not submitted within the next seven days, the protocol will be administratively withdrawn. If the project is administratively withdrawn, the investigator must resubmit the study to the IRB for full review as a new protocol.

The IRB will consider exceptions to this policy in extraordinary circumstances that may be out of the investigator's control, e.g., delay in funding or changes to be made by the sponsor.

VIII. EXEMPTION FROM IRB OVERSIGHT/REVIEW

Projects meeting the definition of research involving human subjects as defined in this P&P and Medical Center Memorandum (MCM) 151-01, and otherwise requiring approval per MCM 151-01 must undergo IRB review and approval before the research project may begin. If it appears that the study includes human subjects, but may be exempt from IRB oversight, Investigators shall submit a written request to the IRB on the Certification of Exemption form, as prompted by the Proposed Project Questionnaire. The IRB serves as the R&D Committee's designee in the review of exempt status based on categories stipulated at 38 CFR 16.101.

Research must meet the definition of human research in order to qualify for exemption from IRB review (see Definitions in this P&P). Questions regarding whether or not an activity is considered human research should be directed to an IRB analyst or the Research Assurance Officer.

Categories of exempt research are stipulated in VA regulations at 38 CFR 16.101(b)(1-6) as shown on the Certification of Exemption form located at http://www.portland.va.gov/Research/piservices/rd_forms.asp. Some FDA-regulated research may not qualify for exemption.

Using expedited review procedures, the IRB Chair or a qualified and experienced IRB member will, in a timely manner, determine exempt status. An IRB member's experience and qualifications will be evaluated based on full reviews completed as a primary reviewer and knowledge and application of ethical principles and regulations demonstrated during discussion of protocols at convened IRB meetings. In reviewing the exemption request, the reviewer will assure the research meets the definition of human research and that the research involves no more than minimal risk based on the criteria for exemption as defined by the VA, DHHS and FDA. The convened IRB will be informed of the exempt determination by documentation in the agenda and minutes for the next convened meeting.

The IRB will notify the investigator and the R&D Committee in writing of its determination that a research project is exempt from IRB approval requirements. This is accomplished by indicating "approved" on the Certificate of Exemption Form and by applying a signature. The signature may be applied by an IRB Chair, a qualified voting member of the IRB, or a member of the IRB staff.

If it is determined that a study does not qualify for exemption, then the study team will be contacted to request paperwork for a complete submission, and the study will be evaluated for expedited or convened board review.

The R&D Committee will review IRB-exempted projects and make a final determination concerning whether to approve. The research project may begin once written confirmation from the ACOS/R&D of IRB and R&D Committee approval has been received by the PI. If the study is reviewed by another R&D Subcommittee, responsibility for continuing reviews rests with that subcommittee. If there is no other R&D Subcommittee, the R&D Committee conducts continuing reviews of the study at least annually.

If a revision is made to a previously IRB-exempted project, the PI must submit the change to the IRB using a Protocol Revision/Amendment Form (PRAF) as well as other relevant study documents affected by the revision. If the change is determined by the IRB reviewer to have affected the previously approved exempt status, the PI must submit applicable forms for review by the IRB of the

project as non-exempt human research. If the IRB reviewer determines the project remains exempt, the PRAF shall be reviewed by the R&D Committee.

Minor revisions, such as personnel changes, may be acknowledged administratively rather than voted on by the convened R&D Committee. The PI will receive an acknowledgement letter signed by the R&D Chair, a qualified voting member of the R&D Committee, or a member of the R&D staff. The convened R&D Committee will be informed of the revision by documentation in the agenda and minutes for the next convened meeting.

Any individual involved in making the determination of exempt status of a proposed research project cannot be involved in the proposed research.

A. Documentation of Exemptions from IRB Oversight/Review

Documentation regarding the rationale for exemption, the category and circumstances will be completed by the reviewer and will be maintained in Research Service records. The basis for the approval of exempt status must be communicated in writing to the investigator in a timely manner. The IRB will be notified of the review and decision at the next convened IRB meeting and the notification will be documented in the meeting minutes.

IX. ROUTINE IRB REVIEW

A. Initial Review

Unless determined to be exempt from IRB review, all human research conducted at the PVAMC facility by PVAMC employees or agents or otherwise under VA auspices must be reviewed and approved based on regulatory criteria by the IRB prior to initiation. No human research may be initiated or continued at the PVAMC by employees or agents without the appropriate approvals of the IRB and any other applicable R&D C subcommittees, e.g., the Safety Committee, documented by a written notification from the ACOS/R&D.

At the time of initial IRB review for studies that have a mentor as PI and a trainee who is working closely on or has designed the study, the IRB wants to assure that both the mentor and mentee have sufficient understanding of their responsibilities before research commences. In such cases, the PI (mentor) at minimum, and ideally the mentee as well, should attend a training held by the research office on good clinical practices and basic research considerations. Alternatively, the PI who is mentor can attend the IRB meeting and assure understanding of and responsibility for the research.

For convened IRB reviews, primary reviewer(s), will (1) review and lead discussion on the proposal, (2) provide an assessment of the soundness and safety of the protocol, (3) make recommendations for protocol and informed consent revisions and (4) take appropriate action(s) regarding approval. The Principal Investigator is invited attend the portion of the IRB meeting at which his/her initial protocol review occurs, and may be invited to attend for reviews of other items related to the research, e.g., major protocol changes or problems involving risk. When the Principal Investigator attends, s/he may make a brief presentation, answer questions or provide clarification, but may not be present during deliberations or voting on the proposal.

At the time of initial review, the IRB or reviewer for expedited review will determine the frequency of continuing review of the research, designating an interval not less than one year. Protocols determined to have a higher degree of risk or a higher risk:potential benefit ratio will require a shorter interval for continuing review, e.g., six (6) months. Members will use the IRB Primary Reviewer Form provided by IRB analysts to assist in determining the risk level and risk:benefit ratio and ensuring the information provided meets appropriate guidelines.

The primary reviewers conduct a review of the materials provided for initial review, and apply the criteria for approval as noted in this document. Evaluation of the approval criteria is facilitated through the use of primary reviewer checklists located on the Research Service website, which capture VA and other Federal regulations, required elements for informed consent, etc. Evaluation of the study includes distinguishing which research is being conducted at the PVAMC, and which research is being conducted elsewhere. The IRB only approves the components of the research that are conducted at the PVAMC, using PVAMC resources, or utilizes the VA time of a VA employee.

B. IRB Continuing Review

The IRB will conduct substantive and meaningful continuing review based on regulatory criteria of research at intervals appropriate to the degree of risk, but not less than once per year.

Investigators are notified in writing of the approval date and the expiration date at the time of final initial IRB approval. The investigators are additionally notified of which materials to submit in order to allow for a complete continuing review to be conducted. The IRB continuing review date is set approximately two months prior to the expiration of IRB approval.

The IRB continuing review materials will include all applicable IRB submission materials as noted in Section VIII, Materials for IRB Review, B. The IRB employs the Primary Reviewer System at the time of continuing review.

1. In addition to reviewing the study to determine that it continues to meet approval criteria outlined in this document, the IRB reviews the following:
 - a. changes to the research;
 - b. local serious adverse event reports, reports of problems involving or suggestion previously unknown risk, sponsor reports and safety reports, including IND, IDE and MedWatch;
 - c. Data and safety monitoring reports;
 - d. reportable protocol violations /deviations;
 - e. significant new findings;
 - f. sponsor-imposed suspensions and device recalls; and
 - g. whether or not the currently approved or proposed consent document is accurate and complete, and whether or not any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with HHS regulations.
3. Studies may meet expedited review criteria for continuing review. The IRB chair or the chair's qualified designee will determine if criteria are met.
4. A research project that is contingently approved at the time of continuing review may not enroll new subjects or access medical records after the research project's expiration date, unless the contingencies are met and final approval is received from the IRB.

C. Process for Continuing Review

Approximately 90 days before the current approval for a research project will expire, an IRB analyst will send an e-mail notification of the IRB continuing review schedule with the Continuing Review Questionnaire (CRQ) to be completed to the Principal Investigator. Investigators are asked to submit the materials in time for the next month's meeting, allowing for review approximately 60 days before the protocol's expiration date. An IRB analyst will send an email reminder to investigators who do not respond by the continuing review due date. If the material is not submitted in a timely manner and it is not possible to get the materials to the IRB meeting prior to the approval expiration date, the approval for the study will automatically lapse, per the procedures outlined in Section XI, G.

D. Ongoing Review

1. Review of Amendments and Changes in IRB Approved Research Procedures and Consent Forms

The IRB must conduct a review of all proposed modifications to IRB approved research projects, including even minor changes and modifications to informed consent forms. The IRB must approve any changes prior to the implementation of the proposed changes, except when necessary to eliminate apparent immediate hazards to the subject. In the latter case, changes must be submitted for review by the IRB promptly after the change.

Proposed modifications should be submitted to the Research Service office with the "Project Revision/Amendment Form" (PR/AF) available online at http://www.portland.va.gov/Research/piservices/rd_forms.asp#alphabetical. Modifications are reviewed by the IRB analysts to determine potential eligibility for expedited review. Those that appear eligible for expedited review are sent to a primary reviewer with the expedited review checklists and any other applicable checklists for review to occur. Amendments determined to be substantive modifications, by either the IRB analyst or the primary review, will be reviewed by the Primary Reviewer System, presented to and voted on at the full IRB at the convened meeting. (Substantive, in Version: 4/02/2012

this case, means a change great enough to no longer meet the criteria for expedited review, as outlined in Appendix 1 of this P&P.)

In cases where the amendment is reviewed by the convened IRB, the Primary Reviewer and all IRB members will receive the "PR/AF," most current IRB-approved consent form (if applicable), documents that include the proposed changes or changes made that the investigator thought necessary to eliminate apparent immediate hazards to the subject and the current IRB-approved document that has been changed, if one exists.

If an investigator is submitting any changes to the informed consent form for review, the following should be submitted:

- 1) a Project Revision/Amendment Form detailing the changes to the informed consent form;
- 2) a clean copy of the modified informed consent form;
- 3) a copy of the modified informed consent form with all changes tracked/highlighted.

The date of continuing review of a study is not changed based on the approval date of an amendment, unless the IRB specifies that the continuing review interval must change as a result of the amendment to the study.

If an amendment addresses an issue related to biosafety, investigators are required to submit appropriate paperwork to the Subcommittee on Research Safety as well. Such approval must be received before the amendment is approved by the IRB. In addition, if an amendment addresses an issue related to radiation safety, an IRB analyst will send it to the Radiation Safety Officer (RSO) for review. The RSO will submit a report to the PVAMC Radiation Safety Committee.

2. Review of Significant New Findings

The IRB will require that any significant new findings arising from the review process and that might relate to participants' willingness to continue participation are provided to participants. The IRB will verify at the time of continuing review that no unapproved changes have occurred since the last IRB review, but investigators can notify the IRB at any time of significant new findings.

3. Review of Study Termination Reports

Investigators must submit a notice of study termination ("Research Project Termination Report" form) to the IRB upon completion of the research project.

At the completion of the entire study, a copy of the master list of all enrolled individuals must be provided to the research office, who will share it with the Privacy Officer (who serves in the role of Health Information Management program manager) and the Information Security Officer to document that access to participant health records is no longer required for a study.

4. Review of Proposed International Research

The PVAMC IRB recognizes the crucial problems of oversight in the conduct of scientific research in foreign countries and will consider such research given sufficient justification.

The PVAMC IRB will review all requests from principal investigators related to foreign research. However, the IRB also recognizes the problems that exist with oversight of such foreign research and recognizes that such research requests will be rare and most typically under the oversight of the National Institutes of Health (NIH) or another federal regulatory agency. Even in these rare cases where research may be conducted in a foreign country, the principal investigator will be required to document approval by a federal agency for the research study as well as approval by IRBs at all foreign sites. When appropriate, all policies and procedures applied to domestic research will also

apply to research in other countries and take into account local laws and cultural context. In addition, approval from the VA Chief Research and Development Officer (CRADO) must be obtained before international research may begin.

5. Absence of a Principal Investigator

When a principal investigator will be absent for a prolonged period, e.g., more than one month, and thus unable to oversee the research and carry out all PI responsibilities, the PI must notify the IRB at least two months prior, except in the case of an unforeseeable absence due to an emergency.

The principal investigator must verify to the IRB that the quality of the research being conducted and the safety and treatment of the human subjects involved will not be compromised, i.e. whether or not treatment of the research subjects currently enrolled will continue and how these subjects will be monitored for safety per protocol. Active recruitment of research subjects into the research study must be suspended until the PI returns or until the PI appoints and the IRB approves a new individual to assume the absent investigator's responsibilities and justifies their credentials to perform the related responsibilities.

If currently enrolled subjects will be undergoing research intervention or follow-up and serious adverse events are possible during the PI's absence, another qualified investigator with appropriate clinical privileges must be approved by the IRB to serve as PI during that time. Before approval, the individual(s) must complete the required education and credentialing (and if applicable, privileging) requirements, consistent with HRPP policies [Credentialing of Personnel Involved in Research](#) and [Education for Conducting Research](#) to perform the absent investigator's responsibilities.

If a co-investigator will be absent, active recruitment in the research project may continue, unless the individual's role in the research was essential and the individual will not be replaced while s/he is absent. If the co-investigator will be replaced, the new co-investigator must complete the required education and credentialing (and if applicable, privileging) requirements, consistent with HRPP policies [Credentialing of Personnel Involved in Research](#) and [Education for Conducting Research](#), and be approved by the IRB.

IRB review and approval of a new individual to serve as PI may be expedited, if it is determined that it meets the criteria for expedited review, such as if a co-investigator will take over as PI in the absence of the original investigator. If an individual new to the study team is identified, the IRB may decide that the change is significant enough to warrant review by the convened board. Each change in PI will be evaluated independently to determine appropriateness for expedited review.

X. EXPEDITED IRB REVIEW OF RESEARCH

The IRB Chairs or a qualified IRB member designated by the IRB chair will make a determination on whether or not a protocol may be reviewed using expedited procedures. An IRB member's experience and qualifications will be determined based on full reviews completed as a primary reviewer and knowledge and application of ethical principles and regulations demonstrated during discussion of protocols one-on-one and at convened IRB meetings. The individual(s) making this determination may not be involved in the proposed research. A protocol may be reviewed by expedited procedures if:

1. The research is not greater than minimal risk and falls within the categories listed in Appendix 1 of this P&P as well as at <http://www.hhs.gov/ohrp/policy/expedited98.html>, and/or
2. A requested change submitted during the period of one year or less for which approval is authorized is minor, excluding the addition of procedures involving more than minimal risk or that did not fall into any of categories 1-7 for expedited procedures, in previously approved research.
3. Per OHRP Guidance Expedited Review Category, at continuing review, an expedited procedure may be used even if initial review was by convened IRB if any of the following is true:
 - a. Research is permanently closed to enrollment, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects;
OR
 - b. No subjects have been enrolled and no additional risks have been identified; OR
 - c. Remaining research activities are limited to data analysis.

IRB analysts will review each submission they regard as possibly eligible for expedited review, and may use the Expedited Review Checklist

(<http://www.portland.va.gov/research/documents/irb/expedited-review-checklist.doc>)

as a guide. The checklist has been designed to capture all eligible components of the expedited review list referenced above. If it appears that the item(s) is appropriate for expedited review, materials will be sent to the chair or another qualified reviewer. The reviewer will receive all materials that the convened IRB would receive. The reviewer may exercise the authority of the IRB using the same criteria for approval as would the convened IRB, but may not table or disapprove the research. If the IRB Chair or qualified designee does not approve the research through expedited procedures, then the research project will be reviewed by the convened IRB. The research may only be disapproved after non-expedited review by the convened IRB.

The fully convened IRB will be notified of all research approved under expedited procedures in the IRB meeting agenda and minutes. All correspondence resulting from an expedited review will note such and be filed with the Research Services research project file kept in the appropriate Research Service space. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

XI. Convened IRB Meetings

Unless the research falls into one or more categories appropriate for expedited review, the IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum of the members is present, including a member whose primary interest is non-scientific and, for FDA-regulated studies, a member who is a licensed physician.

A. IRB Meeting Schedule

Current IRB meeting schedules and deadlines for investigator submissions are on the Research Service website (<http://www.portland.va.gov/portland/research/Committees/irb/index.asp#deadlines>). The IRB agenda, minutes, review materials and all applicable primary reviewer materials are dispersed to the IRB members approximately one week prior to the next convened meeting to allow for sufficient review in order to discuss the items for review adequately and determine the appropriate action during the convened meeting. IRB review materials include all of the materials as described in Section XI, G. Once a research project is reviewed by either IRB #1 or #2, the research project will stay with the same IRB for the life of the protocol.

Unless otherwise noted, the PVAMC IRBs will meet in Bldg. 101, Room 433.

B. Agenda and Meeting Materials

A meeting agenda and all applicable review materials will be prepared by the IRB analyst or designee and distributed with the meeting materials to IRB members approximately one week prior to each meeting.

C. IRB Meeting Procedures

The IRB chair or alternate chair (if the chair is not present) will call the meeting to order, once a quorum is established. The IRB will review and discuss the IRB minutes from the previous meeting and determine whether or not any changes to the minutes are necessary. The chair/alternate will call for a vote for approval as written or to be amended.

The IRB will review and discuss each agenda item requiring action and vote to approve, contingently approve, table or disapprove.

Review and determination of approval for a protocol may be deferred when necessary, e.g., if there is not appropriate representational expertise for a particular protocol at the convened meeting or a quorum is lost.

If the IRB is unable to review all agenda items in the allotted time, enough members leave or are recused to lose the quorum, or neither the chair nor alternate chair is available to preside over the meeting, the meeting will be reconvened within 30 days at a time and date agreed upon by a majority of the members.

Principal investigators may attend meetings to summarize a protocol or give other information as they or the IRB finds necessary. PIs may be present only for the portion of the meeting when they are actually interacting with the board about their protocol and must leave when the IRB wishes to discuss and vote.

IRB analysts will record minutes of each IRB meeting.

D. Actions Taken by the Convened IRB

The minutes shall include all applicable actions (listed below) and votes by the convened IRB.

1. **Approved:** Approved means that the study (or material reviews) was approved with no changes or no additional changes.
2. **Contingently Approved (Approved with minor changes):** Contingent approval means to approve the research project only after the described **specific** minor changes have been made by the Investigator and verified by the Primary Reviewer. Appropriate criteria on the applicable checklist have all been met or they will be met **if** a few **specific** changes are made.
3. **Tabled pending receipt of additional substantive information or substantive changes:** The IRB determines that it lacks sufficient information about the research to proceed with its review or that necessary changes are substantive, thus requiring re-review by the full board.
4. **Disapproved:** The IRB determines that the research may not be conducted at the facility or by employees or agents of the facility.
5. **Acknowledged:** acknowledged is used when one of the actions above does not apply, for example for a revised HIPAA authorization which the IRB is not allowed to approve, or if information is shared with the IRB that does not require action. Acknowledged may also be used for documents such as updates to the investigator's brochures, which are not in the control of the investigator.

E. Use of Subcommittees to Support IRB Activities

The IRB Chair may appoint subcommittees on an ad hoc basis to perform non-review functions as needed, such as monitoring compliance with IRB regulations.

F. Use of Primary Reviewers

1. Assignment of Primary Reviewers

The IRB analysts of the Research Service will make a preliminary review of the IRB application at the time of receipt and generally assign at least two primary reviewers at the time of initial and continuing review to review the protocol for the next IRB meeting, according to consistency with the protocol content and reviewer knowledge and expertise. The IRB Chairs will assist the IRB analysts, as necessary, in completing this responsibility. Physicians, Pharmacist, Nurses, PhD, and master's level physical, biological, or social scientists, as well as other biomedical health professionals are considered to have primary concerns in the scientific area. In general, two reviewers will be assigned, but for more complex research project proposals, additional reviewers may be assigned. In addition, when research involves categories of participants vulnerable to coercion or undue influence, IRB analysts will consult with the IRB Chair, if necessary, to identify a reviewer or a consultant who is knowledgeable about or experienced in working with such participants.

All other events reviewed by the IRB, with the exception of the initial and continuing reviews, will be assigned one primary reviewer consistent with the protocol content and reviewer knowledge and expertise.

If a reviewer is absent from the meeting a new reviewer may be assigned, as long as the new reviewer has reviewed the requisite materials prior to the meeting. An absent reviewer may submit written comments to be read at the meeting, as long as another reviewer is present to serve as primary reviewer.

2. Responsibilities of Primary Reviewers

The primary reviewers for each item reviewed by the IRB, including the initial review, continuing review, and review of all proposed modifications to research as well as required reports to the IRB of SAEs, unexpected problems, Data and Safety Monitoring Board reports, etc., are considered the lead reviewers on the IRB for the research project assigned to them. They are responsible for

1. thoroughly familiarizing themselves with all details of the research;
2. conducting an in-depth review of the research (see applicable checklists, which include criteria for approval of the review as appropriate) and systematically evaluating the protocol to determine whether a consultant is needed.
3. completing the applicable IRB reviewer forms; and
4. in cases where the items are reviewed at a convened meeting, leading the discussion of the research at the convened meeting, voicing any concerns that arose during their review and changes that may be required.

3. Absentee Primary Reviewer

If a reviewer is absent from the meeting a new reviewer may be assigned, as long as the new reviewer has reviewed the requisite materials. An absent reviewer may submit their written comments to be read at the meeting, as long as another reviewer is present to serve as a primary reviewer.

G. Materials for IRB Review

All IRB members, including alternate members and consultants, when applicable, shall be provided with sufficient information to ensure thorough initial and continuing review of each research proposal. All IRB members shall be afforded full opportunity to discuss each research proposal reviewed during convened meetings. The entire IRB file is also available for review to any IRB member upon request.

1. Initial Review Materials include the following:

All Members: for studies reviewed at convened meetings, all IRB members will be provided access to copies of materials listed below before and during IRB meetings at the time of initial review of a research project. The entire IRB file is also available for review to any IRB member upon request:

- a. Initial Review Questionnaire (IRQ)
- b. Copies of specific pages of the protocol referenced in the IRQ
- c. Any additional attachments. (Attachments include the Human Biological Specimens Questionnaire, or Investigational Device or Drug Information Record, etc.)

The Primary IRB Reviewers for each research project will receive the materials listed above in addition to the following for each research project.

- d. Protocol (complete DHHS-approved protocol and DHHS-approved sample informed consent when one exists). The protocol must include a written plan for a research study that includes, at a minimum, a description of the objectives, rationale, design and methods to be used in the conduct of the research.
- e. Investigator's brochure(s) or equivalent material, if applicable: required if the study involves an investigational drug. If the investigator is the sponsor of the study, an Investigator's Brochure or equivalent material is required. If a study involves an FDA-approved drug, an Investigator's Brochure may not exist. For such a study, equivalent information should be provided (package insert).
- f. IRQ and any additional attachments (Human Biological Specimens Questionnaire, or Investigational Device or Drug Information Record, etc.)

2. Continuing Review Materials include the following:

All IRB members: for studies reviewed at convened meetings, all members will be provided access to copies of materials listed below before and during IRB meetings at the time of continuing review of a research project.

- a. Continuing Review Questionnaire (CRQ) and protocol summary: The CRQ identifies the following: if any additional reportable SAEs, problems involving previously unknown risk, non-compliance or outside reports, or protocol deviations have occurred that have not been reported to the IRB; if new information is available regarding the research project that may change the risk/benefit ratio; any research findings to date, including a summary of subject experiences (benefits, adverse reactions); and enumeration of subjects withdrawn and the reasons for withdrawal.
- b. Informed Consent Form (if applicable and if enrollment is continuing)
- c. Waiver of Informed Consent Documentation and/or Process (if applicable)
- d. Abstract
- e. Initial Review Questionnaire (to provide baseline information)
- f. Any additional applicable forms, based on the enrollment status of the study.

The Primary IRB Reviewers for each continuing review of a research project will receive the above materials in addition to the following for each research project to help ensure a thorough continuing review of the research project.

- a. A copy of the complete protocol including any previously approved modifications.
- b. Most recent report capturing all reportable events to date. (If the research is not FDA-regulated, sponsor safety reports are not required.)
- c. If research is FDA-Regulated, Investigational Device or Drug Information Record, and amended or updated Investigator's brochure, if applicable.
- d. Summary of safety monitoring reports, if the protocol is greater than minimal risk and/or multi-site and therefore includes a data and safety monitoring plan.
- e. Any additional applicable forms, based on the enrollment status of the study.

Note: During the continuing review of a research project, upon request, any IRB member also has access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. This list of documents applies to all continuing reviews, whether they are conducted by an expedited procedure, or at a convened IRB meeting.

3. Ongoing Review Materials

All members and reviewers will have access to all relevant materials submitted for review as well as previously approved materials necessary to determine that regulatory criteria for approval have been met. This includes all modified documents and related originally approved documents (e.g., previously approved protocol, informed consent form, and advertisements), Project Revision/Amendment Form (PRAF), all problem reports, safety reports, etc.

H. Reports from the IRB to other Review Bodies

Prompt written notification will be provided to all applicable persons as outlined in the Required Reports in Human Research Table. In addition, the following applies:

1. Report to the R&D Committee

The R&D Committee is notified of all IRB determinations on reviewed items by review of the IRB meeting minutes. A list of research projects that have received final approval from the IRB is sent to the R&D Committee for review at the next convened meeting.

2. Report to the Chief of Staff

The RAO will notify the Chief of Staff of lapse in IRB approval due to failure of the PI to submit continuing review forms consistent with the policy outlined in Section XIII, C.

3. Report to the Privacy Officer and Information Security Officer

The RAO, with concurrence of the ACOS/R&D, will notify the Privacy Officer as soon as possible after

discovery of any breaches of data security with the potential for loss of privacy of a human subject and in accordance with the Required Reports for Research Information Protection Table (<http://www.portland.va.gov/portland/research/hrpp/index.asp#policies>).

4. Reports to and from Outside Agencies

The IRB and IRB records are subject to regulation and inspection by governmental regulatory agencies (e.g., the FDA, the Office for Human Research Protections (OHRP), and the VA Office of Research Oversight (ORO)). Copies of any applicable reports or correspondence to and from such agencies of concern to the PVAMC R&D Committee must be provided by the IRB to the R&D Committee, which shall determine if any additional notifications are necessary.

5. Report Process

The RAO will facilitate the process of reporting to institutional officials and relevant federal agencies through the following steps within the appropriate timeframe (required time lines for reporting below):

1. Draft a memorandum to the Medical Center Director for signature by the IRB chair to be sent through the ACOS/R&D, the COS, and the RCO.
2. Draft a memorandum addressed to each agency to be signed by the Medical Center Director.
3. Route the memorandum through the ACOS/R&D and COS to the Director for review and signature.
4. Mail and/or fax the signed document to the appropriate agencies (all reports to ORO are sent through the Western Regional Office).

I. Individualized IRB Consultations

Individuals who have questions regarding Institutional Review Board policies and procedures, e.g., questions involving whether or not a project is considered human research and whether it should be submitted to the IRB for review and approval, should direct the question in writing to the IRB analysts. Once received, the IRB analysts will consult with the IRB Members and Chair, if necessary, to address an individual's questions. Investigators should not contact the IRB Members or Chair directly with questions related to IRB policies and procedures. It is not the policy of the PVAMC IRB to provide curbside consults (personal consultations) to individual investigators and medical staff.

If an IRB Member or Chair receives a request for consultation, this request should be forwarded to the IRB analysts for a documented response to the individual's questions.

J. Process for Research Flags

The Research Service will prepare an electronic flag advisory for any project so required by the IRB once the study has received initial approval from the IRB. The VA electronic medical record is programmed such that when participants with electronic record flags make scheduled or unscheduled visits to the medical center and clinics, the participant information display will show a screen with the established type of flag advisory highlighted.

The IRB analyst or R&D staff member will notify the Principal Investigator and study coordinator when the flag is ready to be applied. As participants are enrolled into the research protocol, the Principal Investigator will obtain a signed informed consent and apply the medical record flag to the participants' electronic medical records. The PI is responsible for activating the research flag immediately following the informed consent process with a participant.

On an annual basis, each flag must be reviewed by the Principal Investigator or study coordinator and, if the flag is still appropriate, the flag must be marked for continuation. The Research Office will prompt research teams to conduct the annual review as each flag's annual anniversary nears.

The Research Service is responsible for de-activating the research protocol flag when the study is concluded. However, the Principal Investigator is responsible for de-activating the research flag if a participant withdraws or when research treatment ends, even if the participant will remain in the study for long-term follow-up or if the study as a whole has not yet been terminated.

A participant may only be enrolled in one research study for which the IRB has required a flag advisory in the participant's electronic medical records. An IRB Chair must approve any exceptions in advance.

K. Audits of Research Studies

The Research Compliance Program conducts routine regulatory audits of all research studies once every three years and upon closure of a study. In addition, the program audits 100% of all research Informed Consents signed each year. The Research Compliance Officer (RCO) reports directly to the medical center director and receives guidance and direction from him/her and through the VHA Office of Research and Development and Office of Research Oversight. In order to ensure that the research compliance program can fulfill its auditing responsibilities independently, the activities of the RCO may not be determined or managed by the IRB's, Research Service, research investigators, or any other research personnel.

Routine regulatory audits are conducted using applicable regulatory requirements, including industry standards of good clinical practice, as defined by the VA Office of Research Oversight (ORO). The results of regulatory and informed consent audits completed by the Research Compliance Program are reported in writing to the chair of the IRB (and all other local R&D oversight committee and subcommittees) and reviewed by all IRB committee members at each convened meeting. Research compliance reporting requirements and the responsibilities of all entities involved in the medical center's research activities are detailed in VHA Handbook 1058.01.

The medical center's research service may also maintain its own internal compliance program and Research Assurance Officer (RAO) or equivalent. The RAO may also audit research protocols and informed consents, however, audits performed by the RAO do not override the requirements for regulatory and informed consent audits by the RCO. The IRB may require more frequent audits than those conducted by the RCO, and will generally request that such audits be conducted by the RAO. The requirement to increase the frequency of audits or to audit specific aspects of a study may be based on considerations including, but not limited to:

1. Involvement of vulnerable populations;
2. Level of risk;
3. Phase I or Phase II studies;
4. Involvement of FDA approved drugs for which there has been a new safety warning issued, or change in the labeling that indicates increased risks;
5. Issues of noncompliance; or
6. Data confidentiality or security concerns.

When such audits are requested by the IRB, it must be explicit with regard to the timeframe for reporting audit findings to the IRB. Based on the nature of the study and the results of the audit, the IRB may require corrective action, and will be explicit with regard to the type of corrective action (such as revising study documents or changing recruitment procedures), who should implement and review the corrective actions and how corrective actions will be evaluated.

XII. Appeal of IRB Determinations

The IRB shall provide the PI with a written statement of its reasons for disapproving or requiring modifications in proposed research and shall give the PI an opportunity to respond. This correspondence will be provided to the PI within a reasonable time frame for items reviewed outside of a convened meeting. The PI or appropriate designee shall respond in writing and may submit materials either electronically or in hard copy. A time frame and format for response will be provided on the IRB correspondence based on the nature of the requested response.

When a dispute arises between the IRB and the PI regarding required modifications to the protocol or other parts of the IRB application that cannot be amicably resolved between the parties involved, an appeal to the committee may be made by either the PI or the IRB to the R&D Committee.

The R&D Committee may organize a meeting with the individuals noted above to discuss the issue at hand, and will arrange further meetings with the PI and the IRB or designee as needed. The R&D Committee will facilitate the discussion between the PI and the IRB. Final recommendations for approval remain under the purview of the IRB that made the original determinations that are appealed, i.e., the appeal will not be reviewed and considered by the other IRB. However, the R&D Committee may want to comment on the process and make recommendations to the IRB for future protocols similar to the one under appeal.

XIII. Determination of Continuing Review Date

A. Determination of Continuing Review Date for Studies Reviewed by the Convened IRB

Per federal regulations, the IRB approval period for research may not extend more than 365 days from the time that the convened IRB voted on approval, or approval pending minor modifications. When a study is reviewed by the convened IRB, the continuing review date is determined as follows:

1. **Approved with no condition:** If the convened IRB approves the study with no requirement for modifications, the date of approval is the date of the convened IRB meeting at which approval was granted. The continuing review date is calculated based on that approval date. For example, a study approved outright on 3/2/12 for one year, would expire on 3/1/13.
2. **Approval with minor changes:** If the convened IRB approved the study contingent on specific minor modifications to the protocol or the informed consent form (or other study documents), the study cannot proceed until subsequent review and approval of the materials submitted by the investigator in response to the minor stipulations. Therefore, the date of approval will be after the date of the convened meeting. However, the continuing review date is calculated based on the date of convened meeting at which contingent approval was granted. Therefore, a study contingently approved on 3/2/12, may have stipulations submitted by the PI and subsequently reviewed and approved on 4/1/12. The approval for this study would still expire on 3/1/13, and continuing review must occur prior to the expiration date.

B. Determination of Continuing Review Date for Studies Reviewed by Expedited Procedures

If a study is reviewed and approved by an expedited procedure as outlined in section X, the date of continuing review is based on the date the IRB Chair, or experience IRB voting members, give IRB approval to the research study. For example, a study for which expedited review was conducted on 3/2/12, and which required changes which were submitted and approved on 3/15/12, would expire on 3/14/13 (based on the date of the final approval by expedited review).

Note that the expiration date occurs on the last date that the protocol is approved.

C. Expiration of IRB Approval Period

Per VHA ORD policy, if continuing review does not occur within the timeframe set by the IRB, the research is automatically suspended, i.e. approval lapses. A notification letter to the PI from the IRB chair or RAO will be generated promptly by an IRB analyst once s/he has determined the continuing review has not been submitted, reviewed and approved, or stipulations of contingent approval have not been met and approval has lapsed.

Once notified of the suspension, if research participants are currently enrolled in the research project and their participation is ongoing, the PI must immediately submit to the IRB chair a list of research subjects for whom suspension of the research might cause harm. Enrollment of new subjects may not occur, and continuation of research interventions or interactions with currently enrolled subjects should only continue when the IRB or IRB Chair, in consultation with the Chief of Staff (COS), finds it is in the best interest of individual subjects to do so. The IRB chair through the RAO or ACOS/R&D will notify the COS of any studies suspended due to lapse of the IRB approval period.

If the study is FDA-regulated, the COS and IRB Chair must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.

The sponsoring agency, private sponsor, ORD, ORO, or other Federal agencies must be informed, as appropriate.

Once suspended, IRB review and re-approval must occur prior to re-initiation of the research. If study approval has lapsed more than 2 months, the IRB may require the PI to submit a new application to the IRB for review and approval. If the study approval has been lapsed two months or less, the items requested at the time of continuing review may be reviewed for consideration of continued IRB approval.

Once the PI submits the required information, it will be reviewed as appropriate by the IRB. Principal investigators who fail to comply with continuing review timelines may be suspended from conducting research. This will be evaluated on a case-by-case basis.

D. Criteria for Requiring Review More Often than Annually

The IRB may determine that a protocol should be reviewed more frequently than annually. This may be determined at any time for any reason, including level of risk, nature of adverse events, and study population.

The IRB may consider the following factors in determining the criteria for which studies require more frequent review and what the time frames generally will be:

1. Probability and magnitude (degree or risk) of anticipated risks to subjects.
2. Likely medical condition of the proposed subjects.
3. Overall qualifications of the principal investigator and other members of the research team.
4. Specific experience of the principal investigator and other members of the research team in conducting similar research.
5. Nature and frequency of adverse events observed in similar research at this and other facilities.
6. Vulnerability of the population being studied.
7. Other factors that the IRB deems relevant.

In specifying an approval period of less than 1 year, the IRB may define the period with either a time interval or a maximum number of subjects, i.e., after 3 months or after three subjects. Examples of time intervals for IRB approval periods include 3, 6, 9, or 12 months. The IRB documents in the minutes the determination of risk level for a research project and approval period.

XIV. CONTACT WITH SUBJECTS

A. Appropriate Contact with Subjects

1. Initial Contact

- a. For studies pertaining to a veteran's medical status or that reflect that they were selected based on protected health information (PHI), initial contact must occur through a licensed independent practitioner who has a clinical relationship with the participant, i.e. clinician. If the patient gives permission through his/her clinician either verbally or in writing, the potential subject can then be contacted by research personnel during a clinic visit, by phone or by mail. The permission must be documented in CPRS with the approving clinician as a cosigner.
- b. If the veteran is to be initially contacted by mail and has not given permission for contact, the initial contact must include a letter from either a clinician or the director of the clinic where the veteran receives medical care. The researcher may request permission from the clinician or clinic director in person, by letter or by confidential email to invite veterans to participate. Once approved, the letters to the participants may be signed electronically by the clinic director or clinician, relieving them of the need to sign multiple letters by hand.
- c. The letter from the clinician may acknowledge information about a patient's PHI to allow the patient to understand why s/he has been selected as a possible participant in the study.
- d. The letter from the clinician or clinic director may be accompanied by a separate form letter, from the researcher, that is approved for all potential study participants. The researcher's form letter cannot be individualized since that would indicate direct knowledge of PHI. The letter may include the study title, a copy of the consent form and other relevant study participation information that might infer knowledge of the participant's PHI. The letter should give the participant the option of refusal to participate by returning a separate letter indicating s/he does not wish to be contacted or the veteran may indicate interest in learning more about the study. The letter may also state that if the potential participant does not return a response within two weeks, s/he may be contacted by phone.
- e. If no response is received within two weeks, and the research team can contact the veteran by phone, but with limited interaction. After identifying themselves and explaining they are calling about the study, they should ask if the veteran received the letter. If yes, the research may ask if s/he has reviewed the letter and is interested in hearing more about the study. If the veteran has received but not reviewed the letter, the researcher may ask if s/he is interested in hearing more about the study or receiving more information. If the veteran has not received the letter, the research team may only ask permission to send a second letter and confirm the veteran's address. No other information may be requested at that time.
- f. Investigators may contact veterans directly for studies that do not address specific aspects of the veteran's medical care. For example, studies seeking veterans' view on how to improve VA services, parking, etc.

2. Telephone Contact

Telephone use for initial contact is discouraged, unless there is written documentation (e.g., in a progress note in CPRS based on a clinician's conversation with the potential participant) that the subject is willing to be contacted by phone about the study in question or a specific kind of research. When such initial contact occurs by phone, the initial contact must provide a telephone number or other means that the potential subject can use to verify that the study constitutes VA research. It is recommended that the phone number of the RAO be used in such situations. In addition, in cases that initial contact includes contact by telephone, research team members are prohibited from requesting Social Security numbers by phone.

3. Later Contact

When research team members contact enrolled subjects by phone, the call must begin by referring to previous contacts and, when applicable, the information provided in the informed consent form. The IRB generally requires a script for all phone contacts, and the scope of phone contacts with subjects must be limited to topics outlined in IRB0approved protocols and informed consent forms.

XV. Outreach to Participants and Community

In addition to distributing VHA Research brochures to all participants through the PIs and making brochures and posters available to clinic and public areas within the PVAMC and Community Based Outpatient Clinics (CBOCs), the ACOS/Deputy ACOS/R&D and designated R&D staff will perform the following:

1. Plan and participate in Research Day activities. To evaluate effectiveness, R&D staff will tabulate an estimate of the number of people who are not research staff or investigators who stop to look at displays and ask questions.
2. Work with the Patient and Family Education Office, medical center staff, and research staff to identify forums and group meetings organized by clinic areas for patients and request time to inform and discuss research participation in general and invite community members to offer input. To evaluate effectiveness, R&D staff will tabulate how many community members offer input and ask questions as well as how many were in attendance.
3. Approximately once/month and not less than six times per year, on alternating mornings and afternoons and different days of the week as scheduling permits, an R&D or clinical research staff member will sit at a table identified with an official VA research poster in the main lobby of the PVAMC. The staff person will offer official VA research brochures, answer questions about research in general, assist with questions about specific research studies, and direct veterans and the general public as necessary to the appropriate office or person, if unable to provide the correct information themselves. For those veterans and members of the public who are willing to be surveyed, the staff member will complete a very brief survey to solicit input about the research program in general and how we might better serve veterans. No identifiable information will be recorded. Surveys will be reviewed by the ACOS/R&D and designated R&D staff to determine possible new ideas that might be implemented to increase research interest among community members and better meet their needs. Investigators will also be informed when appropriate.

XVI. Reports of Problems in Research

Events that constitute problems in research are outlined in the Required Reports in Human Research table (<http://www.portland.va.gov/Research/hrpp/index.asp#policies>) and in the Human Research Event Report form (<http://www.portland.va.gov/research/documents/hrpp/human-research-report-form.doc>) and must be reported and reviewed. Definitions for each type of problem are included in the Definitions section of this document under “Adverse Event”.

All investigators conducting research as employees or agents in the PVAMC or under VA auspices are required to report all problems listed below. Principal Investigators are also required to report promptly to the IRB and the ACOS/R&D any adverse event (AE) that is reported to OHRP or the FDA and/or the sponsor in accordance with FDA requirements.

A. Timeline for Reporting

Unless otherwise noted, all events listed below must be reported to the IRB within 5 business days of awareness.

B. Types of adverse events and problems that must be reported

1. All Unanticipated Problems Involving Risk (UPR). Examples of UPRs include:
 - Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others;
 - Any work-related injury to personnel involved in human research, or any research-related injury to any other person requiring more than minor medical intervention or that leads to serious complications or death;
 - Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility’s research projects
 - Any Data Monitoring Committee (DMC, Data and Safety Monitoring Committee –DSMC, or DSM Board) report describing a safety problem.
 - Any sponsor analysis describing a safety problem (**NOTE:** Sponsor AE Reports lacking meaningful analysis are NOT considered problems.)
 - An interim analysis or safety monitoring/DSMB report indicating that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.
 - A paper published from another study shows that risks or potential benefits of the research might be different from those initially presented to the IRB.
2. Any local (occurring at the PVAMC) unanticipated serious adverse event.
3. Apparent Serious and/or Continuing Non-Compliance.
4. Protocol deviations/violations as required by the policy outlined in Section XVI, I & J below.
5. Loss of VA-Sensitive Information, Potential Loss of Subjects’ Privacy. Such losses must be reported to the PVAMC Research Office using any mechanism (telephone, e-mail, in person) within **1 hour** of awareness. Examples of such losses include:
 - signed informed consents or case report forms with any of the 18 HIPAA PHI identifiers cannot be found;
 - a laptop containing identifiable private information is stolen from a research lab, is recovered from a campus dumpster several hours later and data files remain intact

C. How to Submit a Report

If any of the events/problems identified in 2a-3d above are identified, they must be reported to the IRB using the Human Research Event Report Form, which is available at

<http://www.portland.va.gov/research/documents/hrpp/human-research-report-form.doc>

Investigators must fax reports to 503-273-5152 or hand-deliver reports to the R&D Office.

D. Review after Initial Report is Submitted

Once submitted by the PI, research team member, or other individual, the IRB Chair, qualified IRB member-reviewer or the convened IRB will review reports of local serious AEs, protocol deviations, non-compliance, and other unanticipated problems involving risk to subjects or others within 5 business days of receiving the report. During this review, the IRB Chair/qualified reviewer determines whether the event was serious, unanticipated and/or related using the Human Research Event Report Reviewer Checklist, located at

<http://www.portland.va.gov/research/documents/irb/hrer-reviewer-checklist.doc>

E. Determination that an Event is Serious, Unanticipated and Related

In the event that the IRB chair, qualified IRB member-reviewer or convened IRB determines and documents that the local unanticipated SAE or possible serious unanticipated problem involving risks to subjects or others is serious and unanticipated and related to the research through the use of the Human Research Event Report Reviewer Checklist

(<http://www.portland.va.gov/research/documents/irb/hrer-reviewer-checklist.doc>), then the IRB Chair or designee must notify ORO via telephone or e-mail within 48 hours. Generally, the RAO or AO/Research is designated to notify ORO within 48 hours. In addition, a report of the problem or event must be submitted to the facility Director within 5 business days of the determination, with simultaneous copies to the ACOS for Research and the R&D Committee per VHA Handbook 1058.01. As part of the review conducted by the Chair or qualified reviewer, a determination is made regarding whether or not immediate action is warranted, or whether review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted. These determinations are then reported to the convened IRB at the next meeting.

F. Convened IRB Review of a Report

When it is determined that a report meets the criteria to be reviewed by a convened board, an IRB analyst assigns a primary reviewer to review and present the events as required to the convened IRB. The primary reviewer as well as all IRB members are provided copies of the following and are expected to review this information in advance of the meeting:

- The report
- The Human Research Event Report Reviewer Checklist
- The results of any investigation, if applicable
- The current approved consent document, if applicable
- Any other relevant information, e.g., investigator's brochure for drug studies, medical record progress notes, protocol, etc.

The IRB will consider the following actions:

- Modification of protocol
- Modification of information disclosed during consent
- Providing of additional information to past participants
- Notification of current participants if new information might affect willingness to continue in research
- Requiring current participants to re-consent
- Modification of continuing review schedule
- Monitoring of the research
- Monitoring of the consent process

- Referral to other organizational entities
- Suspension of research
- Termination of research

Remedial actions for serious or continuing non-compliance involving a specific study or research team must be completed within 90-120 days after the IRB's determination.

Remedial actions involving programmatic serious or continuing non-compliance must be completed within 120-180 days after the IRB's determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, or legal negotiations.

G. For-Cause Suspension or Termination of IRB Approval of Research

The IRB Chair or a designated reviewer may require an immediate, temporary suspension of enrollment of new subjects and/or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB, if there is an unanticipated problem involving risk to participants or others or if research is not being conducted in accordance with the IRB's requirements. The ACOS/R&D may also suspend or terminate research on an urgent basis if it is not being conducted in accordance with the IRB's requirements. The IRB Chair or designee or the ACOS/R&D may call an emergency IRB meeting or place the item on the agenda for the next regularly scheduled meeting.

If the IRB determines there is an unanticipated problem involving risk to participants or others or that there is serious or continuing non-compliance, they may vote to suspend or terminate approval of research.

The IRB shall notify the principal investigator in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of action must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

In the event of any suspension or termination of approval of research, the IRB or the IRB Chair or designee (in the case of the need for immediate action) shall consider actions to protect the rights and welfare of currently enrolled participants and whether procedures for withdrawal of enrolled participants take into account their rights and welfare. Possible actions may include the following:

1. Inform current participants of the suspension/termination;
2. Require any resulting adverse event or outcome be reported to the IRB;
3. Require arrangements for medical care outside the research study;
4. Transfer the research to another investigator; and/or
5. Require continuation of the participant in the research under independent monitoring.

Any termination or suspension of research related to concerns about the safety, rights or welfare of human research subjects, research staff, or others must be reported following the reporting path outlined in the Required Reports in Human Research table

(<http://www.portland.va.gov/Research/hrpp/index.asp#policies>)

H. Reporting to organizational offices and external agencies

Reports will be facilitated by the RAO and/or RCO, depending on the report (see Required Reports in Human Research, <http://www.portland.va.gov/Research/hrpp/index.asp#policies>)

1. Contents of Report:

- a. Name and any relevant assurance number of facility
- b. Title of the research project(s)

- c. The number(s) used by the IRB to identify the project
- d. Name of any external sponsor(s) of the projects
- e. Funding source
- f. Name of any external entities to VA that were notified or are to be notified.
- g. Detailed description of event
- h. Detailed description of actions or proposed actions to address the event including systemic actions when warranted.

The reports to the organizational offices and external agencies must occur in the timeframes outlined in the Required Reports in Human Research table.

I. Recognizing Deviations from the IRB Approved Protocol

The IRBs presume that what is occurring in the implementation of protocol procedures is consistent with what was approved by the IRB. However, the IRBs recognize that deviations and exceptions to approved IRB protocols may occur. A protocol deviation occurs when there is an inconsistency in a research study between the approved protocol and the actual activities being done. Protocol deviations may directly harm or present the risk of harm to human subjects, or may be administrative in nature, such as those related to data or records-keeping. The PVAMC categorizes protocol deviations into minor, moderate, or major, and within those categories applies criteria for direct harm/risk of harm or administrative deviations, as follows:

1. Minor Protocol Deviations

- Direct harm/risk of harm:
 - The deviation resulted in no substantive direct harm or risk of harm to research participants or others.
 - The deviation did not result in or require any substantive action to be taken or result in a substantive change to the subject's condition or status (i.e., did not affect the subject's participation in a substantive way, did not result in a change to the subject's emotional or clinical condition, did not cause an adverse experience or require a change to the clinical care of the subject, etc.)
- Administrative:
 - The deviation had no substantive effect on the value of the data collected (i.e., the deviation does not confound the scientific analysis of the results); or
 - The deviation did not result from willful or knowing misconduct on the part of the investigator(s); or
 - The deviation (e.g., consenting a subject with an old version of a consent form, recording data on an expired/incorrect form, forgetting to record data that may be acceptable recorded at the next visit) is easily corrected.

2. Moderate Protocol Deviations

- Direct harm/risk of harm:
 - The deviation resulted in a direct harm or risk of harm that is not greater than the minimal risk levels defined in Appendix 1 of this P&P; or
 - The deviation resulted in the need for minimal risk interventions, such as those defined in Appendix 1 of this P&P;
- Administrative:
 - The deviation resulted in the loss or improper collection or recording of some data for one or more subjects, but did not invalidate the entire data set for the study; or
 - The deviation resulted in a regulatory violation that can be acceptably resolved; or

- Repeated minor protocol deviations from the same laboratory, site or research team (the threshold for repeated minor protocol deviations becoming a moderate deviation will depend on the nature of the study and the nature of the deviations); or
- There has been a failure to follow action ordered to correct minor or moderate protocol deviations.

3. Major Protocol Deviations

- Direct harm/risk of harm:
 - The deviation resulted in or required a substantive action to be taken or resulted in a change to the subject's condition or status;
 - The deviation has harmed or posed a significant risk of substantive harm to research participants.
- Administrative:
 - The deviation has substantially damaged the scientific integrity of the data collected for the entire study; or
 - The deviation is evidence of willful or knowing misconduct on the part of the investigator(s); or
 - The deviation involves serious or continuing non-compliance with federal, state, or local research regulations; or
 - There have been repeated minor and/or moderate protocol deviations from the same laboratory, site or research team; or
 - There has been a failure to follow action ordered to correct minor and/or moderate protocol deviations; or
 - There has been a failure to take emergency corrective action ordered by an IRB Chair when, in the IRB Chair's assessment, it appears that research subjects may be at risk of harm due to a reported protocol deviation.

J. Reporting and Review Procedures of Protocol Deviations

The principal investigator makes the initial determination of whether a protocol deviation is minor, moderate, or major. In cases that a deviation must be reported, it should be reported on the Human Research Event Report Form found at <http://www.portland.va.gov/research/documents/hrpp/human-research-report-form.doc>. All reportable deviations must be reported within 5 business days of awareness, unless otherwise noted below.

1. Minor Protocol Deviations

- Minor protocol deviations do not need to be reported.
- If a minor protocol deviation is reported, an IRB Chair or qualified IRB member will review the reported deviation using the Human Research Event Report Reviewer Checklist. The IRB Chair or member may require corrective action to be taken when there is a pattern of repeated minor protocol deviations.
- In cases where an IRB Chair or member determines that a reported deviation can be categorized as minor or that no deviation actually occurred, the investigator/study coordinator will be notified via e-mail that the deviation was determined to be minor, and that no further action is needed. In addition, the deviation will be included on the summary report that is provided to the IRBs with the monthly meeting agenda.

2. Moderate Protocol Deviations

- All moderate protocol deviations must be reported.
- When a moderate protocol deviation is reported, an IRB Chair or qualified IRB member will review the reported deviation using the Human Research Event Report Reviewer

Checklist, and will confirm that the protocol deviation meets the definition of moderate. If necessary, the IRB Chair or member will seek consultation from other IRB members or experts to make a determination that a deviation is moderate.

- If an IRB Chair or IRB member determines that the reported deviation is actually a minor protocol deviation, the investigator/study coordinator will be notified via e-mail that the deviation was determined to be minor, and that no further action is needed. In addition, the deviation will be included on the summary report that is provided to the IRBs with the monthly meeting agenda.
- If an IRB Chair or IRB member determines that the reported deviation meets the definition of moderate, the IRB Chair may require corrective action to be taken for moderate protocol deviations. In such cases, the IRB Chair or member may serve as the reviewer for any required changes (to the protocol, consent, etc.) or corrective action, utilizing an expedited review procedure. In such situations, the deviation will be included on the summary report that is provided to the IRBs with the monthly meeting agenda, with a notation that the deviation was categorized as moderate and what corrective action, if any, was required.
- The IRB Chair or member may alternately choose to refer the moderate deviation report to the convened IRB for discussion and determination of corrective action.

3. Major Protocol Deviations

- All major protocol deviations must be reported.
- If there is a direct harm/risk of harm due to a major protocol deviation, it must be reported to the IRB within 24 hours of discovery of the deviation. All other major protocol deviations must be reported within 5 business days of awareness.
- When a major protocol deviation is reported, it will be reviewed initially by the IRB Chair and Alternate Chair, who will make a determination regarding whether the reported action meets the definition of major deviation. In cases that the Chair and Alternate Chair agree that the protocol deviation is major, or if they disagree (and one determines it is major and the other determines it is moderate), the report will be referred to the next convened IRB meeting for discussion and determination of corrective action (if any). In cases where both the IRB Chair and Alternate Chair rate the deviation as moderate (or minor, or that no deviation occurred), they can recommend corrective action and serve as the reviewers for any required changes (to the protocol, consent, etc.) or corrective action, utilizing an expedited review procedure. In such situations, the deviation will be included on the summary report that is provided to the IRBs with the monthly meeting agenda, with a notation regarding how the deviation was categorized by the Chair and Alternate Chair and what corrective action, if any, was required.
- In cases where the protocol deviation is determined to be major by both the Chair and the Alternate Chair, and the report is referred to the next convened meeting, the PI will be invited to attend the meeting to explain and answer questions. Prior to the meeting, the PI may be notified of additional information that is needed. In addition, the IRB may call in experts to provide an opinion, as needed.

Appropriate reports may be filed with outside agencies depending on the final determination of a protocol deviation, if it falls into the reporting categories outlined in section XVI of this P&P, or if it is suspended or terminated as a result of the deviation.

K. Review of Complaints and Allegations of Non-Compliance in Human Research

The IRB follows the policy titled "Complaints and Allegations of Non-compliance Pertaining to Human Research," with regard to complaints and allegations of non-compliance. In cases where the non-compliance may be serious and/or continuing, it is reviewed as noted in section XVI.

XVII. Regulatory Criteria Applied During IRB Review

A. Required Criteria for IRB Approval of Research

The IRB shall determine the following during initial and continuing review and approval of research, as stated in the Department of Veterans Affairs, Department of Health & Human Services, and Food & Drug Administration regulations. IRB approval of a study means the IRB has determined that the research has satisfied all relevant approval criteria and may be conducted within the constraints set forth by the IRB and by other applicable local, VA and other Federal requirements.

Although the IRB is a subcommittee of the R&D Committee, neither the R&D Committee nor the Medical Center Director may approve research involving human subjects that has not been approved by the IRB of record, nor may they alter an adverse report or recommendation made by the IRB. For example, the disapproval of a research protocol for ethical or legal reasons by the IRB may not be reversed by the Medical Center Director or R&D Committee.

1. Risks to Subjects

The IRB must consider the overall level of risk to subjects in evaluating proposed research during initial and continuing review of research. The IRB identifies the risks to the subject. These risks must be clearly identified in the informed consent form. The IRB determines the level of risk of a protocol by evaluating the nature of several types of risk, including but not limited to physical, psychological, and social/economic harms that could result from participation in the research. The IRB also evaluates the probability of the occurrence of a risk, as well as the severity of each potential risk in order to qualify each protocol as less than minimal, minimal, moderate or high risk. The IRB determines the interval for continuing review based on the level of risk of the research project.

The IRB must distinguish research that is greater than minimal risk from research not greater than minimal risk when considering proposals for expedited review and for vulnerable populations. However, the IRB assesses the risk/benefit in all research protocols.

Generally, research projects that may be considered high risk involve high-risk invasive procedures, a Phase I or II clinical trial, investigational drugs, or a significant risk investigational device.

2. Risks Minimized

To approve research, the IRB must determine at the time of initial and continuing review that risks are minimized by using procedures (1) consistent with sound research design and (2) that do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize standard care procedures performed on subjects for diagnostic or treatment purposes.

The IRB examines the research plan, including research design and methodology, to determine that there are no obvious flaws that would place subjects at unnecessary risk. This includes the risk that the research is so poorly designed or is so lacking in statistical power that meaningful results cannot be obtained.

3. Risks Reasonable Relative to Anticipated Benefits

At initial and continuing review (including amendments, research problems, etc.), the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects and the importance of the knowledge that may reasonably be expected to result. This is determined at the time of initial and continuing reviews, as well as on an ongoing basis for other paperwork (such as amendments) submitted for each protocol. The IRB determines the level of

physical, psychological, and social/economic risk of the research as well as probable individual and societal benefits of the research.

The IRB analyzes risk/benefit by evaluating the most current information about the risks and benefits of the interventions involved in the research and the reliability of this information. The IRB considers only those risks related to the research, and not the long-range effects (e.g., public policy implications) of applying any knowledge gained from the research.

4. Equitable Selection of Subjects

The IRB determines by viewing the IRQ, protocol and other research project materials that selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of people who might benefit from the research.

The IRB evaluates the purposes of the research; the setting; the scientific and ethical justification for including any vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit from the research; participant recruitment and enrollment procedures; amount and timing of payments; and the inclusion/exclusion criteria.

5. Circumstances of Informed Consent Requirements

To approve research, the IRB must determine that legally effective informed consent shall be sought from each prospective subject or the subject's legally authorized representative, unless informed consent requirements may be waived or altered under VA regulations or any state statutes that are determined to be applicable by Regional Counsel. Currently, no state or local regulations affect informed consent.

Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

6. Documentation of Informed Consent

To approve research, the IRB must determine that informed consent shall be appropriately documented, in accordance with, and to the extent required by VA, FDA, the Common Rule regulations and applicable (as determined by Regional Counsel to be more stringent than federal law) state and local regulations. Currently, no state or local regulations affect informed consent at the PVAMC. Requirements for informed consent and documentation are described in Section XVIII, D.

7. Review of Plans for Data and Safety Monitoring

To approve research, the IRB determines that the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. A Data and Safety Monitoring Plan may be required for all multi-site research and for all research with greater than minimal risk. In general, it is desirable for a Data and Safety Monitoring Board (DSMB) to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. The IRB may require a DSMB as a condition for approval of research.

When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this

information be submitted directly to the IRB. However, the IRB shall review all DSMB reports, assess if the risk/benefit ratio has changed and decide independently if any change in the research protocol or informed consent or suspension of research should be required.

1. Review of Safety Monitoring: For studies that are blinded, have multiple sites, recruit vulnerable populations, or employ high-risk interventions, a description of the data and safety monitoring plan must be submitted to the IRB as part of the proposed work. This plan should contain procedures for identification and reporting problems involving previously unrecognized risk and all local serious adverse events. The monitoring provisions must be described in sufficient detail for the IRB to determine whether they are appropriate for the research. All research requires some level of monitoring and principal investigators are responsible for monitoring their studies. However, the IRB must approve the plan for monitoring data and safety for all research except minimal risk research where the PVAMC is the only site. For studies that have a Data and Safety Monitoring Board (DSMB), the research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects.

For research conducted under a DOD Addendum, appointment of a research monitor must be considered by the IRB. A monitor is required for research involving greater than minimal risk, although the IRB can require this for a portion of the research or studies involving no more than minimal risk if appropriate. The independent research monitor must be appointed by name and has authority as follows:

- a. Stop a research study in progress.
- b. Remove individuals from the study.
- c. Take any steps to protect the safety and well-being of participants until the IRB can assess.

8. Privacy of Subjects and Confidentiality and Security of Data

The IRB requires that subjects' confidentiality be strictly maintained and privacy protected. The IRBs serve as the Privacy Board for Research at the Portland VA Medical Center and abides by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and HRPP policy "Health Insurance Portability & Accountability Act (HIPAA)" (<http://www.portland.va.gov/Research/hrpp/index.asp>). The IRB recognizes the importance of protecting subject confidentiality, and carefully evaluates each protocol for the confidentiality measures taken. Only those authorized by the IRB, which may include the Principal Investigator, Co-Investigator and Research Assistant(s), etc., shall be allowed access to individually-identifiable participant information. Individuals must have prior approval by the IRB before receiving individually identifiable participant data for research purposes. This may include requiring such measures as a set of research codes rather than the use of individually identifiable information, linked to the participant through only one codebook maintained by the Principal Investigator.

At the time of initial and continuing review, the IRB ensures the privacy and confidentiality of research subjects is protected. The IRB evaluates the methods used to obtain information about subjects and individuals who may be recruited to participate in studies; the use of personally identifiable records; and the methods to protect the confidentiality and security of research data, including how and where the data will be stored. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data as noted in section XVII, B.7 of this P&P. The principal investigator will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the Initial Review Questionnaire, any necessary HIPAA Forms, the research protocol, and/or other submitted materials. When applicable, the IRB will assure the HIPAA Authorization is consistent with both the informed consent and the protocol.

In reviewing privacy and confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identifying techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of protections.

B. Additional Considerations During IRB Review and Approval of Research

1. Implementing Flag Advisories in the Electronic Medical Record

An electronic record flag advisory serves as an immediately identifiable alert that promotes safe, appropriate, timely and respectful participant care. The IRB will decide at initial review whether such a research flag must be activated in the participant's CPRS electronic medical record, and require assurance, if applicable, at continuing review that the flag remains activated unless the requirement was lifted by the IRB. Studies that generally require a flag are moderate or high-risk and invasive, including studies requiring surgery and/or utilizing investigational drugs or significant risk investigational devices. Flags may also be required for studies for which the IRB feels it is important that any medical staff member working with an enrolled participant know that they are participating in a research study, such as research involving interventions that will be used in the medical care of the subject or that could interfere with other care, clinical services that could interfere with other care, or for research involving surveys/interviews that could provoke undue stress or anxiety, unless the IRB determines such a flag is not in the subject's best interests. Flags may not be required if (1) participation in the study involves only one encounter, (2) participation involves the use of a questionnaire or previously collected biological specimens, and/or (3) identification as a participant in a particular study will place the participant at greater than minimal risk.

2. Independent Verification from Sources Other than the Investigator that No Material Changes Have Occurred Since the Previous IRB Review

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occur during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research.

The IRB shall consider the following factors in determining which studies require such independent verification:

1. Probability and magnitude of anticipated risks to subjects.
2. Likely medical condition of the proposed subjects.
3. Probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Prior experience with the principal investigator and research team.
5. Other factors the IRB deems relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments and/or adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

3. Advertisements

The IRB is responsible for ensuring that the selection of subjects is equitable, and therefore must approve any and all advertisements (final copy of printed ads and final tape/CD/DVD of audio/video ads) prior to posting and/or distribution for studies conducted under the purview of the PVAMC IRB. Advertisements should be submitted to the IRB with the initial application or as an addendum to the protocol. The IRB will review to assure the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. The IRB will also review the mode of advertisement.

Advertisements may not include any of the following:

1. Statement or implication of a certainty of favorable outcome or other benefits beyond what is outlined in the consent and the protocol;
2. Exculpatory language;
3. Emphasis on payment or amount to be paid, by such means as larger or bold type; or
4. A promise of free treatment when the intent is only to say that participants will not be charged for taking part in the study.

FDA-regulated study advertisements may not include any of the following:

1. Claims inconsistent with FDA labeling, either explicit or implicit, about the drug, biologic or device under investigation;
2. Terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational.
3. Statement offering compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. The following items must be included:

1. The name and address of the clinical investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study (a complete list of eligibility criteria is not required).
4. A truthful and straightforward description of the benefits and burdens to the subject for participating in the study (e.g., payments, no cost treatment, percentage of subjects who will receive a placebo).
5. The time or other commitment required of the subjects.
6. The location of the research and the person or office to contact for further information.
7. A clear statement that this is research and not treatment.

4. Recruitment

The IRB must approve any and all recruitment incentives to investigators, physicians, and other health care providers for identifying and/or enrolling subjects for studies that are conducted under the purview of the PVAMC IRB. The Principal Investigator must disclose this information on the IRQ when a study is initially reviewed by the IRB. The IRB reviews the recruitment incentives to assure that the incentive is not coercive or unduly optimistic, creating undue influence for the researchers to recruit subjects into a study overall or by a certain date. Recruitment incentives will be reviewed according to HRPP policy, "Conflict of Interest in Research" (<http://www.portland.va.gov/Research/hrpp/index.asp>).

Recruitment Incentives to the investigator from a sponsor must not create undue influence to recruit participants for a study and must be reasonable in relation to the work being performed.

For research following a DOD Addendum, when the research involves U.S. military personnel the following additional protections apply:

1. Officers are not permitted to influence the decision of their subordinates.
2. Officers and senior non-commissioned officers may not be present at the time of recruitment.
3. Officers and senior non-commissioned officers have a separate opportunity to participate.
4. When recruitment involves a percentage of a unit, an independent ombudsman is present.

See also Section XIV regarding telephone contact with subjects.

5. **Payment to Research Subjects**

The IRB reviews any financial or other form of payment to research subjects at the time of the initial application to assure that the amount is not coercive given the nature of the research or creates undue influence on the subject to participate. The information is provided in the IRQ, and additional information may be required on an as needed basis.

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 subject's participation up to that point. Any bonus for completion must be reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn. The schedule, amount and conditions of payment must be stated in the informed consent form.

VA policy prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care.

However, payment may be permitted, with prior approval of the IRB, in the following circumstances:

1. **No direct subject benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay participants in this situation.
2. **Others being paid.** In multi-institution studies, where participants at a collaborating non-VA institution are to be paid for the same participation in the same study at the same proposed rate, the IRB may find that payment is appropriate.
3. **Comparable situations.** In other comparable situations in which, in the opinion of the IRB, payment of participant volunteers is appropriate.
4. **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 reimbursed by another mechanism.

Investigators who wish to pay research subjects must indicate in their research project application the justification for such payment which may include consideration of the criteria listed above as well as:

1. Substantiate that 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 of payment in the informed consent form; 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 participant to volunteer for the research study.

The IRB shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of these guidelines. The Research Service office must ensure that such payments to subjects are made from appropriate funds.

For research under a DOD addendum in which U.S. military personnel are involved, dual compensation is limited:

1. An individual is prohibited from receiving pay or compensation for research during duty hours.
2. U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.

6. Compensation for Injury

Information on compensation for injury must be included in all informed consent forms for studies involving more than minimal risk, with contact names and telephone numbers, per the requirements of the text of the informed consent form.

VA medical facilities shall provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by a VA Research & Development Committee and conducted under the supervision of one or more VA employees. (VA employee is defined as any person appointed by VA as an officer or employee and acting within the scope of his or her appointment.) The following exceptions apply:

1. If VA medical facilities cannot furnish the care or services required or cannot furnish such care economically, the principal investigator will notify the ACOS/R&D who will work with the PVAMC Director to contract for the necessary care.
2. If inpatient care must be provided for a non-veteran, the PVAMC Director may contract for such care.
3. If a research participant needs treatment at non-VA medical facility in a medical emergency for a research-related injury, the PVAMC shall provide reasonable reimbursement for that treatment.

However, this requirement does not apply to (1) treatment for injuries due to non-compliance by a subject with study procedures; or (2) research conducted for the VA under a contract with an individual or a non-VA institution.

It should be noted that a sponsor cannot bill a subject's insurance company for research-related injuries, but is responsible for costs incurred for treatment of injury reasonably related to the subject's study participation.

7. Certificates of Confidentiality

Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. In such situations, the IRB may require that an investigator obtain a Certificate of Confidentiality (CoC) from the National Institute of Health (NIH) or other Health and Human Services agency. The CoC was developed to protect against the involuntary release of sensitive information about individual subjects for use in federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. If there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA.

The IRB may determine that an investigator should request a CoC in cases when the information gathered for the research could be held against the research participant in a court of law. If an investigator has submitted a CoC application to the NIH, recruitment of research subjects may begin prior to receiving a final determination. If a CoC is granted for the study, the CoC will apply

retroactively to those research subjects enrolled.

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

Additional information, regarding CoCs, including the application information necessary for applying for a Certificates of Confidentiality may be obtained on the NIH website at:
<http://grants1.nih.gov/grants/policy/coc/index.htm>.

8. Compliance with All Applicable State and Local Laws

The IRB follows and must adhere to all applicable state and local laws in the jurisdictions where the research is taking place. The Research Service and the IRB rely on the Regional Counsel for the interpretation and application of Oregon and Washington State law and the laws of any other jurisdiction where research is conducted as they apply to human research. All consent forms must be consistent with applicable state and local laws.

Currently there are no Oregon or Washington statutes that conflict with or enhance federal requirements on research done at federal facilities. If either state law is amended to require more stringent regulations than are currently required in the federal regulations, the policy is to follow the more stringent state requirements.

9. IRB Considerations About Ethical Study Design

The IRB takes into consideration the study design to assure that research ethics are being followed. This includes careful consideration of issues such as protection of privacy and confidentiality in epidemiological research, genetic research, and family research. Even studies, which, by their epidemiological nature may not require an informed consent form, are carefully evaluated to assure that only the information needed is being gathered, that the confidentiality of the information is carefully protected, and that the risk to the participant remains minimal.

10. IRB Considerations of Conflict of Interest

Please see the PVAMC "Conflict of Interest in Research" Policy (<http://www.portland.va.gov/Research/hrpp/index.asp>) regarding IRB considerations of conflict of interest. The conflict of interest policy applies to all full-time and part-time employees, members of governing panel or board and paid or unpaid consultants participating in research approved by the IRB.

With regard to a conflict of interest identified for an investigator, the IRB will review and approve the management plan instituted by the R&D Committee and assure that the plan includes appropriate disclosure to participants in the Informed Consent document before giving final approval to a research project. Please refer to HRPP Policy "Conflict of Interest in Research," (<http://www.portland.va.gov/Research/hrpp/index.asp>) for more information, regarding how conflicts of interest are identified and managed.

11. Principal Investigator Expertise

The IRB also considers the professional qualifications and resources of the research team as indicated on the IRQ. The PI must designate all research staff on the IRQ and CRQ, including co-investigators, collaborators, and study coordinators. In addition, in all studies outside the PI's medical

specialty, the PI must designate a co-investigator with expertise in the relevant medical specialty. If the PI has no clinical privileges, this co-investigator is designated the "Responsible Clinician" and will be responsible for all participant safety issues related to the checking of all laboratory/study testing in the research, following all laboratory/study results and communicating all moderate or severe results to the study participant, the study participant's primary care and specialty physicians, and assuring the accurate recording of all relevant laboratory/studies in the participant's electronic medical record. This co-investigator and collaborator will usually be involved in developing the scientific protocol section involving his or her area of expertise and training to assure optimal participant safety of follow-up of abnormal laboratory/study results. The co-investigator and/or collaborator will also be responsible with making all relevant communication to the participant's primary care provider about any new abnormalities of a moderate or severe nature and recording the same abnormalities in the participant's electronic medical record.

Clinicians must maintain appropriate professional credentials and licensing privileges. The IRB may request additional information from investigators and participating physicians, such as curricula vitae, to assure the qualifications of the research team are appropriate for the proposed study. Research staff working physically at the VA and/or having direct contact with VA participants and/or their identifiable data or human biological specimens, must be credentialed consistent with VA Office of Research & Development guidelines.

12. Credentialing and Education Verification for New Human Research Projects

The IRB staff will verify new human research personnel included on studies as the Research Service office receives notification they are to be added or as they are appointed. Individuals involved in a study approved by the VA IRB must complete the education and credentialing requirements consistent with HRPP policies "Education for the Protection of Human Research Participants" and "Credentialing of Personnel Involved in Human research" (<http://www.portland.va.gov/Research/hrpp/index.asp>).

13. Participation of Non-Veterans as Research Subjects

Non-veterans may be entered into VA approved research studies only when there are insufficient veterans available to complete the study.

All the regulations pertaining to the participation of veterans as research subjects including requirements for indemnification in case of research-related injury pertain to non-veteran subjects enrolled in VA-approved research.

If an investigator would like to recruit non-veterans in a research project approved by the PVAMC IRB and conducted at the PVAMC, this will be considered by the IRB. The Principal Investigator should submit a request in writing to the IRB.

14. Ionizing Radiation

All studies involving Radiological devices or procedures are reviewed by the Radiation Safety Officer (RSO), who is a member of one IRB. Studies reviewed by the other IRB that include a radiation component are also sent to the RSO for review. The RSO reviews the science of the radiation dose absorbed, performs an additional risk assessment particular to the use of radiation, and assures that the use of radioactivity and the conduct of procedures are appropriate.

The investigator must clearly indicate on the IRQ, whether the research project involves any x-ray or radioactive materials and provide additional information as appropriate on an IRB appendix, including the procedures, frequency and purpose. The PI must also determine if the procedures are those

which the participant would receive even if they were not enrolled in the study, i.e. which procedures are standard of care.

In reviewing the study, the RSO will determine whether the planned exposure is within the allowable limit and whether or not the informed consent form adequately reflects the risks to subjects. The RSO will utilize the following guidelines when evaluating overall risk and the risk-benefit ratio:

- Radiation exposure being done for the standard of care and uses routine procedures: The IRB may request review or consultation by the Radiation Safety Officer. The informed consent form will frequently make only general mention of the exposure.
- Radiation exposure exceeds the standard of care, using routine procedures, and offers the prospect of direct benefit to the subject: The informed consent form must differentiate which procedures are being done for standard of care and which are being done solely for research. The informed consent form must state that the total dose exceeds standard care, and what risks may occur versus standard care. When radiation exposure is research-related, the informed consent form should clearly describe in lay language the quantity, significance, and risk, if any, of the radiation absorbed dose. The informed consent form must include the boilerplate information in the VA Informed Consent Template.
- Radiation exposure exceeds the standard of care, using routine procedures, and offers no prospect of direct benefit to the subject: When radiation exposure is research-related, the informed consent form should clearly describe in lay language the quantity, significance, and risk, if any, of the radiation absorbed dose. The informed consent form must include the boilerplate information in the VA Informed Consent Template.

15. Research Involving Deception or Withholding of Information

Sometimes in psychological or educational research, deception is necessary to prevent participant bias. When the IRB reviews research projects involving incomplete disclosure or deception, it must apply both common sense and sensitivity to the review. The IRB must be satisfied that any deception is necessary and that, if appropriate, the subjects will be debriefed. Debriefing may sometimes be inappropriate, e.g., if the debriefing itself would present an unreasonable risk of harm without a corresponding benefit. The IRB must also assure the proposed subject population is suitable.

Deception may only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in VA regulations and the Common Rule and 38 CFR 16.116(d). Specifically, the IRB must find and document that all four of the following criteria have been satisfied:

1. The research presents no more than minimal risk to subjects.
2. The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB should consider each criterion in turn, and document specifically (in the minutes of its meetings and/or in the IRB protocol file) how the proposed research satisfies that criterion.

XVIII. Informed Consent Requirements and Documentation

A. Purpose of the Informed Consent Documentation

Investigators must obtain the legally effective informed consent of the subject or the subject's legally authorized representative **before** conducting any procedures required by the protocol, unless the informed consent requirements are waived by the IRB. Informed consent is an ongoing process of information exchange between the prospective research participant and a trained individual conducting the consent process. Informed consent presumes two simultaneous concepts: informed decision-making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and potential benefits to reach an **informed decision** as to whether they will **voluntarily participate**.

The consenting process begins during subject recruitment and includes any oral instructions and/or explanations, presentation of the written informed consent form and any other materials approved by the IRB, the opportunity for the individual to ask questions and receive satisfactory answers, signing of the written agreement by the subject or legal representative and, in some cases, a witness. If a potential subject or legally authorized representative seems hesitant about participating in a study or feels they should discuss participation with any family members, the investigator or his/her representative must allow the participant ample time to consider and make his/her decision. The participant may contact the investigator at a later time to agree to participate in the study and sign the formal document. Throughout the study, the principal and other investigators should encourage the participant to ask questions at any time during procedures or study visits or to contact a research investigator if a question arises between visits.

B. Circumstances of Informed Consent Requirements

To approve research, the IRB must determine that legally effective informed consent shall be sought from each prospective subject or the subject's legally authorized representative, unless informed consent requirements can be waived or altered under VA regulations.

Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. These circumstances include:

1. Assessing the prospective research participant's capacity to consent to the research protocol, prior to consenting the individual, to ensure that s/he is able to understand the study procedures and all risks and benefits in order to make an informed decision. The IRB may determine that for a high-risk study, procedures should be put in place to assess the research participant's capacity to consent.
2. Presenting and ensuring the informed consent information is presented in a language that is understandable to the subject (or the subject's legally authorized representative).
3. Excluding any exculpatory language from the informed consent process
 - a. through which the subject is made to waive, or appear to waive, any of the subject's legal rights; or
 - b. through which the investigator, the sponsor, the PVAMC, or the PVAMC's employees or agents are released from liability for negligence.
4. Obtaining informed consent prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.
5. Providing the prospective subject or the legally authorized representative sufficient opportunity to consider whether or not to participate.

6. Ensuring that subjects give consent without coercion or undue influence.

C. Consent after Anxiolysis, Sedation or Anesthesia Care

Care must be given to evaluate a research participant's capacity to consent after they have had anxiolysis, sedation or anesthesia care. This includes taking into account the following:

- a. The ideal informed consent process occurs no sooner than 18-24 hours after anxiolysis, sedation, or anesthesia care, regardless of the type or amount of sedative(s) used.)
- b. No informed consent process shall occur sooner than 12 hours after anxiolysis, sedation, or anesthesia care, regardless of type or amount of sedative(s) used.
- c. If the 12-hour post-sedation time frame occurs during the hours of 10 pm-6 am, the informed consent process shall occur after participants have rested overnight.
- d. No informed consent shall be obtained from a legally authorized representative if the participant is an otherwise competent person and will be able to provide adequate informed consent after the effects of sedation subside.
- e. Researchers who foresee logistical difficulties meeting these guidelines may ask the IRB for consideration of exceptions for a particular study. The ACOS/R&D will also review any concerns raised by investigators.

D. Documentation of Informed Consent

Unless the criteria are met to waive the requirement for an informed consent process and/or document informed consent, VA regulations, the Common Rule, and FDA regulations provide two methods for documenting informed consent:

1. Written Informed Consent Document

In cases that consent must be document, the IRB must determine that informed consent will be documented through use of a written consent document on VA form 10-1086 that embodies all of the required elements of informed consent (these elements are discussed in detail in Section XVIII, K-M). The most current IRB-approved version of the VA Form 10-1086 must be used as the informed consent form. The form must be signed by the subject or the subject's legally authorized representative (LAR), a copy of the signed form must be given to the person signing the form and the subject or LAR must initial the original signed consent form acknowledging receipt of the copy. IRB approval of the consent form must be documented by a stamp, "IRB Approved" with the date of the most recent IRB approval on each page of the document.² The IRB may require a witness, e.g., if the research involves an invasive procedure or an investigational drug or device, except when informed consent is obtained orally. The witness is only witnessing only the signature on the informed consent document. The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person needs to serve both capacities, a note to that effect must be placed under the witness's signature line. When applicable, a copy of the signed informed consent form must also be forwarded to the Research Pharmacy, prior to dispensing any investigational drug. FDA regulations require that the signature be dated. This form may be read to the potential research participant or his/her LAR. The potential participant/LAR must be given adequate time to read the document and make a decision, regarding participation, prior to signing the informed consent document.

² In order to allow for administrative delay from the date the IRB approves an informed consent document and when the PI receives the most recently approved date-stamped document, the previously approved informed consent is valid until 5 business days after the date stamped on the most recently approved document.

2. Additional Considerations Regarding Written Informed Consent

If a photograph, video recording or audio recording of a human subject for research purposes, in addition to including this in the informed consent document, VA Form 10-3203 must be referenced and appended to the informed consent document.

For research following a DOD Addendum, the IRB must determine that the informed consent document includes provisions for research-related injury that follow the requirements of the DOD component. The most recent DOD Informed Consent form may be employed for active duty personnel participating in VA research.

If approved by the IRB, the subject may submit the signed and dated informed consent form to the investigator or designee by facsimile.

3. Short Form Written Informed Consent

Consent may also be documented through use of a "short form" written consent document, which states that the elements of informed consent have been presented orally to the subject (or the legally authorized representative) in a language understandable to the subject. The oral presentation must contain all of the information that is contained in the informed consent document. When this method is used the following is necessary:

- a. The IRB must approve a written summary of what is to be presented orally and the "short form" written consent document. The written summary must embody the basic and required additional elements of disclosure.
- b. There must be a witness to the oral presentation; the witness must speak both English and the language of the participant.
- c. A witness is always required, and the witness must sign both the "short consent form" and the written summary presented to the subject or legally authorized representative.
- d. The "short consent form" and a copy of the summary must be signed and dated by the subject or the representative. If the research is FDA-regulated, the participant or legally authorized representative must date the consent form. In addition, the person obtaining the informed consent must sign and date the written summary and the participant or legally authorized representative must sign and date the informed consent.
- e. A copy of the signed and dated summary and the signed and dated "short form" must be given to the participant or the representative.

E. Approval Date Stamped on Informed Consent Forms

IRB staff apply a stamp with the approval date on each page of the informed consent form. At initial approval, the approval date on the consent form is the date of initial IRB approval. If the informed consent document is amended during the protocol approval period, the IRB must document on the informed consent form the approval date of the amendment rather than the date of the most recent initial or continuing review. At continuing review, the consent form must be stamped with the new approval date, even if no changes have been made to the informed consent form.

F. Individuals Authorized to Conduct the Informed Consent Process

The Principal Investigator is authorized to conduct the informed consent process. If the PI is not available to inform the prospective subject about all aspects of the research project (trial) or conduct the informed consent process, the PI may delegate these responsibilities to properly trained individuals.

The Principal Investigator is responsible for ensuring that the individuals s/he authorizes conduct the informed consent process are knowledgeable of the research project and procedures as well as the informed consent process. The designee should be able to answer questions raised by the potential

research participant or legally authorized representative.

G. Observation of the Informed Consent Process

The IRB has the authority to observe the informed consent process of any currently active research study. Situations where the IRB might consider such observation might include reports of a complaint or possibility of undue influence or coercion, or an audit that raises doubts about the adequacy of the informed consent process. An IRB member or designee may observe a consent session as an impartial observer or conduct structured interviews of research participants.

In addition, informed consent documentation is reviewed by the RCO or designee after each signed informed consent form is scanned as noted in XVIII, O below, to assure that it was correctly completed and that all required signatures are in place.

H. Witnesses of Informed Consent Process

A witness must be present as follows:

1. If the IRB requires, a witness must be present during the signing of the written informed consent document. The witness does not need to witness the entire informed consent process, only the signing of the document. The witness must also sign and date the written informed consent document. The witness may not be the person obtaining consent.
2. When a "short form" written consent is used, a witness is always required to be present during the informed consent process as well as the signing. The witness must sign and date both the short form written consent document and the summary of the oral presentation given to the subject or the subject's legally authorized representative. Again, the witness may not be the person obtaining consent. Ideally, the witness would be a family member or friend of the research participant, but may also be a staff member or member of the study team.

I. Informed Consent Reading Level and Language

VA regulations, the Common Rule, and FDA regulations require that informed consent documentation be written at the appropriate reading level of the potential participant population and be obtained in a language that is understandable to the subject (or the subject's legally authorized representative).

In cases where informed consent must be obtained from non-English speakers, the Principal Investigator is responsible for working with the IRB to determine that an effective and appropriate method is in place. This may include the use of a reliable, certified translator or a certified translation of the informed consent document.

J. Exculpatory Language

The informed consent, written or oral, may not contain any exculpatory language through which the subject or the legally authorized 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.

K. Required Elements of Informed Consent Forms

To ensure an effective informed consent process, Department of Veterans Affairs (VA) regulations, the Common Rule, and Food and Drug Administration (FDA) regulations mandate the inclusion of the fundamental informed consent elements and additional elements when appropriate. Depending on the nature of the research, an investigator may request elimination of any of the elements.

In accordance with regulations, the following information will be provided to each subject:

1. Name of the Study
2. The name of the Principal Investigator
3. A statement that the study involves research
4. An explanation of the purposes of the research
5. The expected duration of the subject's participation
6. A description of the procedures to be followed
7. Identification of any procedures which are experimental
8. Description of any reasonably foreseeable risks or discomforts and possible unforeseeable risks to the subject: Risks may include physical, psychological, social or economic risks. A statement must be included that the particular treatment or procedure might involve risks to the participant that are currently unforeseeable.
9. Reasonably expected benefits to subjects or others: Care must be taken not to overstate the benefits and create an undue influence on subjects. Payment for subject's participation in a research project is not to be considered as a benefit of the research.
10. Appropriate alternatives to participation that might be advantageous to the subject.
11. Extent of privacy and confidentiality: Research often poses the risk of loss of confidentiality to subjects. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' confidential records. In some research, loss of privacy and confidentiality may be the greatest risk of participation. For FDA-regulated studies, consent forms must include a statement that the FDA may inspect research records.
12. Compensation or treatment for injury: Informed consent information for research involving more than minimal risk must include explanations regarding the following:
 - a. Whether any compensation is available, whether any medical treatments are available if injury occurs and if so, what they consist of or where further information may be obtained.
 - b. In accordance with Federal law, a statement that VA will provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA IRB and conducted under the supervision of one or more VA employees. **Note:** This does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances must be included in the consent form.
13. Contact information must include details, including telephone numbers, about whom to contact for the following types of information:
 - a. For answers to questions or to voice concerns about a specific research project, the principal investigator and other members of the research team are appropriate contacts.
 - b. For answers to questions about subjects' rights, contact the Research Assurance Officer or VA Regional Counsel.
 - c. In the event of a research-related injury, the VA Regional Counsel, the Research Assurance Officer and the Investigators are all appropriate contacts.
 - d. To speak with someone unaffiliated with a specific research project to ask questions or voice concerns about subject's rights, offer input, or to voice complaints about any VA research, subjects should be given contact information for the Research Service, the Research Assurance Officer, and the VA Regional Counsel.
14. Voluntary participation statement: It is particularly important at the VA for subjects and prospective subjects to understand and have complete confidence that failure to participate will not jeopardize their VA-provided care. Informed consent information must contain the following statements:
 - a. Participation in the research is voluntary.

- b. 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 subjects is entitled.
15. Payment for treatment: Informed consent information must include a statement that veteran subjects shall not be required to pay for treatment received as a subject in a VA research program. Investigators should note, however, that certain veterans are subject to co-payments for medical care, pharmaceutical, and services provided by VA.

L. Additional Elements Where Appropriate

In accordance with regulations, the following information will be provided to each subject, when appropriate.

1. Unforeseeable risks to subjects, embryos, or fetuses: 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 may become pregnant).
2. Investigator-initiated termination of participation: The informed consent information must specify anticipated circumstances (e.g., subject non-compliance with research, subject not benefiting from research) under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Additional costs: Any additional costs to the subject that may result from participation in the research with consideration of Federal laws concerning veterans' eligibility for medical care and treatment.
4. Early withdrawal/procedures for termination: Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent documentation must inform subjects of the possible consequences of a decision to withdraw. Note also the following:
 - If there are procedures regarding how to withdraw safely from the research, these must also be described.
 - It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions to subjects who have decided to withdraw unless required for the safety of the subject.
 - The consent document cannot give the participant the option of having data removed if they withdraw. The data already collected remains part of the study database. Investigators may also consult public records, e.g., records establishing survival status.
 - If a participant chooses to withdraw only from the interventional portion of a study and wishes to continue to be followed for associated clinical outcome information, informed consent must be obtained for this as described in the original approved informed consent form. The IRB must approve a new consent form for this purpose.
5. Significant new findings: The subject must be informed that any significant new knowledge or findings developed during the course of the research that might affect the risks or benefits and therefore the subject's willingness to continue participation will be provided to the subject. The informed consent document must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.
6. Approximate number of subjects to be involved in the study.
7. FDA-regulated studies: Research involving an FDA-regulated test article, requires a statement that the FDA may choose to inspect research records that includes the subject's individual medical records. In addition, there must be a statement in the informed consent form that the study will be registered on Clinicaltrials.gov.
8. Payment for participation: If appropriate, the informed consent information should include a clear statement describing any payment the subject is to receive for participation, the required

conditions for payment, and the payment schedule. Since VA regulations, the Common Rule, and FDA regulations all state that subjects may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. Therefore, the informed consent information should be a description of how payment will be prorated and calculated for subjects who withdraw early.

M. Human Biological Specimen Consent Form Requirements

If human biological specimens will be obtained as part of a research study, VA policy and VHA regulations must be followed.

1. If the researchers believe that the bodily fluids, substances or tissues of a research subject could be part of or lead to the development of a commercially valuable product, the following verbatim statement is required. "By consenting to participate, I authorize the use of my bodily fluids, substances, or tissues."
2. Statement of whether or not the specimen will be used for future research and allow the choice of how the specimen will be used (any research, research by the PI, or other researchers, genetic analysis, research related to specific area, etc.).
3. Whether or not the research results of future use of the specimen will be conveyed to the subject.
4. Whether or not the subject will be re-contacted after the original study is completed.
5. If the subject requests, the specimen and all links to the clinical data will be destroyed.

N. Routing of Signed Informed Consent Forms

PVAMC policy requires the **original** signed consent documents and the signed HIPAA Authorization for all research participants be brought to the Research Service as soon as possible, preferably within 3 business days of consenting the participant. If informed consents are signed by subjects at home and then returned by mail, they must be stamped with a "received date" and brought to the Research Service as soon as possible, preferably within 3 business days of receipt.

O. Medical Records and Scanning Informed Consent Forms

The PI is responsible for assuring that a medical record is created in the Computerized Patient Record System for all research participants who are admitted as in-patients, treated as outpatients, or when research procedures or interventions are used in the medical care of the research participant. A record is also created when the research requires the use of any clinical resources, such as radiology, cardiology, clinical laboratory, pharmacy, etc., or if the research intervention may lead to physical or psychological adverse events.

The Research Service scans the consent form into the electronic medical record in CPRS. Informed consent forms for non-VA patients or for human subjects who do not meet the above criteria for a patient record, e.g., caregivers or family members completing questionnaires, will be scanned into a password-protected folder on a VA server behind the VA firewall. After the signed forms are scanned appropriately, the originals will be returned to the Principal Investigator for inclusion in his/her case history files.

P. Progress Notes

Progress notes must be entered for individual participants as noted below. The Principal Investigator is responsible for ensuring that the progress notes are assigned appropriately for each individual subject as soon as possible and no later than 24 hours after a research visit. Progress notes must be identified as research notes to differentiate from other clinic visits and must include the name of the study.

1. A progress note documenting the informed consent process must be placed in the subject's CPRS medical record. (See Section XVIII, O., to determine when CPRS medical record is required.) At a minimum, the progress note documenting consent must include:

- a. The name of the study,
 - b. The person obtaining the subject's consent,
 - c. A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,
 - d. A statement that the study was explained to the subject or the subject's LAR,
 - e. A statement that the subject or the subject's LAR was given the opportunity to ask questions, and
 - f. A statement that the subject or the subject's LAR consented before participation in the study began.
 - g. A copy of both the signed and dated Informed Consent and the separate HIPAA Authorization must be delivered to the R&D Service for scanning into the record for this progress note.
2. An entry must also be placed in the patient record when the human subject is actually enrolled or randomized into the study and when participation is terminated. Consent and entry notes may be combined when both occur at the same visit.
 3. A progress note for each clinic visit and inpatient care for research purposes must be entered. Encounters and/or procedures for research must be coded as non-billing events.
 4. A progress note must be entered when the subject's participation in the study has ended, either because the research procedures are complete, or because authorization has been revoked. A progress note must also be entered for the following:
 - a. For drug studies, the investigator must enter a progress note when a participant is enrolled listing any drug interactions and/or toxicities, e.g. in the target subject population, that are not included or are not listed in sufficient detail on VA Form 10-9012 or directing attention to the 10-9012 if no additional information is needed. VA Form 10-9012 or superseding forms as defined in VHA Handbook 1108.04 per HB 1907.01 are entered by the Research Pharmacy.
 - b. VHA Form 10-3203, Consent for Use of Picture and/or Voice, if applicable (should be brought to the Research Office with the Informed Consent and HIPAA Authorization to be scanned and attached to the progress note documenting the informed consent process).
 - c. A copy of any research results used for medical care.

Q. Waiver of Documentation of Consent

An IRB may waive the requirement to obtain written documentation of informed consent based on criteria below. (**Note:** This provision can be used only for the waiver of documentation of consent, not for waiver or alteration of consent itself.)

To approve such a waiver, the IRB will review a written description of the information that will be provided to participants. The IRB may also require the investigator to provide participants with a written statement regarding the research. The IRB also must find and document **either** of the following conditions:

1. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each subject may be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (This waiver provision is **not** applicable to FDA-regulated research).

OR

2. The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the principal investigator to provide subjects with a written statement regarding the research. (allowable for both FDA and non-FDA regulated research)

IRB minutes shall clearly reflect this waiver provision and the justification for its use. The IRB may also waive the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for

an authorization for research purposes. In these cases, the IRB must additionally document the justification for its use. Please see HRPP policy "Health Insurance Portability & Accountability Act (HIPAA)". (<http://www.portland.va.gov/Research/hrpp/index.asp>).

R. Waiver or Alteration of Informed Consent Requirements (Waiver of Consent Process)

VA regulations permit the IRB to approve a consent procedure that does not include or that alters some or all of the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. To approve such a waiver or alteration, the IRB must find and document the following:

1. The research is to be conducted by, or was subject to, the approval of state or local government officials and is designed to study, evaluate, or otherwise examine
 - a. public benefit or service programs;
 - b. procedures for obtaining benefits or services under those programs;
 - c. possible changes in or alternatives to those programs or procedures; or
 - d. possible changes in methods or levels of payment for benefits or services under those programs and
 - e. The research could not practically be carried out without the waiver or alteration.

OR

2. The research involves no more than minimal risk to the subjects and
 - a. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - b. The research could not practically be carried out without the waiver or alteration;
 - c. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

These findings and their justifications shall be clearly documented in IRB minutes. The IRB may not approve such alterations or waivers for FDA-regulated research. The waiver or alteration of informed consent requirements for FDA-regulated articles is applicable only for emergency use.

The IRB may also waive the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for an authorization for research purposes, but must document justification the waiver. See HRPP policy "Health Insurance Portability & Accountability Act (HIPAA)" (<http://www.portland.va.gov/Research/hrpp/index.asp>).

For research conducted under a DOD Addendum, if the research participant meets the DOD definition of "experimental subject," (see Section III. Definitions) a waiver of the consent process may not be granted unless a waiver is obtained from the Secretary of Defense. If the research participant does not meet the definition of "experimental subject," a waiver may be approved based on criteria above.

S. Exceptions from Informed Consent for Emergency Use of a Test Article

Please see also HRPP policy "Investigational Device and Drug Usage in Research & Development Service" (<http://www.portland.va.gov/Research/hrpp/index.asp>). **Note:** Even in an emergency situation, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing the four items outlined below.

An exception under FDA regulations permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

1. The subject is confronted by a life-threatening situation (as defined by the FDA) 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 and there is a medical emergency or urgency.
3. Time is not sufficient to obtain consent from the subject's legally authorized representative.
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 immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required above in advance of using the test article, the determinations of the clinical investigator shall be made and, within five working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. All of the documentation from the investigator and non-participating physician must be submitted to and reviewed by the IRB within five working days after the use of the test article. The IRB will determine if FDA criteria for emergency use without consent was met and whether or not the activity was a systematic investigation designed to develop or contribute to generalizable knowledge. Any subsequent use of the test article is subject to IRB review.

XIX. Review of Research Involving Potentially Vulnerable Subject Groups

The PVAMC considers the following populations of potential subjects to be vulnerable: minors (children), fetuses, prisoners, pregnant women, mentally impaired, and economically or educationally disadvantaged persons. The IRB must be cognizant of the vulnerable nature of many VA human subjects. However, veterans are not as a whole considered a vulnerable population

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity. The IRB may require that someone other than the primary care provider conduct the informed consent session and that additional measures for evaluating capacity to consent be in place. The IRB carefully evaluates each protocol to determine if vulnerable subjects are included in the study population and what measures have been taken to protect them. The PVAMC does not conduct research with children or prisoners (unless approved by the CRADO), or fetuses and the PVAMC IRBs do not review research involving these vulnerable populations.

Vulnerable populations as listed in the Federal regulations include

- Pregnant women and fetuses;
- Prisoners;
- Mentally disabled and those with impaired decision-making capacity;
- Children; and
- Economically and educationally disadvantaged persons.

A. Elements to Consider in Reviewing Research Involving Vulnerable Subjects

Department of Veterans Affairs (VA) regulations and Food and Drug Administration (FDA) regulations require the IRB to give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB is required to consider the scientific and ethical reasons for including vulnerable populations in research. The IRB is also required to have adequate representation on the IRB to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

The IRB must pay special attention to specific elements of the research plan when reviewing research involving vulnerable subjects. These specific elements may include the following:

1. Strategic issues such as inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
2. The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
3. Investigators are not permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.
4. Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to

approve or disapprove research involving vulnerable subjects, the IRB shall look to see that such procedures are a part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples may include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.

5. The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB requires that the investigator submit each signed informed consent form to the IRB. The IRB may also require that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.
6. The IRB has access to legal counsel at the PVAMC for assistance in interpreting laws for the protection of research participants, e.g., in the case of determining whether a participant is competent to consent.

B. Pregnant Women and Fetuses as Vulnerable Populations

The Department of Health and Human Services (DHHS) regulations detail special protections for research involving pregnant women, fetuses, and human *in vitro* fertilization. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent.

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. However, given compelling scientific justification this option may be considered by the IRB. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

Per VHA Handbook 1200.05, research in which the subject is a fetus, *in-utero* or *ex-utero* (including human fetal tissue) must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

Per VHA Handbook 1200.05, research related to *in vitro* fertilization must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

For research involving the participation of pregnant women as research subjects, the IRB must:

1. Determine that the proposed research meets the requirements outlined in Section XIX, A., regarding Elements to Consider in Reviewing Research Involving Vulnerable Subjects.
2. Determine that adequate provision has been made to monitor the risks to the subject and the fetus.
3. Determine that the individual providing informed consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus.
4. Determine that adequate consideration has been given to the manner in which potential subjects are going to be selected, and that adequate provision has been made to monitor the actual informed consent process such as:
 - a. 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
 - b. 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.

NOTE: These determinations should be documented in the IRB minutes.

4. General limitations

- a. Activities related to pregnant women must not be undertaken unless:
 - (1) Appropriate studies on animals and non-pregnant individuals have been completed, and data for assessing potential risks to pregnant women and fetuses is provided.
 - (2) 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.
 - (3) Individuals engaged in the activity will have no part in
 - (a) Any decisions as to the timing, method, and procedures used to terminate the pregnancy;
 - (b) Determining the viability of the fetus at the termination of the pregnancy.
 - (c) Introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy.
- b. No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of research activity.
- c. No pregnant woman may be involved as a subject in a research activity unless
 - (1) 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
 - (2) The risk to the fetus is minimal.
- d. Informed consent of the pregnant woman is required if the research holds out
 - (1) The prospect of direct benefit to the pregnant woman.
 - (2) The prospect of direct benefit to the pregnant woman and the fetus.
 - (3) No prospect of benefit for the woman or fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
- e. Consent of the father is required in addition to that of the pregnant woman if the research holds out the prospect of direct benefit solely to the fetus except when
 - (1) the father is unavailable,
 - (2) the father is incompetent,
 - (3) the father is temporarily incapable or
 - (4) the pregnancy resulted from rape or incest.

C. Human Fetal Tissue Transplantation Research

The PVAMC does not conduct research with human fetal tissue transplantation.

D. Prisoners as a Vulnerable Population in Research

The PVAMC does not conduct research involving prisoners, including prisoners of war as defined by the DOD, unless a waiver is received from the CRADO.

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. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects. **NOTE:** Requirements for requesting a waiver may be obtained through the Research Office by contacting the Office of Research and Development at VA Central Office or by accessing the VA research web site at <http://www.va.gov/resdev>.

E. Minors (Children) as a Vulnerable Population in Research

The PVAMC does not conduct research involving minors (children) unless a waiver is received from the CRADO.

The VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans. Therefore, research involving children or neonates must not be conducted 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. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects. **NOTE:** For requirements for requesting a waiver, the Research Office will contact VA Central Office.

XX. Review of Research on Human Subjects Likely to Need Surrogate Consent

Research involving subjects who may have impaired decision-making capacity warrants special attention. Research involving these populations may present 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 may be vulnerable to coercion. Such subjects must be protected from exploitation and harm while allowing the conduct of essential research on problems that are unique to this population.

Capacity should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. An individual is presumed to have decision-making capacity unless any one or more of the following apply: a qualified practitioner (may be a member of the research team) has documented in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study or the individual has been ruled incompetent by a court of law. The decisional capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation. In cases where research involving cognitively impaired individuals is approved, the IRB may require additional safeguards (e.g., involvement of subject advocates, independent consent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

The IRB will evaluate whether the proposed plan of assessment of the capacity to consent has been met, assure that assent is required and whether the plan for assent is adequate. If the IRB finds that these criteria have been met, incompetent subjects may be enrolled. Such approval may be sought with the initial application, may be requested later as a study modification, or approval may be sought as needed on a case-by-case basis.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent or the individual must have been ruled incompetent by a court of law. For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

A. IRB Composition During Review of Surrogate Consent

1. When reviewing studies that include subjects likely to need surrogate consent, the IRB membership must include at least one member who has experience working with those who need surrogate consent and/or conducting research with such populations. When participants may be

vulnerable to coercion or undue influence, an individual who is knowledgeable about or experienced in working with such participants may be invited to attend the meeting as a consultant. Consideration may be given to adding another member who is a member of the population, such as a family member of such a person or a representative of an advocacy group for that population.

2. The IRB may utilize ad hoc members as necessary to ensure appropriate expertise.

B. Fluctuating Capacity to Consent

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. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

For research protocols involving subjects who have fluctuating or limited decision making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

C. Determining capacity to consent

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring: (1) ability to evidence a choice; (2) ability to understand relevant information; (3) ability to appreciate the situation and its likely consequences; and (4) ability to manipulate information rationally. A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias or the other underlying cause of lack of capacity, and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

The majority of studies conducted at the PVAMC only allow enrolling subjects who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, a qualified practitioner must assess capacity of each potential subject to consent or a legal determination must be made (the PVAMC legal counsel may be consulted). If feasible, the practitioner should explain the proposed research to the prospective participant. The PI, using an assessment tool or process approved by the IRB, must determine whether a potential subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. The determination must be documented in the person's medical record in a signed and dated progress note.

D. Legally Authorized Representative

In instances where the subject may not be able to give consent for him/herself, the subject's ability to consent must first be assessed. If it has been verified that the potential research participant is unable to give informed consent for him/herself, his/her legally authorized representative may consent on

behalf of him/her to participate in the procedure(s). The definition of Legally Authorized Representative, consistent with VA policy, is on the definitions section of this P&P.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. Should the person object to participating, this objection must be heeded.

A surrogate must be fully informed of the study and have sufficient opportunity to consider what the wishes of the potential subject would be and whether or not to consent on behalf of the subject. The surrogate must receive all of the information a regular enrollee would receive in language that is understandable to the surrogate. Surrogate consent will be accepted in the order identified in this P&P (see DEFINITIONS: Legally Authorized Representative). If the potential subject indicates that s/he does not wish to participate then the surrogate consent cannot be honored.

When surrogate consent is used, it must be documented in writing by the investigator that the surrogate is named; made aware of their responsibility; that they have been informed about risks/benefits of the study and are aware that the subject had consented to participate; that they are aware of their rights to withdraw and to contact the PI or Research Service for questions/problems; that the subject, if possible, has given their assent to participation in the study; that the surrogate will be informed of future information that is needed to be an informed participant. Progress notes during the period of surrogate consent should note that subject himself/herself demonstrates no dissent from participation in the study.

XXI. SPECIAL CONSIDERATIONS FOR SPECIAL TYPES OF RESEARCH

A. Behavioral and Social Sciences Research

This type of research generally involves surveys, observational studies, or personal interviews.

1. Social and Psychological Harms

The primary concerns when evaluating behavioral and social science research are the risk of harm to subjects with respect to social or psychological harm. Therefore, the IRB should pay particular attention to the following:

1. The potential for participants to experience stress, anxiety, guilt, or trauma that could result in genuine psychological harm.
2. The risks of criminal or civil liability or other risks that could result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.
3. If information is to be collected on living individuals other than the consented subjects, e.g., subject's family members, the IRB should consider the risk of harm to those individuals.

To mitigate such risks, the IRB shall review the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

2. Privacy and Confidentiality Concerns

The use of confidential information is an essential element of much social and behavioral research. Methods used to identify potential research subjects or to gather information about subjects must not compromise the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject, even for activities intended to identify potential subjects who will later be approached to participate in research. See HRPP policy, HIPAA Human Subjects Research Policies and Procedures (<http://www.portland.va.gov/research/documents/hrpp/hipaa.pdf>).

The IRBs serve as the Privacy Boards for Research at the Portland VA Medical Center and abide by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and HRPP policy "Health Insurance Portability & Accountability Act (HIPAA)" (<http://www.portland.va.gov/Research/hrpp/index.asp>). The Information Security Officer and Privacy Officer shall review all human research protocols and approve measures to protect confidentiality and privacy. All HIPAA authorizations must be approved by the Privacy Officer, not the IRB. However, the IRB must assure the HIPAA authorization is consistent with the informed consent and the protocol, and the IRB may approve a waiver of the HIPAA authorization.

When information linked to individuals will be recorded as part of the research design, the IRB shall ensure that adequate precautions will be taken to safeguard the confidentiality of the information and the privacy of the individuals.

B. Research with Existing Materials/Data

Planning to use materials or data that will exist separate from the research, but are not currently in existence, as well as research that proposed to use materials or data already in existence, each have special considerations. These types of studies often use or create data repositories (banks).

1. **Prospective Use of Existing Materials**

Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents or records) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do not qualify for **exemption** under VA regulations because the materials in these studies are not in existence at the time the study is proposed and initiated.

2. **Retrospective Use of Existing Materials**

Retrospective studies involve research conducted by reviewing materials (data, documents or records) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

1. Such research may be exempt under VA regulations if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects.
2. If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.
3. However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited review raised concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

When investigators will access data directly from the facility in which participants were seen, then IRB approval is needed from each investigator's IRB of record. If the records will be accessed from the Austin data center or through a network database or access point, then documentation of IRB approval from the IRB of record for each investigator is required. However, facilities who release data are not engaged in research. Only the facility/facilities where the investigator(s) are accessing data are considered to be engaged in research and therefore require IRB approval.

3. **Research Utilizing Large Existing Data Sets**

The use of large, existing data sets, i.e. data that must be "on the shelf" at the time the protocol is initiated, requires IRB review when the data contain individually-identifiable private information about individuals. In such cases, the IRB must determine whether the information may be used without additional informed consent from the subjects.

3. In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.
4. If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements.
5. In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses de-identified data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities.
6. An alternative to de-identifying data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP) and VA.

4. **Research Utilizing Data- and or Biorepositories (Banks)**

Repositories of research data and or human biological specimens are often established over the course of a study, as well as utilized for future research.

Repository activities involve three components: (a) the **collectors** of data/specimens; (b) the **bank/repository** storage and data management center; and (c) the **recipient** investigators. Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters may involve formal, written agreements between the investigator and the repository stipulating conditions as follows:

1. The repository shall not release any identifiers to the investigator.
2. The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.
3. The investigator shall use the data only for the purposes and research specified.
4. The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

Repositories of human biological specimens that will be maintained at the Portland VAMC must meet the policy outlined in the "IRB Review of Repositories Located at the Portland VA Medical Center" Policy at <http://www.portland.va.gov/research/documents/hrpp/repository-policy.pdf> If human biological specimens will be maintained outside the PVAMC for future research purposes, they must be kept either in a VACO-approved tissue bank, or obtain a waiver from the Office of Research & Development.

C. Epidemiological Research

Epidemiological research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research. Epidemiological studies often present significant problems regarding both privacy and confidentiality.

1. The IRB must first consider privacy issues and satisfy that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any individually-identifiable information to be utilized. Regional Counsel will be consulted if questions arise whether state laws might apply to a specific instance.
2. Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained. Confidentiality protections will be in accordance with HIPAA.
3. Because epidemiological research typically requires large numbers of subjects, investigators almost always request that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met.

D. Family History Research

Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member about other family members (third parties).

1. It is important to recognize that VA regulations include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information." Thus, the family

members (third party) identified and described by their family member may be human subjects under the regulations if the investigators obtain identifiable private information about them.

2. The IRB must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 38 CFR 16.116(d). There is not total consensus in the available guidance on this issue. 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. The IRB may consider if informed consent from third parties may be waived in accordance with Section 45 CFR 116 (d) and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

E. Research Involving Potentially Addictive Substances

Research involving potentially addictive substances often involves the use of what may be termed "abuse-liable" substances. Abuse-liable substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:

1. When this type of research is proposed, the IRB must consider the subjects' capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.
2. If such research involves institutionalized subjects, the subjects' ability to exercise autonomy could be impaired.
3. The IRB must also consider requirements for equitable selection of subjects and protections for maintaining confidentiality, since such a population may be at risk for discrimination or over-selection.
4. The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.
5. It is critical that the IRB focus on the considerations of risk and benefits of such research.

F. Research Involving PVAMC Employees, Students and Trainees

The IRB upholds all ethical standards in approving research involving PVAMC employees, students and/or trainees. The IRB takes into consideration undue influence an employee may experience when approached to participate in a research project. The IRB ensures that no employees, students, or trainees feel obligated to participate in research to avoid loss of employment or privileges. VA employees may participate during work time with supervisor approval if the research is directly related to their duties and responsibilities. For research that is not related to their employee duties, employees may participate only on their own time outside their normal tour of duty (including lunch break). VA employees are eligible for the same participation incentives as non-VA employees.

G. Research Involving Deceased Persons

In the rare cases of proposed research involving deceased persons, the IRB will evaluate the nature of the research and determine if consent of family members is necessary, or whether the deceased may be treated in the same manner as that of donated tissue. The IRB also ensures appropriate confidentiality measures.

Under HIPAA, investigators who propose research involving decedent's protected health information must complete the (HIPAA) Research on Decedents' Information Application (<http://www.portland.va.gov/portland/research/documents/hrpp/hipaa-decedents-research.doc>). This application will be reviewed and approved by an IRB Chair, alternate chair, or designee, since the Common Rule does not cover research involving decedent's information. The investigators will be

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expected to adhere to the provisions of HIPAA. Additional information regarding research on decedent's information is detailed in HRPP policy "Health Insurance Portability & Accountability Act (HIPAA)" (<http://www.portland.va.gov/Research/hrpp/index.asp>).

XXII. FOOD AND DRUG ADMINISTRATION (FDA) REGULATED RESEARCH

A. Investigational Drugs, Devices, and Biologics

Investigational drugs, devices and biological utilized in research, or utilized for emergency and/or one-time compassionate use, are covered in the HRPP policy titled "Investigational Device and/or Drug Usage in Research & Development Service" (<http://www.portland.va.gov/Research/hrpp/index.asp>). That document outlines responsibilities for all parties, as well as definitions and procedures for the IRB review of studies with investigational drugs, devices and/or biologics.

1. FDA Requirements in Relation to VA, Common Rule, and DHHS Requirements

The human subject protection requirements found in FDA regulations are substantially the same as the VA and Common Rule requirements. However, there are important differences:

1. The FDA has different definitions for "human subject" and "clinical investigation (research)." See Definitions in this P&P for research and human subject.
2. The FDA definition of research in the Investigational New Drug (IND) regulations is as follows: Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.
3. Conditions for exemption, exception, and waiver of IRB review and informed consent requirements differ.
4. FDA regulations require specific determinations for the IRB review of device studies (see HRPP policy "Investigational Device Usage in Research & Development Service" (<http://www.portland.va.gov/Research/hrpp/index.asp>)).
5. FDA regulations include specific requirements for reporting adverse events that are not found in VA regulations, the Common Rule, or DHHS regulations.
6. DHHS regulations include specific additional protections for pregnant women, fetuses, and human in vitro fertilization; prisoners and children that are not contained in the VA and Common Rule requirements. In April 2001 FDA issued regulations to protect children in research. In April 2001 the VA Office of Research and Development issued Directive 2001-028, requiring a centralized waiver.

In addition to regulations governing human subject protection, the FDA also has regulations governing the use of investigational drugs and (21 CFR 812).

2. Additional VA Requirements

VA policy requires that all research comply with the VA human subject regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents. The following applies to studies using an investigational drug, an approved drug used for an unapproved indication or an approved drug used as a comparator in a study.

1. A VA Investigational Drug Information Record (VA Form 10-9012) must be completed by the principal investigator and submitted to the Research Office.
2. Upon approval of the research by the IRB, a copy of the final approval notification signed by the IRB chair or IRB reviewer and the 10-9012 must be forwarded to the investigator and the Pharmacy Service.

3. FDA and Pharmacy Benefits Management Warnings

Drug Warnings: The Research Pharmacy is aware of all investigational drugs currently in use in active research studies.

- a. Pharmacy will email Pharmacy Benefits Management (PBM) warnings based on FDA warnings to the ACOS/R&D, the Administrative Officer (AO) and the Research Assurance Officer (RAO).
- b. The RAO (or ACOS/R&D or AO) will ask the Research Pharmacy to determine if any research studies are using the relevant drug(s).
- c. Research Pharmacy will email the names of relevant PIs to the ACOS/R&D, the AO and the RAO. No action will be required if no investigator is using the drug.
- d. ACOS/R&D or an R&D staff member designated by the ACOS/R&D will contact any PI using the drug, IRB Chairs, and if necessary all IRB members. PIs will be requested to submit a Human Research Event Report within five business days (see Section XVI of this P&P).
- e. The IRB chair or designated IRB voting member will determine if immediate action is required, if an emergency meeting of the IRB is warranted, or if the issue may wait until a convened IRB meeting.
- f. PIs will notify study participants if directed by the warning (based on level) or by the IRB.
- g. A file containing correspondence as well as all PBM/FDA warnings will be maintained by the Research Pharmacy.

Device warnings: The research database, MIRB, allows a report indicating current device investigations

- a. When the FDA issues an alert/warning, the RAO or an IRB analyst will generate a report. No action will be required if no investigator is using the device.
- b. ACOS/R&D or an R&D staff member designated by the ACOS/R&D will contact the relevant PIs, IRB Chairs, and all IRB members. PIs will be requested to submit a Human Research Event Report promptly (see Section XVI of this P&P).
- c. The IRB chair will determine if immediate action is required, if an emergency meeting of the IRB is warranted, or if the issue can wait until a convened IRB meeting.
- d. PIs will notify study participants if directed by the warning (based on level) or by the IRB.

REFERENCES: [VHA Handbook 1200.5](#), Requirements for the Protection of Human Subjects in Research.

CONCURRENCES: Endorsed by the R&D Committee 4/02/2012.

RESCISSION: IRB SOP endorsed by the R&D Committee 10/03/2011.

FOLLOW-UP RESPONSIBILITY: ACOS, Research & Development Service (R&D)

Michael P. Davey, M.D., Ph.D.
ACOS, Research & Development Service

Appendix 1: Categories of Research That May Be Reviewed by the IRB Through Expedited Procedures

The following categories are used to evaluate studies for possible expedited review. This list is directly from the Office for Human Research Protections at <http://www.hhs.gov/ohrp/policy/expedited98.html>

These categories are also used to evaluate the minimal risk levels referenced in the protocol deviation reporting policy included in this P&P.

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - a. from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
 - b. from other adults and 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 2 times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible

for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101\(b\)\(4\)](#). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101\(b\)\(2\)](#) and (b)(3). This listing refers only to research that is not exempt.)
8. Continuing review of research previously approved by the convened IRB as follows:
 - a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
 - b. where no subjects have been enrolled and no additional risks have been identified; or
 - c. where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.