

**PORTLAND VETERANS AFFAIRS
MEDICAL CENTER**

INSTITUTIONAL REVIEW BOARD

Standard Operating Procedures

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Changes in this revision are summarized below:

- **page 19, item E. The Principal Investigator**
- **pages 87-88, B. 1.(a) through (e) Circumstances of Informed Consent Requirements**
- **page 119, U. FDA Warnings Announced by VA**
- **Editorial corrections were also made. Please note, revisions may have caused a change in pagination.**

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INTRODUCTION

The Portland VA Medical Center (PVAMC) Institutional Review Boards' (IRB) Standard Operating Procedures (SOP) for the protection of human subjects in research is a reference for IRB members, IRB Coordinators, investigators, and other individuals associated with the Human Research Protection Program (HRPP). This SOP details the policies and procedures based on the regulations and policies governing human subjects research and the requirements for submitting research proposals for review by the IRB and the Research & Development Committee. All references to IRB in this document refer to both PVAMC IRB#1 and PVAMC IRB#2. Each IRB shall adhere to the policies and procedures outlined in this SOP.

Questions regarding the PVAMC IRB SOP may be directed to the IRB Coordinators and/or the Research Assurance & Compliance Coordinator.

Additional information about the Research Program and the Human Research Protection Program may be found on the PVAMC Research & Development Home Page, accessed through the following link:
<http://www.visn20.med.va.gov/portland/research/>.

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
DPAHC	Durable Powers of Attorney for Health Care
DSMB	Data 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
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
PHI	Protected Health Information
PI	Principal Investigator
PVAMC	Portland VA Medical Center
R&D	Research & Development
RACC	Research Assurance & Compliance Coordinator
RSO	Radiation Safety Officer
SAE	Serious Adverse Event/Experience
SOP	Standard Operating Procedures
UAE	Unexpected Adverse Event/Experience
UPR	Unanticipated <u>P</u> roblem Involving <u>R</u> isks to Subjects or Others

DEFINITIONS

- **Adverse event (AE):** (VHA Handbook 1200.5, July 15, 2003, (3.a.)) An AE is defined as 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, or any risk associated with the research or the research intervention, or the assessment.

(1) Serious Adverse Event/Experiences (SAE): An SAE is defined as a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes; or death [21 CFR 312.32(a)(1)].

(2) Unanticipated Adverse Event/Experiences (UAE): (OHRP Adverse Event Guidance January 15, 2007 and ORO Memo December 6, 2006) Any adverse event occurring in one or more subjects participating in a research protocol, the *nature, severity, or frequency* of which is **not** consistent with either

- a. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (i) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (ii) other relevant sources of information, such as product labeling and package inserts; or
- b. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **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 VI, RR, 601, C for more information. In such a case the PI will be notified of the withdrawal and a new submission will be required if the project is to resume.
- **Anonymous Research:** Scientific or medical research conducted in such a manner that the identity of an individual who has provided a sample, or the identity of an individual from whom genetic information has been obtained, or the identity of the individual's blood relatives cannot be determined. "Anonymous research" does not include research conducted in such a manner that the identity of such an individual, or the identity of the individual's blood relatives, can be determined by the use of a code, encryption key or other means of linking the information to a specific individual.
- **Blinded:** (VHA Handbook 1200.5, July 15, 2003, (3.c.)) 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 interest 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” <http://www.visn20.med.va.gov/portland/research/pdf-documents/hrpp/coi-policy.pdf>.

- **De-Identified:** De-identified information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. 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.
- **Exempt Research:** (VHA Handbook 1200.5, July 15, 2003, (3.d.)) Exempt research is research determined by the Institutional Review Board (IRB) to involve human subjects only in one or more categories. **NOTE:** Categories of exemption are listed on the Certification of Exemption form (http://www.visn20.med.va.gov/portland/research/p-i-services/rd_forms.htm).
- **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:** are defined in the 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):** (VHA Handbook 1200.5, July 15, 2003, (3.f.)) An HRPP is 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 are 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.

FDA regulations [21 CFR 50] define a human subject as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. 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.”

- **Individually-identifiable Information:** (VHA Handbook 1605.1, December 31, 2002) is any information, including health information maintained by VHA, pertaining to an individual that also identifies the individual and, except for individually-identifiable health information, is retrieved by the individual’s name or other unique identifier. 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 of the individual which is or may be readily ascertained by the investigator or associated with the information, even through the use of a codebook. Typically, “individually identifiable information” is considered to be information that is attached to one or more unique identifiers. The 18 unique identifiers defined through HIPAA are in the Health Insurance Portability & Accountability Act (HIPAA) Policy and Procedure. These include patient’s name, social security number, address, telephone number, etc.
- **Individually-identifiable Health Information:** (VHA Handbook 1605.1, December 31, 2002) is a subset of health information, including demographic information collected from an individual, that is: 1) created or received by a health care provider, health plan or health care clearinghouse; 2) relates to the past, present, or future condition of an individual and provision of or payment for health care; and 3) identifies the individual or a reasonable basis exists to believe the information can be used to identify the individual.
- **Institutional Review Board (IRB):** The IRB is a formally established subcommittee of the Research and Development (R&D) Committee with and for the purposes expressed in the Common Rule (38 CFR 16.102 (g)) and VHA Handbook 1200.5, July 15, 2003, (3.p.). The IRB, also known as the Subcommittee on Human Studies, 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, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR 812.3(g)). Investigational devices include transitional devices (21 CFR 812.3(r)) that are objects of investigations. According to the VHA Handbook 1200.5, July 15, 2003, (3.j), an investigational device may be an approved device that is being studied for an unapproved use or efficacy.
- **Investigational Drug:** (VHA Handbook 1200.5, July 15, 2003, (3.k.)) An investigational drug is a drug or biological drug that is used in a clinical investigation. The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug (21 CFR 312.3). However, for purposes of this IRB SOP, an Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.
- **Investigational Device Exemption (IDE):** (VHA Handbook 1200.5, July 15, 2003, (3.1.)) An IDE is an FDA approval of the application for an exemption that permits an un-marketed device to be shipped for the purpose of doing research on the device. **NOTE:** See 21 CFR 812.1 and 812.2 for scope and applicability.

- **Investigational New Drug (IND):** (VHA Handbook 1200.5, July 15, 2003, (3.m.)) An IND is used to refer to either an investigational new drug application or to a new drug that is used in clinical investigations. IND is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” **NOTE:** See 21 CFR 312.2(a)-(b) for applicability and exemptions.
- 1. **Investigator:** (VHA Handbook 1200.5, July 15, 2003, (3.n.)) An investigator is an individual under the direction of the Principal Investigator (PI) who is involved in some or all aspects of the research project, including the: design of the study, conduct of the study, analysis and interpretation of the collected data, and writing of resulting manuscripts. An investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may 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:** (VHA Handbook 1200.5, July 15, 2003, (3.o.)) Ionizing radiation is 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 its use is part of the 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:** (VHA Handbook 1200.5, July 15, 2003, (3.q.)) 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. A “legally authorized representative” 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. Court appointed guardians of the person
 - b. Spouse
 - c. Adult children (18 years of age or older)
 - d. Parent
 - e. Adult siblings (18 years of age or older)
 - f. Grandparent
 - g. Adult grandchild (18 years of age or older)

Note: The list above contains the only surrogate entities who are 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 the consent.

- **Minimal Risk:** (38CFR16.102(i)) a risk is minimal 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):** are 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:** means newborn.
 - **Viable neonate:** means being able, after delivery, to survive to the point of being independently maintaining heart and respiration (given the benefit of available medical therapy).
 - **Non-viable neonate:** means the same as a non-viable fetus.

- **Non-Compliance:** Failure to adhere to federal regulations or the requirements or determinations of the IRB.
 - Serious non-compliance is defined as willful and neglectful failure to adhere to IRB or Human Research Protection Program (HRPP) regulations, requirements, or determinations or violations of procedures, policies, regulations, or laws that results in increased risks to participants or in adverse effects on the rights and welfare of research participants.
 - Continuing non-compliance refers to a pattern of non-compliance that suggests an inability or unwillingness to maintain compliance with R&D, IRB/HRPP, regulations, requirements, or determinations.
- **Office of Research and Development (ORD):** (VHA Handbook 1200.5, July 15, 2003, (3.r.)) ORD is the office within VA 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 that is responsible for training, education, and policy development related to human subjects protection.
- **Office of Research Oversight (ORO):** (VHA Handbook 1200.5, July 15, 2003, (3.s.)) ORO is the primary VHA office for advising the Under Secretary for Health on all matters regarding compliance and oversight of research in the protection of human subjects, animal welfare, and research safety. ORO oversees investigations of allegations of research misconduct.
- **Pregnancy:** is the 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):** (VHA Handbook 1200.5, July 15, 2003, (3.t.)) Within VA, a PI is 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, is the responsible leader of that team. The FDA considers a PI and an investigator to be synonymous.
- **Prisoner:** is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- **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.” Please see the definition for “identifiable” above.
- **Qualified Designee:** a qualified designee for the IRB Chair is either the IRB Alternate Chair or other voting IRB member with commensurate experience.
- **Quorum:** (VHA Handbook 1200.5, July 15, 2003, (3.o.)) more than half of the voting members of a committee being present and including at least one member whose primary concerns are in non-scientific areas and, for FDA-regulated studies, at least one member is a licensed physician. 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 (38 CFR 16.102 (d)) as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

- The FDA regulations (21 CFR 50.3) 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 [21 CFR 312.3(b)], “or 520(g),” (i.e. any activity that evaluates the safety or effectiveness of a device [21 CFR 812.2(a)]), “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. [21 CFR 312.3(b)]
- 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) it involves evaluating the safety or effectiveness of a device and/or 3) data will be submitted to or held for inspection by FDA.

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."

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 3 or fewer clinical records by one or more members of the care team) are not considered research, but do require submission of a Case Report Review application to an IRB Coordinator. 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.

Research involving human subjects means any activity that either:

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

- **Research Records:** (VHA Handbook 1200.5, July 15, 2003, (3.w.)) Research records consist of IRB records as well as case histories (also referred to as investigator’s research records) or any data gathered for research purposes.

(1) **IRB Records.** IRB records include but are not limited to: all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, investigator brochures, any supplemental information including recruitment and informational materials, consent forms, information submitted for continuing review, all correspondence, and IRB membership with a resume for each member.

(2) **Case History.** A case history is a record of all observations and other data pertinent to the investigation on each research subject. An investigator is required to prepare and maintain adequate and accurate case histories. Case histories include the case report forms and supporting data including signed and dated consent forms, any medical records including, but are not limited to: progress notes of the physician, the individual’s hospital chart(s), and nurses’ notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

- **Researcher:** (VHA Handbook 1200.5, July 15, 2003, (3.x.)) A researcher is the PI and/or investigator.
- **Suspension:** A directive of the convened IRB or IRB designee either to temporarily or permanently stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review.

- **Termination of IRB approval:** A directive of the convened IRB or IRB designee to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.
- **Termination:** 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:** (VHA Handbook 1200.5, July 15, 2003, (3.y.)) For purposes of this SOP, a test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.
- **Unanticipated Problems:** Unanticipated problems involving risks to participants or others means any event, problem, occurrence, or new information that is (1) unexpected and (2) indicates that participants or others are at increased risk of harm.
- **VA-approved Research:** (VHA Handbook 1200.5, July 15, 2003, (3.z.)) VA-approved research is research that has been approved by the VA Research & Development Committee.

BG 101

Ethical Principles Governing the IRB

VA Research must be carried out in an ethical manner (38CFR16.103(b)(1)). 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/e/policy/b3.htm>), and the Belmont Report (<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>). .

A. The Nuremberg Code

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

B. 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.

C. The Belmont Report

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

1. **Respect for persons**, which is applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
2. **Beneficence** is applied so that possible benefits are maximized and possible risks are minimized to the persons involved.
3. **Justice** is evidenced in the equitable selection of subjects.

BG 102

The Regulatory Mandate to Protect Human Subjects

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

A. 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.

B. VA regulations at 38 CFR 16 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.

C 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)

D. 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 VA Med Ctr, Portland, OR IRB#1 Registration number is: IRB00001976.

The VA Med Ctr, Portland, OR IRB#2 Registration number is: IRB00003313.

The Community Based Outpatient Clinics identified for this assurance include East Portland, Bend, North Coast, and Salem.

Information regarding the FWA may be found by accessing the U.S. Department of Human Services [Office for Human Research Protections](#) web site and entering the FWA number. The Portland VAMC IRBs abide by the terms in the FWA.

IA 201

The Authority of the IRB

(38 CFR 16; 21 CFR 50, 56; and 45 CFR 46)

A. PVAMC IRBs

The PVAMC IRBs, designated by the PVAMC Director and the R&D Committee (VHA Handbook 1200.5), and named in the Federalwide Assurance (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 subjects research;
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 human subject research to whatever extent it considers necessary to protect human subjects.

B. 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. Any 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.

IA 202

Purpose of the IRB (38 CFR 16.109)

The PVAMC IRBs' primary responsibility is to ensure that the rights and welfare of subjects are protected in the VAMC human subject research program (38 CFR 16.109). In doing so, the IRBs must ensure that human subjects 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 Federalwide Assurance (FWA), and the PVAMC's institutional policies and procedures. The IRBs accomplish prospective and continuing review of the PVAMC's human subject research projects. This includes, but is not limited to, review of the protocol, the informed consent process, and all procedures used to enroll subjects.

IA 203

Review of Policies and Procedures

This Standard Operating Procedure Manual of the IRB must remain current and in compliance with all applicable regulations. To remain current, this SOP Manual must be reviewed and periodically updated. The Research Assurance & Compliance Coordinator (RACC) with the assistance of the IRB Chairs, IRB Coordinators, 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 SOP Manual will be distributed to members as appropriate.

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.

Shared Responsibilities of the Institution in Protecting Human Subjects

Although the IRB is a subcommittee of the R&D Committee (VHA Handbook 1200.5), neither the Medical Center Director nor the designated R&D Committee may approve research involving human subjects that has not been approved by the IRB of record (38 CFR 116.112; VHA Handbook 1200.5), nor can it 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.

A. Medical Center Director

(38 CFR 16.112; VHA Handbook 1200.5, MCM No. 151-01)

The **Medical Center Director** is the Federalwide Assurance Signatory Official. The Signatory Official is the official legally authorized to represent the institution under the Department of Health & Human Services approved Federalwide Assurance. The Medical Center Director is responsible for ensuring compliance with all Federal and VA regulations governing research and is accountable for the HRPP including the protection of human research subjects within the facility. The Director appoints the chairs, alternate chairs, members, and alternate members of the R&D Committee and all of its subcommittees and reviews and approves all R&D Committee meeting minutes. (VHA Handbook 1200.1)

The Director delegates the authority to administer the R&D program to the Associate Chief of Staff/R&D.

B. Chief of Staff

(MCM No. 151-01)

The Chief of Staff (COS) at PVAMC reports to the Medical Center Director and has overall responsibility for all clinical activities under the purview of the PVAMC.

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

(MCM No. 151-01)

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. 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).
5. Administering the facility's R&D programs, including the R&D Committee and applicable subcommittees.
6. Managing the finances of the facility's R&D Program.
7. Assisting investigators in their efforts to carry out the VA's research mission.
8. Developing and implementing needed improvements and ensuring follow-up of actions as appropriate for the purpose of managing risk in the research program.
9. 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.
10. Reviewing, or designating a reviewer for, all sponsor agreements to assure ethical standards and practices in research are upheld.
11. Fulfilling all other responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.

D. Research & Development Committee

(VHA Handbook 1200.5, MCM No. 151-01)

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. This oversight includes the assessment of scientific quality of research and development projects and protection of human research subjects. The R&D Committee is responsible for the following:

1. Assuring the continuing quality of the facility's R&D program.
2. Planning and developing broad objectives of the R&D program so that it supports the patient care mission of the facility.
3. Evaluating critically and deciding approval/disapproval of
 - (a) research based on the quality, design, desirability and feasibility of each new R&D proposal;
 - (b) continuing R&D projects;
 - (c) application for funding;
 - (d) manuscripts to be submitted for publication; and
 - (e) other reporting activities to assure maintenance of high scientific standards, protection of human subjects, adequate safety measures and proper use of animal subjects.
4. Reviewing and declaring approval/disapproval of recommendations from its subcommittees (The R&D Committee will not approve any proposal that has been disapproved by any subcommittee, nor will it alter any documents or recommendations made by any subcommittees.):
 - (a) Institutional Review Board (IRB);
 - (b) Institutional Animal Care and Use Committee (IACUC);
 - (c) Subcommittee on Research Safety (SRS); and
 - (d) Subcommittee on Research Space.
5. Recommending the distribution of R&D funds, space, personnel, equipment, supplies, use of animal facilities and other common resources on the basis of such evaluations and after consideration of other needs. This includes an annual review of the budget assigned to the HRPP.
6. Reviewing on an annual basis the subcommittees' chair and members and their qualifications and experiences. These subcommittees include the IRB, IACUC, SRS and Subcommittee on Research Space.
7. Reviewing, evaluating, and as needed, recommending appropriate corrective actions, regarding the reports and results of compliance assessment and continuous quality improvement activities (CQI) related to research.
8. Reviewing and declaring approval/disapproval of new and revised HRPP policies and procedures.
9. Evaluating annually, investigator compliance with HRPP and IRB requirements.
10. Fulfilling all other responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.
11. Reviewing all disclosed conflicts of interest in human research and creating a management plan to reduce or eliminate such conflicts of interest.

E. The Principal Investigator

(VHA Handbook 1200.5, (10); PVAMC MCM No. 151-01)

The IRB recognizes one Principal Investigator (PI) for each project. Anyone with a Research Appointment, either VA or WOC, may be designated as PI unless 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. For human research, at the time of initial IRB review, the PI who is mentor must attend the IRB meeting and assure responsibility for the research.

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. 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. 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.

1. **Principal Investigators** planning to conduct human studies research at the PVAMC are responsible for adhering to the responsibilities, policies and procedures outlined in the MCM No. 151-01, IRB SOP and HRPP policies and procedures. Specific responsibilities follow:
 - (a) Submit the following forms, as applicable, to the Administrative Officer of R&D Service in a timely manner prior to submitting a research proposal to a funding agency:
 - (1) Proposed Project Questionnaire (PPQ),
 - (2) Administrative Review forms,
 - (3) Project proposal (protocol) and abstract,
 - (4) Institutional Review Board forms,
 - (5) Institutional Animal Care and Use Committee forms, and
 - (6) Subcommittee on Research Safety forms.

These forms may be obtained from the R&D Service website:

http://www.visn20.med.va.gov/portland/research/p-i-services/rd_forms.htm .

- (b) Submit annual and continuing reviews of the research project to the R&D Service administrative office. All required reports must be submitted by the due date(s) specified by the R&D Service administrative office to comply with federal, VACO and local requirements.
- (c) Complete educational requirements, educate their staff and monitor all safety rules and regulations in their laboratory including the requirements for annual safety training. Each employee must comply with all requirements of the Subcommittee on Research Safety.
- (d) Submit 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.
- (e) Fulfill all other responsibilities and adhere to the policies and procedures outlined in the appropriate institutional, HRPP, and R&D Service committees' policies and procedures.
- (f) Complete all required education in the protection of human research participants.
- (g) Maintain credentials and, as appropriate, privileges at the PVAMC appropriate 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.
- (h) Submit the proposed research and obtain IRB approval or exemption from IRB review from the PVAMC IRB. As part of the review process, the principal investigator must comply with all requests for information to assess conflicts of interest. **Note:** Payments to professionals in exchange for referrals of potential participants ("finder's fees") and Payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments") are prohibited.
- (i) Initiate the study only **after** receiving written approval from **both** the IRB and the R&D Committee.
- (j) Adhere to all assurances given to the IRB at the time the project was approved.
- (k) Give a copy of the signed consent form to the patient and assure the patient initials the original signed consent form acknowledging receipt of the copy.
- (l) For studies involving drugs, provide the pharmacy with a signed copy of Form 10-1223 indicating IRB and R&D committee approval and a signed copy of Form 10-1086 documenting each participant's consent to participate in the study.
- (m) Forward the original signed informed consent form (VA Form 10-1086) for each patient enrolled in the research project to the R&D Service for scanning into the patient's electronic medical record. After scanning the informed consent form into the patient's electronic medical

- record, 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.
- (n) Create a progress note in the Computerized Patient Record System (CPRS) documenting the informed consent process with the patient, when the subject is consented into the study, when actual randomization occurs if there is a period of time between consent and randomization, and when the human subject's participation is terminated.
 - (o) Submit all original adverse events occurring in the study to the IRB in a timely manner consistent with PVAMC policy.
 - (p) Complete annual review forms for continuing approval of ongoing research.
 - (q) Cite PVAMC IRB approval in the methods section of all manuscripts involving human studies.
 - (r) Inform the Chief, Pharmacy Service and the R&D Committee when a study involving investigational drugs has been terminated. (VA Handbook 1200.5, 14).
 - (s) Fulfill all other responsibilities and adhere to the policies and procedures as outlined in the appropriate institutional and HRPP policies and procedures, and the IRB SOP.

2. **Required Investigator Reports**

The investigator shall meet these reporting requirements to the IRB. See section FO 505, item H., of this SOP for required timelines for reporting:

(a) **Changes in Approved Research:**

- The investigator must promptly report any items listed in item G.1. of RR 602 "Ongoing Review" in this SOP.
- All other changes in approved research, during the period for which approval has already been given, may not be initiated without IRB review. The proposed modifications should be submitted to the Research Service office with the "Project Revision/Amendment Form" (PR/AF- http://www.visn20.med.va.gov/portland/research/p-i-services/rd_forms.htm#alphabetical).
- If an amendment addresses an issue related to biosafety, investigators will submit a "Grant Approval Request Form" to the Subcommittee on Research Safety. Such approval must be received before the amendment is approved by the IRB.
- If an amendment addresses an issue related to radiation safety, the IRB coordinators will send it to the Radiation Safety Officer (RSO) for review. The RSO will submit a report to the PVAMC Radiation Safety Committee.
- An investigator must submit any changes to the informed consent form to the IRB for review and approval as follows: submit a 1) Project Revision/Amendment Form detailing the changes to the informed consent form, 2) a clean copy of the modified informed consent form, and 3) a copy of the modified informed consent form with all changes highlighted.

(b) **Withdrawal of FDA approval or sponsor termination**

Promptly report any items listed in item G.1. of RR 602 "Ongoing Review" in this SOP.

- More information regarding changes in IRB approved research may be found in Section VI, RR, 602, A.

(c) **Continuing Review Submission:**

Investigators are responsible for requesting re-approval in anticipation of the expiration of the approval period (generally 60 days before the expiration date). The investigator must submit the following for IRB continuing review approval: 1) Continuing Review Questionnaire (CRQ); 2) any additional information as prompted and required by the CRQ; 3) updated

abstract; 4) a clean copy of the current informed consent form or, if applicable a copy of the modified informed consent form with all changes tracked.

More information regarding continuing review approval may be found in Section VI, RR, 602, D.

(d) **Termination Reports:**

Investigators must submit study termination reports upon completion or termination of the study. The notice should be submitted on the “Research Project Termination Report” form. However, if at the time the continuing review paperwork is submitted to the IRB, the CRQ indicates that the study is terminated, then the CRQ is reviewed as a research project termination and the “Research Project Termination Report” form is not required.

More information regarding termination reports may be found in Section VI, RR, 602, K.

(e) **Unanticipated Problems:**

All investigators conducting research as employees or agents in the PVAMC are required to promptly report any items listed in item G.1. of RR 602 “Ongoing Review” in this SOP.

For FDA-regulated studies, see additional reporting requirements in Section X, FD 1001.

(f) **Protocol Deviations/ Violations:**

All investigators must promptly report any items listed in item G.1. of RR 602 “Ongoing Review” in this SOP.

More information regarding protocol deviations/violations may be found in Section VI, RR, 602, B.

(g) **Absence of an Investigator:**

This policy helps to ensure that when an investigator is called to active duty in times of war or national emergency and thus decreases the number of staff available to conduct research, the research will be conducted properly. More importantly, proper treatment of the human subjects involved in the research will not be jeopardized.

If in the course of the research an investigator will be absent, the principal investigator must notify the IRB. 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. Before approval, the individual(s) must complete the required education and credentialing requirements, consistent with HRPP Policies & Procedures Nos. 4 and 10 and be credentialed and, if applicable, privileged 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 requirements, consistent with HRPP Policies & Procedures Nos. 4 and 10, be credentialed and, if applicable, privileged to perform the absent co-investigator’s responsibilities and approved by the IRB.

If the principal investigator leaves the PVAMC, the original research records must remain at the PVAMC.

F. PVAMC Subcommittees

The R&D Committee may require projects to be reviewed and approved by the PVAMC Subcommittee of Research Safety (SRS), Institutional Animal Care and Use Committee (IACUC), and/or Subcommittee of Research Space, relevant committees of collaborating institutions and/or by *ad hoc* reviewers.

G. Regulatory 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 (See section FO 505 for further details.)

H. IRB Staff and Resources

Full- and part-time IRB coordinators report to the IRB Chair, the AO/R&D, and ACOS/R&D. The coordinators act as a liaison between the investigators and the IRB. Space for the IRB Coordinators and IRB files is under the purview of the Research Service.

1. The IRB Coordinators are responsible for adhering to the responsibilities for the Research Service Administrative Staff outlined in the MCM No. 151-01:
 - (a) Review research proposal submissions, advise principal investigators about federal, VACO, state, and local requirements for conducting research, place research proposals on the IRB agenda, and coordinate the final approval by the R&D Committee.
 - (b) Maintain 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.
 - (c) Track the progress of submitted research protocols.
 - (d) Fulfill all other responsibilities and adhere to the policies and procedures outlined in the appropriate institutional, HRPP, and R&D Service committees' policies and procedures.
2. Additionally, the IRB Coordinators or other designated R&D Service administrative personnel shall carry out the following responsibilities:
 - (a) Respond to requests for consultation, (i.e. questions regarding IRB policies and procedures, e.g., questions involving whether or not a project is considered human subjects 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. They may consult with IRB members and chairs and/or the RACC if necessary to address an individual's questions.
 - (b) Scan original informed consent forms into the patient's electronic medical record and ensure that the original informed consent form is returned to the Principal Investigator.
 - (c) Assign the primary and *ad hoc* reviewers to review material submitted to the IRB. The IRB Chairs will assist the IRB Coordinators, as necessary, in completing this responsibility.
 - (d) Evaluate each protocol to determine whether a consultant is needed.
 - (e) Obtain 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.
3. Contact information for the IRB Coordinators is included online at <http://www.visn20.med.va.gov/portland/research/committees/irb/index.htm>.

OM 301

IRB Membership and Responsibilities (38CFR16.107; VHA Handbook 1200.5)

A. IRB Membership Requirements

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.

NOTE: 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, East Portland, or Salem, and who is not part of the immediate family of a person affiliated with the medical center (a volunteer or a patient receiving care at the PVAMC is not considered an affiliated member);
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 Roster

See IRB roster online at <http://www.visn20.med.va.gov/portland/research/committees/irb/index.htm> for the current composition of each IRB:

- names
- degrees
- voting and alternate status and representative capacity
- representative capacities regarding vulnerable populations, if any, each member was knowledgeable about or experienced in working with
- affiliation status (whether the member or an immediate family member of the member was affiliated with the organization)
- indications of experience sufficient to describe each IRB member's chief anticipated contributions; and
- employment or other relationship between each IRB member and the organization

In addition, members are listed by name and affiliation status on the full board meeting minutes of the IRB.

C. IRB Chair

1. Appointment

One chair for each IRB is nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the PVAMC Director. The chair must hold a VA appointment, compensated or without compensation (WOC).

2. Length of Service

The chair serves a one-year term and may be re-appointed indefinitely.

3. Responsibilities

- (a) Conduct IRB meetings.

- (b) Call special meetings when necessary.
- (c) Consult the IRB Coordinators 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 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 patient 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 IRB approvals, VA Form 10-1223, unless the Alternate Chair is presiding, for protocols or actions approved by the IRB;
- (j) Notify the RACC 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 RACC and determine if a special meeting of the IRB must be convened to address an immediate patient safety issue or if the issue can be held until the next scheduled meeting.
- (k) Forward any requests for private consultation received from investigators, research staff, clinicians, etc., to the IRB Coordinators for a documented response to the individual's questions. Members of the PVAMC IRB shall not provide individual private consults to individual investigators and medical staff.
- (l) Report any attempts by investigators or research staff of undue influence toward approval of research to the RACC.
- (m) Report to appropriate regulatory bodies consistent with VHA policies and procedures.
- (n) Fulfill all responsibilities and adhere to the policies and procedures as outlined in the appropriate institutional, HRPP and R&D Service committees' policies and procedures.
- (o) Assist the IRB Coordinators, as necessary, in assigning primary and ad-hoc reviewers to review material submitted to the IRB.

D. IRB Alternate Chair

1. Appointment

One Alternate Chair for each IRB is nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the PVAMC Director. The Alternate Chair must hold a VA appointment, compensated or Without Compensation.

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.

E. IRB Members

(38CFR16.107)

1. Appointment

IRB members are nominated by the ACOS/R&D, resumes for members are submitted to and individuals voted on by the R&D Committee, and members are then formally appointed by the Medical Center Director.

2. Length of Service

Members serve 3-year terms and may be reappointed indefinitely. 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) Ensure the rights and welfare of research subjects are protected.
- (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) Vote to approve as presented, approve contingent upon minor modifications made and to be verified by the Primary Reviewer(s) (contingent approval), table for major modifications, or disapprove research submitted to the IRB.
- (h) Serve as primary reviewers when assigned, generally within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings.
- (i) Conduct expedited reviews on behalf of the IRB when so designated by the IRB chair.
- (j) Participate in other subcommittees, audits, and education, so long as there is no conflict of interest with IRB responsibilities.
- (k) 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” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>).
- (l) As indicated in the “Conflict of Interest in Research Policy and Procedure” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>), avoid real or perceived conflicts of interest. The IRB chairs and members may find themselves in any of the following potential conflicts of interest:
 - i. The IRB Chair or member is listed as an investigator on the research.
 - ii. An investigator must report to or is under the supervision of an IRB chair or member.
 - iii. 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.
 - iv. An IRB member is a family member of an investigator whose research is scheduled for review.
 - v. For further information regarding the responsibilities of an IRB member and conflict of interest in human research, please see HRPP policy “Conflict of Interest in Research” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>).
- (m) Forward any requests for consultation from investigators, research staff and clinicians, etc. to the IRB Coordinators for a documented response to the individual’s questions. PVAMC IRB members shall not provide private individual consults to individual investigators and medical staff.
- (n) Report any attempts by investigators or research staff of undue influence toward approval of research to the RACC.
- (o) Fulfill all responsibilities and adhere to the policies and procedures as outlined in the appropriate institutional, HRPP and R&D Service committees’ policies and procedures.

F. **Alternate IRB Members**

1. **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.

2. 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.

3. Responsibilities

An alternate IRB member has the same responsibilities as a full time IRB member listed in Section III, OM, 301.E.

These alternates replace regular IRB members who are, on occasion, unable to attend convened meetings of the IRB. All alternates are identified on the IRB rosters (<http://www.visn20.med.va.gov/portland/research/committees/irb/index.htm>) and are identified as to whom they may substitute for at convened meetings. IRB minutes will record when alternate members act in the absence of primary members. All alternate members will receive the same reviewer information as primary IRB members when they will be attending meetings for the absent member. The alternate member is allowed to vote in the absence of the member s/he represents.

G. Ex-Officio Members

The IRB does not include "non-voting" members, other than ex-officio members, who are appointed due to their position at the PVAMC. These members must adhere to the same conflict of interest policies and procedures as the voting IRB members. The ex-officio members may not vote with the IRB. These members are not nominated and appointed by the Medical Center Director. The Administrative Officer/Research & Development serves as an ex-officio member of the IRB.

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

(VHA Handbook 1200.5 6.h., 38 CFR 16.107(f))

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 which require 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 coordinators 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.

I. Compensation for IRB Service

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

OM 302

Training of IRB Chairs and Members

As a condition of the FWA, IRB members are provided education about human research protection.

A. **Responsibilities**

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.visn20.med.va.gov/portland/research/hrpp/index.htm>), and any other requirements of the IRB chair.

The chairs of each IRB and the RACC and/or a designated IRB coordinator shall provide members with an initial orientation to their committee activities and appropriate continuing education related to the IRB.

B. **IRB Standard Operating Procedures**

All IRB members receive a copy of the PVAMC IRB SOP Manual prior to their first meeting with the IRB. This manual includes the IRB SOP and all PVAMC HRPP policies and procedures and pertinent regulations.

C. **Continuing IRB Education**

The IRB members are responsible for completing the annual educational requirements as set forth in HRPP policy “Education for the Protection of Human Research Participants in the Research & Development Service” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>).

D. **New IRB Member Training**

Each new IRB member’s training, as of (August 2007), consists of the following:

1. The RACC or an IRB coordinator shall give each new member a copy the IRB SOP Manual and offer the opportunity for questions and discussion.
2. 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.
3. 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.
4. One-on-one presentation by the RACC or an IRB coordinator of a PowerPoint show covering key aspects of the HRPP and IRB member responsibilities.

EI 401

Exemption from IRB Oversight/Review (38 CFR 16.101(b)(1-6)) (21 CFR 56.108-109)

Investigators shall submit a written request to the IRB on the “Certification of Exemption Form” and the “Request for Expedited Review” for an exemption from IRB review. 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 page 11 of this SOP). Questions regarding whether or not an activity is considered human subjects research should be directed to an IRB Coordinator or the Research Assurance and Compliance Coordinator.

A Project Proposal Questionnaire (PPQ) is submitted for all research. IRB staff review and/or the Research Assurance and Compliance Coordinator determine if the project is human research, i.e. whether the IRB must review. The IRB coordinator will communicate the determination to the investigator and if human research, what further procedures and forms are needed.

Using expedited review procedures, the IRB Chair or a qualified and experienced IRB member appointed by the IRB chair will recommend approval of the exempt status to the R&D Committee. In reviewing the exemption, 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 (38 CFR 16), DHHS (45 CFR 46) and FDA (21 CFR 56.108-109).

The R&D Committee will review IRB-exempted projects and make a final determination (VHA Handbook 1200.5). The research project may begin once written confirmation from the IRB and R&D Committee has been received by the PI. Once approved by the R&D Committee, the project must be included in the R&D Committee’s annual review of research projects.

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

Categories of exempt research are stipulated in VA regulations at 38 CFR 16.101(b)(1-6) as shown on the Certification for Exemption form (http://www.visn20.med.va.gov/portland/research/p-i-services/rd_forms.htm). Some FDA-regulated research may not qualify for exemption.

FO 501

IRB Recordkeeping and Required Documentation (38CFR16.115)

A. Record Retention

(38 CFR 16.115(b), 45 CFR 164.528)

The IRB shall keep records for at least six years after consideration for disapproved proposals and six years after the conclusion of research for approved proposals or as required by study sponsors, as indicated through the IRQ. Records of protocols cancelled without participant enrollment will be kept for six years. All IRB records collected over the course of the protocol will be maintained by the IRB Coordinators in the PVAMC Research Service space. If a study does not receive funding and the PI decides not to conduct the research without funding, the records will also be kept for six years. If an investigator leaves the PVAMC facility, the original research records must be retained at the PVAMC for six years. All other records will be retained for five years or longer as required by law and VHA Records Control Schedule 10-1.

B. Access to IRB Records (38 CFR 16.115(b))

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, or in storage areas in locked file cabinets behind magnetic security doors in order to maintain the privacy and confidentiality of research subjects' information. 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 chair 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 Coordinators 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.

C. IRB Records

IRB records include the following:

1. Standard Operating Procedure manual
2. Convened IRB meeting minutes
3. IRB membership information
4. Education/training records
5. Research project files - Research project records are in organized files and contain all documentation associated with the research project: the research protocol reviewed (DHHS-approved protocol when it exists) and all modifications, scientific evaluations by reviewers, records of continuing review activities, copies of all correspondence between the IRB and the investigator, scientific evaluations, DHHS-approved sample consent documents when they exist, progress reports and any reports of injuries to subjects, statements of significant new findings provided to participants, when applicable.
6. Federalwide Assurance (FWA)

D. IRB Membership Roster

The IRB Coordinators maintain the current IRB membership rosters and report any changes to the OHRP with a

copy to the Office of Research Oversight (ORO). The IRB Membership Information binder contains copies of the IRB members' curriculum vitae/resume or equivalent and appointment letters.

E. Education Records

The Research Service office shall maintain accurate records of research investigators, research staff, IRB members, and IRB staff who have fulfilled the PVAMC HRPP education requirements.

F. Written Standard Operating Procedures

(38 CFR 16.103(b) (4, 5) and 108(a), 115(a)(6))

IRB members are provided with their choice of either electronic or hard copies of the PVAMC IRB SOP at the time they join the IRB and each time the SOP is updated.

The ACOS/R&D, AO/R&D, IRB Chairs, IRB Coordinators, and Research Assurance & Compliance Coordinator work together to write and maintain the IRB SOP. The SOP will be reviewed and modified as needed to reflect updated and applicable regulations, policies, and institutional procedures.

G. IRB Correspondence

(38 CFR 16.115(a)(4))

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 coordinator present at the meeting or at such time as the text of such correspondence is confirmed with the IRB Chair. 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.

After initial or continuing review, an IRB coordinator will notify the principal investigator or designated study coordinator of the result within three weeks of the convened meeting date. In cases of contingent approval, once the reviewer has reviewed the PI's response to the contingencies, an IRB coordinator will send the final approval letter signed by the IRB chair to the PI or study coordinator within a reasonable time frame or inform if further clarifications/stipulations are needed.

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 coordinator and/or staff.

H. 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. A separate unique VA grant number is also assigned associated with each protocol. This VA grant number serves as another method of identifying the grant. 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:

1. Determinations required by the regulations and protocol-specific findings supporting those determinations for waiver or alteration of the consent process.
2. For each protocol's initial and continuing review, the frequency for the next continuing review.
3. Unexpected adverse events submitted to the IRBs.
4. Protocol violations submitted to the IRBs.

I. Research Tracking System

The IRB uses a reliable computerized tracking system, the MIRB computer program maintained by the IRB coordinators and Research Service staff. IRB coordinators enter specific documents received, date received, date reviewed, and results of review into the MIRB database.

Additionally, MIRB is used to track IRB stipulations from contingent approvals, when those changes were 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.

J. Activities Requiring IRB Review

Projects meeting the definition of research involving human subjects as defined in this document (page 8) and Medical Center Memorandum (MCM) 151-01 (page 1), and otherwise requiring approval per paragraph 1. POLICY of MCM 151-01 must undergo IRB and R&D Committee review and approval before the research project may begin. The IRB and R&D Committee will determine whether or not a research activity that meets the definitions for human research is exempt from the human subjects regulations and purview of the IRB based on a completed "Certification of Exemption" form available on the R&D website:

http://www.visn20.med.va.gov/portland/research/p-i-services/rd_forms.htm#alphabetical. If questions arise in completing this form, investigators should contact the Research Assurance and Compliance Coordinator.

K. Documentation of Exemptions from IRB Oversight/Review

The IRB Chair or Alternate Chair or a qualified and experienced IRB member appointed by the IRB Chair or Alternate Chair will review and recommend approval of the exempt status to the R&D Committee. Documentation regarding the rationale for the 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. 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.

More information, regarding the determination of Exemption from IRB Oversight/Review is located in Section IV, EI, 401.

L. Documentation of Expedited Reviews

(38 CFR 16.110(b); 63FR 60364-60367, November 9, 1998)

Upon request by a principal investigator for expedited review, the chair or the chair's qualified designee will determine if expedited review is appropriate, based on the requirements referenced in Section VII, EX,700. If appropriate, s/he will review submitted material and approve or disapprove. The review and decision will be documented in the research project file and the next meeting agenda and minutes of the IRB.

M. Documentation of Convened IRB Meetings – Minutes

(38 CFR 16.115(a)(2))

IRB Coordinators 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; review of protocol or informed consent modifications or amendments; unanticipated problems involving risks to subjects or others; unanticipated adverse event reports; reports from sponsors, cooperative groups, or Data 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. Votes and deliberations on each action reviewed by the 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.”

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.

Recused applies if a member has a conflict of interest. The member leaves the room and does not participate in the deliberations or vote.

Excused applies when a member is out of the room for the vote, i.e. restroom, emergency, etc.

7. 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 doc.;
8. 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.
9. Research protocols approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of each;
10. Approvals of minor changes, 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 during the period for which approval is authorized utilizing expedited review procedures, and the specific citation for the category of expedited review of the minor changes;
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; and
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.

N. **Attendance at IRB Meetings**

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, and 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 absent/excused members, according to their voting status;

Excused applies when a member notifies an IRB Coordinator in advance that s/he will be absent.

Absent applies when a member has not notified an IRB Coordinator in advance of the meeting that s/he will be absent.

3. Names of 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 *ad hoc* reviewers present;
5. Names of Research Service staff present and/or excused/absent; and
6. Names of guests present.

Note: (2) – (6) will be documented as appropriate.

O. Quorum Requirements and Voting at IRB Meetings

(VHA Handbook 1200.5 7.f.)

The IRB will not conduct business unless a quorum, including a non-scientific member, is present and maintained. The IRB observes the following rules:

1. A majority of the IRB members (or their designated alternates), including at least one member whose primary expertise is non-scientific 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 members present at the meeting.
2. Members may be present in person or by telephone or audio-visual teleconference. Minutes will indicate any members present via teleconference and that all members received all pertinent information prior to the meeting and participated actively and equally in all discussions.
3. IRB minutes shall include documentation of quorum and number of votes for (); against (); abstained (); recused (); and excused ().for each IRB action:
4. Members absenting themselves due to conflicts of interest will be documented as “recused” during the vote. Recusals may not be counted toward quorum requirements.
5. 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.
6. At least one non-scientist must always be present for a vote to be taken. If a non-scientific member of the IRB is absent during the meeting, i.e. if the non-scientific member is absent or excused, this is indicated in the meeting minutes.
7. When a member and his/her alternate both attend a meeting, only one may vote.
8. If research involving an FDA-regulated device is to be reviewed, a licensed physician must be included in the quorum.
9. A VA member will always be present during review of VA research.

P. Actions Taken by the Convened IRB

(38 CFR 16.109; 115)

The minutes shall include all actions taken by the convened IRB and the votes underlying those actions.

IRB actions for review of research include the following:

1. **Approved (Approved with no changes or no additional changes).** At **initial** review of the research project, IRB, R&D Committee and any other applicable subcommittee written approvals are required **prior** to study initiation.

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. Questions 1-3 and 7-8 on the IRB Primary Reviewer Checklist have all been answered “Yes”, and questions 4 and 5 have either been answered “yes” or meet the criteria for a waiver or alteration of informed consent and/or a waiver of documentation of informed consent, or they will be answered “yes” as appropriate *if* a few **specific** changes are made. *Note:* A study undergoing initial review that has been contingently approved by the IRB may proceed to review by the R&D Committee. The study may not begin until final approval by both committees and any other applicable subcommittees.
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 so numerous as to require re-review by the full board. The research may not proceed until the convened IRB has approved a revised application at a convened meeting and the investigator has received final written approval from the IRB, R&D Committee and any applicable subcommittees.
4. **Disapproved.** The IRB determines that the research may not be conducted at the facility or by employees or agents of the facility.

Q. Situations of IRB Deferral

A deferral may be documented in the IRB minutes when the IRB did not take an action on an item scheduled for review either because 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.

R. The Basis for Requiring Changes in or Disapproving Research (38 CFR 16.109(d))

The minutes of IRB meetings shall include the basis for requiring changes in or disapproving research.

S. Use of VA form 10-1223, Report of Institutional Review Board

Form 10-1223 is generated for signature of the IRB chair in the following circumstances: at the time of initial approval, at the time of continuing review approval, any time a protocol amendment or revised consent form is reviewed and approved, at the time a revised investigator’s brochure is reviewed and approved, and at the time of approval of any change to the protocol or research team affecting conduct of the research, e.g., addition to the research team or a change of age range of potential participants.

VA form 10-1223 is not generated in cases where IRB review is for the purposes of assuring ongoing patient safety but no change in the research conduct is indicated. This includes review of unanticipated problems, protocol deviations/violations, and notifications. The IRB reserves the right to request more information or a change in research procedures. In these cases, the IRB coordinators will generate a separate memorandum noting whether or not any further action is needed on the part of the principal investigator or research coordinator.

T. Summary of Controverted Issues at Convened Meetings

(38 CFR 16.115(a)(2))

The minutes of IRB meetings shall include a written summary of the discussion of controverted issues and their resolution. An issue is controverted when there is lack of consensus, regardless of whether there is a split vote. When an issue is controverted, the summary of the controverted issue must be documented.

U. IRB Findings and Determinations where Documentation is Required by Regulation

(OHRP and FDA Guidance)

The IRB members shall use the appropriate “IRB Primary Reviewer Checklist” in reviewing protocols at the

time of initial and continuing review. Checklists are available from IRB coordinators. 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 Coordinator 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). Generally the IRB Coordinator is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts convened in accordance with Subpart D. 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.
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 page 130 of this SOP). **(Note: Please refer to VHA Handbook 1200.5 14.h. and i.)**
11. Rationale for significant/non-significant risk device determinations.

FO 502

IRB Meetings (Review by the Convened IRB) (38 CFR 16.108(b))

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, unless the research falls into one or more categories appropriate for expedited review.

A. IRB Meeting Schedule

Current IRB meeting schedules and deadlines for investigator submissions are on the Research Service website (<http://www.visn20.med.va.gov/portland/research/committees/irb/index.htm#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 FO 504. 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

A meeting agenda will be prepared by the IRB Coordinators or designee and distributed with the meeting materials to IRB members 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.

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 at a later time within the month 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 Coordinators will record minutes of each IRB meeting.

D. 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.

FO 503

Use of Primary Reviewers with Convened IRB Reviews

A. Assignment of Primary Reviewers

The IRB Coordinators 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 Coordinators, 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 coordinators 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.

B. 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 unexpected problems, Data 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 IRB Primary Reviewer Checklist which includes criteria for approval);
3. completing the applicable IRB reviewer forms; and
4. leading the discussion of the research at the convened meeting, voicing any concerns that arose during their review and changes that may be required.

C. 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 can submit their written comments to be read at the meeting, as long as another reviewer is present to serve as a primary reviewer.

FO 504

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. The IRB members will receive these materials approximately one week prior to the scheduled convened meeting. All IRB members shall be afforded full opportunity to discuss each research proposal during the convened meeting.

A. Initial Review Materials

1. **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:

Item for Review	Additional Information
Initial Review Questionnaire (IRQ), copies of specific pages of protocol referenced in the IRQ and any additional attachments	Attachments include the Human Biological Specimens Questionnaire, or Investigational Device or Drug Information Record, etc.
Abstract, i.e., protocol summary	NA
Informed Consent Form, or 1) Request for Waiver Or Alteration Of Informed Consent <u>Process</u> And Waiver Of Authorization To Release Medical Records Or Health Information Or 2) Request For Waiver Of Informed Consent <u>Documentation</u> And Waiver Of Authorization To Release Medical Records Or Health Information, if applicable.	NA
HIPAA Forms, if applicable	NA
Advertisements or other materials provided to subjects, if applicable	NA

2. **The Primary IRB Reviewers** for each research projects will receive the materials listed above in addition to the following for each research project. **Note:** during the initial review of a research project, the entire IRB file is given to the primary IRB reviewers prior to the convened meeting.

Item for Review	Additional Information
Protocol (complete DHHS-approved protocol 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.

Investigator's brochure(s) or equivalent material, if applicable	This is 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).
Subject Surveys, questionnaires, if applicable	NA
Merit Reviews or Grant Applications, if applicable	NA
IRQ and any additional attachments	Attachments include the Human Biological Specimens Questionnaire, or Investigational Device or Drug Information Record, etc.
Any other applicable material submitted by the Principal Investigator to ensure the application is complete and a thorough initial review of the research project proposal can be made. This may include phone scripts, and/or a DHHS-approved sample consent document if one exists.	NA

B. Continuing Review Materials

1. **All IRB 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. The entire IRB file is also available for review to any IRB member upon request:

Item for Review	Additional Information
Continuing Review Questionnaire (CRQ)	The CRQ identifies the following: if any additional unanticipated problems 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); any unanticipated problems involving risks to subjects; and enumeration of subjects withdrawn and the reasons for withdrawal.
Initial Review Questionnaire (IRQ), copies of specific pages of protocol referenced in the IRQ and any additional attachments	Attachments include the Human Biological Specimens Questionnaire, or Investigational Device or Drug Information Record, etc.

upon which initial approval of the protocol was based.	
Updated Research Project abstract, i.e., protocol summary	NA
Most current IRB approved informed consent form and any newly proposed consent document.	NA

2. **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. **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.

Item for Review	Additional Information
Continuing Review Questionnaire (CRQ)	The CRQ identifies whether or not: any additional unanticipated adverse events have occurred that have not been reported to the IRB; new information is available regarding the research project that may change the risk/benefit ratio; any research finds to date, including summary of subject experiences (benefits, adverse reactions); any unanticipated problems involving risks to subjects; and enumeration of subjects withdrawn and the reasons for withdrawal.
Initial Review Questionnaire (IRQ) and any additional attachments upon which initial approval of the protocol was based.	Attachments include the Human Biological Specimens Questionnaire, or Investigational Device or Drug Information Record, etc.
Updated Research Project abstract, i.e., protocol summary	NA
Most current IRB-approved informed consent form and any newly proposed consent document.	NA
Complete protocol	NA
Most recent report capturing all reportable events to date, if applicable	If the research involves no risk and is non-interventional or if no subjects have been enrolled, this factor is not applicable. If the research is not FDA-regulated, sponsor safety reports are not required.
Amended or updated Investigator's brochure, if applicable	If the research project does not involve a drug or device, this is not applicable.
Summary of safety monitoring reports, if applicable	If the protocol is minimal risk, and it does not include a data monitoring plan, this is not applicable.

C. 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 unexpected problem reports, safety reports, etc.

Notifications and Reports

A. Report to the R&D Committee

The IRB shall notify the R&D Committee in writing of its determinations as determined in Section V, FO, 501. The R&D Committee is notified of all IRB determinations of items for review through the review of the IRB meeting minutes.

It is the responsibility of the IRB Chairs and/or the ACOS/R&D to provide prompt written notification to the R&D Committee of suspensions and terminations of IRB approved research projects and of any unanticipated problems involving risks to subjects or others and the resolution of those problems. This does not include expirations of IRB approval.

B. Notification of the Investigator

The IRB shall notify the Principal Investigator in writing of its determinations as detailed in Section V, FO, 501. Copies of all correspondence between the IRB and the investigator will be filed in the appropriate research project file.

Regardless of the type of review (approved as exempt, expedited or reviewed at a convened IRB meeting), the investigator is notified in writing of the IRB's and R&D Committee's determinations:

1. Approval, disapproval, or require modifications
2. Explanation and delineation of all modifications and clarifications required
3. Reasons/regulatory criteria for approval or disapproval

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.

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

C. Report to the Chief of Staff

The RACC 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 VI, RR 602, E.

The IRB Chair and/or the ACOS/R&D will provide prompt written notification to the Chief of Staff of suspensions and terminations of IRB-approved research projects and of any unanticipated problems involving risks to subjects or others and the resolution of those problems.

D. Report to the Privacy Officer and Information Security Officer

The RACC, 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.

E. Report to the Medical Center Director

It is the responsibility of the IRB Chairs and/or the ACOS/R&D to provide prompt written notification to the Medical Center Director of suspensions and terminations of IRB approved research projects and of any unanticipated problems involving risks to subjects or others and the resolution of those problems. This does not include expirations of IRB approval.

F. Reports to Outside Agencies

It is the responsibility of the IRB Chairs and/or the ACOS/R&D to provide prompt written notification to relevant Federal agencies, including ORO, OHRP, FDA (for FDA-regulated research reporting requirements, see FO 1001 of this SOP) VA Privacy Office and VHA ISO (in the case of loss of data security or privacy of research subjects), of suspensions and terminations of IRB-approved research projects; of any unanticipated problems involving risks to subjects or others and the resolution of those problems; and of serious or continuing non-compliance with HRPP and IRB policies and procedures. Such reports shall be done as soon as possible and within designated timelines of each agency (see below, item H.2). The PVAMC will report information at the discretion of the R&D Committee, regarding the protection of human subjects in research consistent with the ORO Memorandum dated November 12, 2003, and other regulatory requirements. This does not include routine study closures, study completions or expirations in IRB approval.

G. Report Process

The RACC 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. Inform ACOS/R&D of the need and reason for a report.
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).

H. Timelines for Reporting to the IRB, R&D Committee, and outside Regulatory Agencies **See RR 602, item G.2.**

FO 506

Appeal of IRB Determinations (38 CFR 16.109(d))

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 for those items requiring a signature (such as a revised initial review questionnaire), but may submit other revisions electronically to the IRB Coordinator. A time frame and format for response will be provided on the IRB correspondence based on the nature of the requested response.

In such cases as there is a dispute between the IRB and the PI regarding required modifications to the protocol or other parts of the IRB application which cannot be amicably resolved between the parties involved, an appeal to the R&D Committee may be made by either the PI or the IRB.

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.

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 subjects research and whether it should be submitted to the IRB for review and approval, should direct the question in writing to the IRB Coordinators. Once received, the IRB Coordinators 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 Coordinators for a documented response to the individual's questions.

FO 508

Audits of Research Protocols or Study Procedures

The IRB or designee may audit a research protocol or study procedures at any time for any reason. The IRB will maintain documentation that such an audit occurred, the result of the audit, and, if a response was required from the principal investigator or other designated person, the response generated.

Continuous Quality Improvement audits are conducted consistent with HRPP Policy “Continuous Quality Improvement in the Human Research Protection Program” available on our website:
<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>.

RR 601

Initial Review by the Convened IRB (38 CFR 16.103(b)(4) and 21 CFR 56.108-109)

Unless determined to be exempt from IRB review, all human subjects 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 and by the R&D Committee prior to initiation. No human subject research may be initiated or continued at the PVAMC by employees or agents without the appropriate approvals of both the IRB and R&D Committee.

Both the IRB and R&D Committee must grant final approval to a proposed research project prior to initiation of the research project. An investigator must have received all final written approvals from all applicable subcommittees and the R&D Committee, prior to beginning the research.

During initial review, the IRB reviews proposals for research involving human subjects submitted by investigators. The purpose of initial review is to ensure compliance with existing Federal laws and regulations for the protection of human subjects. The IRB has the authority to disapprove, require modifications to secure approval, and approve research protocols 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.

At the meeting the IRB, led by the primary reviewer(s), will (1) review and discuss 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 may attend the meeting at the invitation of the IRB. The Principal Investigator may answer questions or provide additional clarification, but may not be present during deliberations or voting on the proposal.

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 can submit their written comments to be read at the meeting, as long as another reviewer is present to serve as a primary reviewer.

At the time of initial review, the IRB 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 staff to assist in determining the risk level and risk:benefit ratio and ensuring the information provided meets appropriate guidelines.

Members of the IRB vote upon the recommendations made by the reviewers according to the criteria for approval in Section VI, RR, 603 & 604. A majority of voting members present must vote in favor of an action for that action to be accepted by the IRB. Only regular members, or in their absence alternate member(s), may vote. A record of the vote will be recorded in the minutes, as indicated in Section V, FO 501, M.

A. Initial Review Process: These guidelines should be followed in the conduct of the initial review of all proposals:

The primary reviewers should lead the discussion by presenting their findings and recommendations resulting from the review of the application materials.

1. Review of the Protocol: The proposed protocol will be reviewed by the primary reviewers and the abstract will be reviewed by the full IRB to determine if the research project meets the criteria for approval in Section VI, RR, 603 & 604. Recommendations for protocol modifications will be made by the primary reviewers and voted upon. The reviewer should complete the IRB Primary Reviewer

Summary to document that each of the specific criteria for approval have been met. All IRB Primary Reviewer Summaries will then be filed in the appropriate research project file.

2. Review of the Setting: If the study is a multi-site study, the IRB at each center must approve the study and provide contact information for each site. Investigators must promptly report any items listed in item G.1. of RR 602 “Ongoing Review” in this SOP. If the PVAMC investigator is the lead investigator in a multi-site study, all unanticipated problems involving risks to participants or others, interim results, and protocol modifications must be reported to the IRB. The IRB will evaluate whether the management of information relevant to the protection of participants among sites is adequate.

3. Review of the Informed Consent Form: All IRB members are provided a copy of the proposed informed consent form. The IRB will determine if it meets the criteria outlined in Section VIII, IC, 801 N-P. The IRB may approve consent forms with minor changes only at the meeting. Such changes will be reviewed and approved by the primary reviewer and/or IRB Chair. If substantive modifications are required the consent form must be reviewed again by the convened IRB prior to approval.

4. Review of Requests for Waiver/Alteration of Consent or Waiver of Documentation: All IRB members are provided a copy of the 1) Request for Waiver Or Alteration Of Informed Consent Process And Waiver Of Authorization To Release Medical Records Or Health Information Or 2) Request For Waiver Of Informed Consent Documentation And Waiver Of Authorization To Release Medical Records Or Health Information, if applicable. The IRB will determine if it meets the criteria outlined in Section VIII, IC 801, L or M. The IRB may approve the request for waiver of informed consent requirements and HIPAA Authorization or contingent on only minor changes at the meeting. Minor changes will be reviewed and approved by the primary reviewer and/or IRB Chair. If substantive modifications are required, the form must be reviewed again by the full IRB prior to approval.

5. Review of the Initial Review Questionnaire: All IRB members are provided a copy of the IRQ. The IRQ captures essential information required for the IRB review and approval. The IRB primary reviewers are responsible for ensuring that this form is completed appropriately and in its entirety. Any concerns regarding the IRQ will be commented on at the convened IRB meeting and documented in the correspondence to the principal investigator.

6. Review of the IRQ Attachments: All IRB members are provided a copy of the other IRB forms complementing the IRQ. These forms may include the: Investigational Device Information Record, Investigational Drug Information Record (VA Form 10-9012), FDA Form 1572, Human Biological Specimens Questionnaire, and Human Biological Specimens Memo of Understanding. Any concerns, regarding the IRQ attachments will be commented on at the convened IRB meeting and documented in the correspondence to the principal investigator. The reviewer will verify that IND or IDE numbers are valid based on the following documentation:

- Commercial sponsor protocol with the IND or IDE #;
- Written communication from the commercial sponsor noting the IND or IDE #;
- Written communication from the FDA noting the IND or the IDE #.

Note: If the investigator holds the IND or IDE, the only acceptable form of verification is written communication from the FDA.

The reviewer will also determine if a device fulfills requirements for an abbreviated IDE or one of the IDE exemption categories based on the regulatory requirements from 21 CFR 812.2 (see FD 1001 C., page 122, of this IRB SOP) or if a drug fulfills requirements for an IND exemption based on the regulatory requirements from 21 CFR 312.2 (see FD 1001 C., page 12).

When the PVAMC or investigator holds the IND or IDE, the IRB will evaluate, based on the applicable IRQ Appendix C or E, whether the investigator is knowledgeable about and able to follow FDA

regulatory requirements for sponsors. If no IRB member has expertise in this area enough to make this determination, an outside consultant with the necessary expertise will be asked to review the IRB submission.

7. Review of the HIPAA Forms: All IRB members are provided a copy of any submitted HIPAA forms complementing the IRQ. These forms may include the: Application for a Partial Waiver of Authorization for Screening/Recruitment Purposes, and the De-Identification Certification Forms. Any concerns, regarding the HIPAA Forms will be commented on at the convened IRB meeting and documented in the correspondence to the principal investigator.

8. Protection of Vulnerable Populations: If the research study proposes to recruit vulnerable populations of subjects, the IRB will review, discuss, and/or require modification to secure approval of the investigator's plan for minimizing undue influence on vulnerable subjects in accordance with Section VI, RR, 603, I.

9. Protection of Privacy and Confidentiality: Privacy refers to the right of an individual to control access to themselves and his/her personal information and not have it divulged or used by others without his/her permission. Confidentiality is at issue once an individual's personal information has been received by another entity. Confidentiality is a means of protecting that information, usually by safeguarding it from unauthorized disclosure. Privacy concerns people, whereas confidentiality concerns data. Security applies to the spectrum of physical, technical and administrative safeguards that are put in place to protect the integrity, availability and confidentiality of information and thus the privacy of the individual.

The IRB will determine whether there is an appropriate plan to protect the privacy of participants and the confidentiality of research data and health information that may include coding, removal of identifying information (in order to protect personally identifiable information), limiting access to data, use of Certificates of Confidentiality, waiver of documentation of consent, physical or computerized methods for maintaining the security of stored data, or other effective methods. The IRB will evaluate the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research and the effectiveness of the proposed methods. The IRB will also determine whether methods used to identify and recruit and obtain information about potential participants protect subject privacy and confidentiality of information and whether the informed consent form adequately discloses the risks to privacy and confidentiality. The IRB may require that the investigator obtain a Certificate of Confidentiality if it determines that special protections are needed to protect subjects from the risks of investigative or judicial processes. The IRB will ensure that the required language for a valid authorization to release health information under HIPAA is included as part of the informed consent document(s), or in the HIPAA Authorization if separate from the informed consent. The IRB may waive the requirement for an authorization or may alter the form or content of the authorization as permitted by HIPAA and described in the HRPP "Health Insurance Portability and Accountability Act (HIPAA) Human Subjects Research Policies and Procedures" (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>). These actions and their justification will be documented in the IRB minutes.

10. Conflict of Interest: If a conflict of interest has been identified, 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.visn20.med.va.gov/portland/research/hrpp/index.htm>) for more information, regarding how conflicts of interest are identified and managed.

11. Payment to subjects: The IRB will determine whether proposed payments to subjects are appropriate and do not represent an undue influence on the trial subjects as determined in Section VI, RR, 604, F.

12. Recruitment Incentives: The IRB will determine whether or not recruitment incentives to the investigator from a sponsor may create undue influence to recruit patients for a study and are reasonable in relation to the work being performed as described in Section VI, RR, 604, F. Bonus or “finder’s fee” payments to investigators or to the institution in excess of reasonable costs incurred for a study are not allowed at the PVAMC.

13. Review of Advertisements and Recruitment Methods: Members will review the content of all submitted proposed advertisements, proposed recruitment methods, and all other written material to be provided to subjects.

All IRB members are provided a copy of any submitted advertisements. The primary reviewer may complete the Advertisement Primary Reviewer Checklist to document that each of the criteria in Section VI, RR, 604, D for approval have been met. All completed Advertisement Primary Reviewer Checklists will then be filed in the appropriate research project file.

14. 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 of unanticipated problems/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 VA is the only site. For studies that have a Data Safety Monitoring Board (DSMB), the research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects.

15. Placebo-Controlled Studies: At the time of initial review, Principal Investigators should complete the PVAMC Checklist for Placebo-Controlled Studies, if their study involves a placebo-controlled design. The completed checklist will be distributed to the IRB primary reviewers. During the review and consideration of the research project and placebo-control study design, the convened IRB will discuss and complete the PVAMC Checklist for Placebo-Controlled Studies.

B. 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 in the most rare of circumstances.

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 the IRB recognizes that such research requests will be rare and most typically under the oversight of the National Institute of Health (NIH) or other federal regulatory agency. Even in these rare cases where research may be conducted in a foreign country, the principal investigator will be required to demonstrate approval of a federal agency for the research study, and demonstrate local foreign approval.

C. Approval of Modifications Required to Secure 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 Coordinators will contact the PI to remind them about their contingencies and to determine whether or not the PI will be submitting the contingencies or terminating the study.

This deadline may be extended up to another three months for a total of six months, provided that the investigator keep 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, this will require the investigator to submit the study as a new protocol for full review if they intend to pursue IRB approval.

The IRB will consider exceptions to this policy in extraordinary circumstances that may be out of the investigator's control. These circumstances may include: awaiting word regarding funding status, or awaiting changes being made by the sponsor, which may extend the time that an investigator needs to make required modifications.

RR 602

Ongoing Review

A. 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 (see timeline in section FO 505) for review by the IRB. The proposed modifications should be submitted to the Research Service office with the “Project Revision/Amendment Form” (PR/AF) available online at http://www.visn20.med.va.gov/portland/research/p-i-services/rd_forms.htm#alphabetical. These modifications will be reviewed by the Primary Reviewer System, presented to and voted on at the full IRB at the convened meeting. The Primary Reviewer and all IRB members will receive the “PR/AF,” most current IRB approved consent form, 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.

Approval of modifications that affect one or more regulatory criteria will be based on regulatory criteria. 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. To ensure such changes are reported promptly and are not initiated without IRB approval, the IRB will verify at the time of continuing review that no unapproved changes have occurred since the last IRB review. The RACC will also report any unapproved changes found during random CQI audits.

B. Violations/Deviations to IRB Approved Research Protocols

1. Review of Violations/Deviations from the IRB Approved Protocol

A violation/deviation can be any unplanned or unapproved research activity that is committed or omitted contrary to the terms of the IRB-approved research.

The IRB presumes that what is occurring in the implementation of protocol procedures is consistent with what was approved by the respective committees. However, the committees recognize that deviations and exceptions to approved IRB protocols may occur. A deviation/violation is defined as any change to the IRB approved protocol and/or procedures without prior IRB notification and approval (modification). The cause of the deviation/violation may be within the investigator’s control (e.g., change a protocol procedure or medication), or may not be in the control of the investigator (e.g., a subject fails to show-up for a procedure defined in the protocol). All changes to the IRB approved protocol must have prior approval of the IRB. Any non-approved change is a deviation/violation. It is the responsibility of the Principal Investigator to notify the IRB of all protocol deviations/violations (see timeline in section FO 505). The IRB will review to determine whether each deviation/violation was 1) non-compliance, 2) was an unanticipated problem involving risks to participants or others and 3) whether the deviation/violation was consistent with ensuring the participants’ continued welfare.

2. In regards to violations/deviations, the FDA regulations at 21 CFR 56.108 (a) (3-4) state that, “In order to fulfill the requirements of the regulation, each IRB shall follow written procedures:
 - (a) For ensuring prompt reporting to the IRB of changes in research activity and
 - (b) For ensuring that changes in approved research, during the period for which IRB approval has been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.”

C. Review of Non-Compliance in Human Research

The IRB will address any research-related complaints and allegations of non-compliance with HRPP and IRB policies, including undue influence of a participant or an IRB member, raised against a principal investigator or research staff.

Please see “Complaints and Allegations of Non-compliance Pertaining to Human Research,” <http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>, for more details concerning procedures.

D. IRB Continuing Review

(38 CFR 16.103(b)(4) and 109(e))

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. The IRB reserves the right to change the approval period at any time for any reason. 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, or the date of approval resulting from the expedited review process if expedited review was performed.

Investigators are notified in writing of the approval date and the expiration date at the time of final initial IRB approval. 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 V, FO, 504, B. The IRB employs the Primary Reviewer System at the time of continuing review.

1. During the continuing review, the IRB reviews the following and determines whether any involved an unanticipated problem involving risks to participants or others:

- (a) changes to the research;
- (b) unanticipated adverse event reports, sponsor reports and safety reports, including IND, IDE and MedWatch;
- (c) reports of unanticipated problems,
- (d) data safety monitoring reports;
- (e) protocol violations /deviations;
- (f) significant new findings;
- (g) sponsor-imposed suspensions and device recalls; and
- (h) overall investigator non-compliance, including non-compliance with IRB requirements for frequency of periodic continuing review.

The IRB shall also determine 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 at 45 CFR 46.116(b)(5).

- 2. Approximately 90 days before the current approval for the research project expires the IRB Coordinator(s) send an e-mail notification of the IRB continuing review schedule and the continuing review form 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 Coordinator 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 VI, RR, 602, E.
- 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. The Principal Investigator must respond to the IRB contingencies by the date specified. If the Principal Investigator does not respond, s/he will receive a letter from the ACOS/R&D notifying the PI that s/he has violated the Investigator Assurances agreed to on the Initial Review Questionnaire. The IRB may administratively terminate the study.

E. Expiration of IRB Approval Period

(38 CFR 16.109(e))

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, or the date of approval resulting from the expedited review process if expedited review was performed. The date of expiration shall be calculated based on the date at which the IRB approved or contingently approved the protocol with modifications. The expiration date will occur on the last date that the protocol is approved. For example, if a protocol was approved on 06/06/2007 for a period of six months, the approval will expire 12/5/2007; if approval was for one year, approval will expire on 6/5/2008.

Per VHA ORD policy, if the 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 and RACC will be generated promptly by an IRB coordinator once s/he has determined the continuing review has not been submitted or stipulations of contingent approval have not been met and approval has lapsed.

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the suspension, the PI must immediately submit to the IRB chair through the RACC 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 RACC 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 the 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 lapsed less than or equal to 2 months, the items requested at the time of continuing review may be reviewed for consideration of continued IRB approval.

The Research Service will notify the COS as to whether or not the PI will be terminating or requesting re-approval of the research project by the IRB.

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.

F. Interim Reports

If the IRB determines that a study requires an Interim Report, the investigator may be asked to submit a Continuing Review Questionnaire by a specified date, upon enrollment of a specified number of subjects, or upon reaching a specified point in the study. If interim reports are not received as scheduled, the IRB may suspend enrollment until reports are reviewed. The IRB will review the Continuing Review Questionnaire at a convened meeting, and may require modifications or take other actions within its authority. During a review of interim reports, the following must be considered:

1. Proposed changes (if any) to the research study and any accompanying changes to the informed consent form.
2. Unanticipated problem reports
3. Reports of unanticipated problems impacting the risks to subjects
4. Summary of data safety monitoring board (DSMB) reports (if available)

5. All protocol violations/deviations
6. Overall investigator compliance

G. Review of Reports of Unanticipated Problems, including Non-Compliance

This covers any unexpected problems (see definition of “Unanticipated Problem” on page 12 of this SOP) including those involving risks to patients and unanticipated adverse events (21 CFR 312.66), as well as Safety Reports, IND, IDE and Medwatch Reports and non-compliance.

All investigators conducting research as employees or agents in the PVAMC or under VA auspices are required to notify the IRB of all problems listed below in item G.1. Principal Investigators are also required to report promptly to the IRB any unanticipated adverse event (AE) that is reported to ORO, OHRP or the FDA and/or the sponsor in accordance with FDA requirements.

To ensure compliance with all regulatory and policy requirements, ORO recommends adherence to the broad definition of AEs found in VHA Handbook 1058.1§5.a. where an AE is defined as “any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research” and where “the imminent threat of an AE” is included as a reportable event (VHA Handbook 1058.1§6.a.).

1. Types of adverse events and unexpected problems that must be reported (VHA Handbook 1058.1§6.a.). (ORO Memo December 6, 2006)

- (a) Any unanticipated deaths¹
- (b) any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research and where “the imminent threat of an AE” is included as a reportable event
- (c) Any research-related problems **involving risks** not anticipated in terms of nature, severity, or frequency of occurrence (as documented in the protocol, consent document, or other materials approved by the IRB). Both **risks to subjects** and **risks to other individuals** (e.g., research personnel, subjects’ family members) are included. Risks may reflect any type of potential harm (e.g., physical, psychological, social, economic). Some problems may not necessarily be adverse events.
- (d) Loss of VA-Sensitive Information, Potential Loss of Subjects’ Privacy: Investigators must inform the IRB and the Privacy Officer of any loss of VA-sensitive information, i.e. any information stored either electronically or on paper with individually identifiable information the loss of which could result in a loss of privacy for a human subject. Such loss shall be reported as soon as possible after discovery. In the event of suspected theft of such items, the investigator shall notify VA security immediately upon discovery. *Examples:* 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.
- (e) Allegations and Findings of Non-Compliance: Investigators and research staff must report all allegations and findings of non-compliance with applicable regulatory requirements or with the determinations of the IRB to the IRB.
- (f) Changes in approved research implemented to eliminate immediate hazards to subjects
- (g) All protocol deviations/violations
- (h) All unanticipated device or drug effects, anything reportable to the FDA (see Section FO 1001 in this SOP)
- (i) Unanticipated problems might also include events that are not a result of research procedures, for example, a new publication that indicates a change in risk and/or benefit related to the research, any change in FDA labeling, any breach of confidentiality. The following are possible examples:

¹ From VHA Handbook 1058.1: Unexpected death is defined as “The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject’s death. A subject’s death that is determined to be clearly not associated with the research is also not an “unexpected death” for purposes of the reporting requirements of this Handbook.”

- An interim analysis or safety monitoring 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.
- (j) More examples of reportable problems follow:
- A subject mistakenly receives twice the dose of an investigational drug than was stipulated in the protocol, but suffers no side effects and no indication of harm.
 - A subject receives one dose of active drug instead of placebo but suffers no side effects and no indication of harm.
 - A research assistant suffers a severe burn due to malfunctioning research equipment.
 - During an interview on children's play, a parent-subject confesses a continuing problem with child abuse. The protocol, consent document, and other materials approved by the IRB did not address how such situations would be handled.
 - The investigator receives a DSMB report indicating that researchers should look out for a particular side effect that may be occurring more frequently than anticipated.
 - The sponsor suspends new enrollments in a trial due to suspected manufacturing problems.
 - New studies in the published literature suggest that the drug being used in an investigator's research may be associated with a previously unknown risk of stroke.
 - Incarceration of a participant in a protocol.
 - Any other event that in the investigator's judgment is unanticipated and might affect risk and benefit of the research to participants or others.

2. **Timeline for Reporting Adverse Events and Unexpected Problems to the IRB**

Reports may be faxed to 503-273-5152 or hand-delivered to the R&D Office.

Investigators must report within the following timelines:

- (a) Changes in approved research implemented to eliminate immediate hazards to subjects: report to the IRB within five (5) working days of said changes.
- (b) All protocol deviations or violations to the IRB: report within 15 calendar days after recognition or notification.
- (c) All allegations and findings of non-compliance: report to the IRB promptly and no later than within seven calendar days.
- (d) Any loss of VA-sensitive information, i.e. any information stored either electronically or on paper with individually identifiable information the loss of which could result in a loss of privacy for a human subject.
 - Inform the IRB and the Privacy Officer as soon as possible after discovery.
 - In the event of suspected theft of such items, notify VA security immediately upon discovery.
- (e) Any unanticipated deaths¹ and life-threatening SAEs: report to the IRB within seven (7) calendar days of awareness for all subjects.
- (f) If the FDA withdraws the approval of an IND or IDE or if a study is suspended or terminated by the sponsor: report to the IRB within five (5) working days.
- (g) If the IRB withdraws approval, respond to notice from the IRB immediately with a list of subjects for whom suspension of the research would cause harm.
- (h) All other unanticipated problems: report to the IRB within 15 calendar days.

Reporting to organizational offices and external agencies (see FO 505, item G. for process facilitated by RACC):

- (a) Any unexpected death of a human subject under VHA Handbook 1058.1¹: report to PVAMC

¹ From VHA Handbook 1058.1: Unexpected death is defined as "The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's

ACOS R&D, COS, Director, and ORO through Western Regional Office:

- within 24 hours of the IRB's determination that the death was unexpected or
 - within 10 working days if the IRB has not yet made a determination about whether the death was unexpected.
- (b) Any unanticipated problem involving risks to subjects or others (NOTE: item c. indicates further requirements):
- (1) Report promptly, no later than 10 working days after IRB determination, to:
- PVAMC ACOS R&D,
 - PVAMC COS
 - PVAMC Director
 - PVAMC Privacy Officer and Information Security Officer (if problem involved unauthorized use, loss, or disclosure of individually identifiable patient information),
 - sponsors,
 - ORO through Western Regional Office,
 - VA Office of Research & Development (ORD),
 - VA Central Office (when report involves and adverse event), and
 - OHRP promptly, no later than 10 working days after IRB determination
 - other Federal agencies as appropriate, e.g., funding agencies. (VHA Handbook 1200.5)
- (c) Any suspension or termination of VA human subject research by the IRB, the VA facility, or a VA affiliate institution:
- (1) Report to ORO through Western Regional Office as soon as possible, but no later than 10 working days after the issue has come before the responsible facility official or oversight committee.
- (2) For FDA-regulated studies, see Section FD 1001, items H., I., and J. of this SOP and 21 CFR 56.108(b)(3).
- (3) Report to PVAMC Officials as soon as possible, but no later than 10 working days after the issue has come before the responsible facility official or oversight committee.:
- ACOS
 - COS
 - Director
- (4) Report as soon as possible, but no later than 10 working days after the issue has come before the responsible facility official or oversight committee to:
- sponsors,
 - ORD,
 - VA central Office (when the event relates to an adverse event), and
 - other Federal agencies as appropriate. (VHA Handbook 1200.5)
- (5) Report to OHRP promptly, no later than 10 working days after event.
- (d) Any serious or continuing noncompliance with IRB requirements, federal regulations, or VHA policies for the protection of human subjects:
- (1) report to ORO through Western Regional Office
- (2) Report as soon as possible, but no later than 10 working days after the issue has come before the responsible facility official or oversight committee to:
- PVAMC ACOS
 - PVAMC COS
 - PVAMC Director
 - Sponsors

death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of this Handbook."

- VA Central Office, and
 - other Federal agencies as appropriate. (VHA Handbook 1200.5)
- (3) Report to OHRP promptly, no later than 10 working days after event.
- (e) Subsequent information and determinations related to items above: provide promptly to appropriate officials and agencies reported to earlier.
- (f) Any change in the facility's accreditation status from a VA-recognized accreditation organization for human research protections, or in the accreditation status of an affiliate institution or other VA facility upon which the facility relies: report to ORO through Western Regional Office as soon as possible, but no later than 10 working days after the issue has come before the responsible facility official or oversight committee.
- (g) Any change in the facility's Federalwide Assurance (FWA) or designated IRB(s) as filed with OHRP: Report such changes directly to ORO Central Office and simultaneously copy the ORO Regional Office as soon as possible, but no later than 10 working days after the issue has come before the responsible facility official or oversight committee.

3. Contents of Report

The contents of the report must include

- Study Information: Title, PI, VA IRB#, Sponsor/award #, IND/IDE#
- Number of subjects enrolled to date and currently actively involved in research procedures.
- Date of UP, Date notified of UP
- Classification as VA Adverse Event, Non-VA Adverse Event, different protocol event or Other Unanticipated Problem
- Participant ID, if applicable
- Description of event and analysis as to why the event represents a “problem” for the study and why it is “unanticipated.” For instances of increased frequency or severity, it must state how the frequency or severity diverges from the expected.
- Agent involved if applicable (for example, drug, device, placebo)
- Relationship of the agent or research procedures to the UPR.
- Basis for UPR determination.
- Response Plan. Description of proposed actions, including modifications, to be taken by investigators in response to the UPR.

4. Applicability

These guidelines apply to unanticipated problems/adverse events and or non-compliance occurring at any site. However, for large multi-site clinical trials involving a coordinating center, unanticipated adverse events occurring at other sites may be reported consistent with the study sponsor's coordinating center policy, with the exception of adverse events occurring at Oregon Health & Science University and the PVAMC which should be reported directly to the PVAMC IRB.

5. Review of reports by the IRB (including problem reports, allegations of non-compliance, and findings of non-compliance)

An IRB Chair or alternate chair reviews each report.

(a) Non-Compliance:

If the report involves an allegation of non-compliance (see definition, page 12 of this SOP), the reviewer evaluates whether there is a basis in fact. The reviewer may request an investigation by the RACC or the ACOS/R&D to obtain additional information.

- If there is a basis in fact, the report is considered a finding of non-compliance; the reviewer then further considers as detailed below under (b) **Unanticipated Problems Involving**

Risks To Participants Or Others and determines whether the non-compliance is serious or continuing (see definition in this SOP, page 12). The reviewer may request an investigation to obtain additional information.

- If there is no basis in fact for non-compliance, the reviewer makes no further considerations with regard to non-compliance, but continues to make the considerations below under (b) **Unanticipated Problems Involving Risks To Participants Or Others**.

(b) **Unanticipated problems involving risks to participants or others:**

The reviewer evaluates whether the problem is:

- (1) Unexpected; AND
- (2) Indicates if participants or others are at increased risk of harm.

- If the answer to both questions is yes, the convened IRB reviews the report as in **Convened IRB Review** below.
- Otherwise, no further action is taken under this policy.

At any time during the above review, the IRB chair may order a suspension of IRB approval in accordance with the IRB SOP in this section, item L., on suspension and termination of IRB approval.

(c) If the IRB chair, alternate, or RACC acting as reviewer determines that non-compliance is neither serious nor continuing, the reviewer works with the investigator to develop an appropriate corrective action plan.

(d) The convened IRB reviews all non-compliance determined by the IRB chair, alternate, or RACC to represent serious or continuing non-compliance and all reports determined by the IRB chair, alternate, or RACC to represent an unanticipated problem involving risks to participants or others.

(e) **Convened IRB Review:**

IRB staff assign a primary reviewer to review and present the unanticipated problem involving risk to participants or others or the serious or continuing non-compliance at the next convened IRB meeting.

All IRB members are provided copies of the following and are expected to review this information in advance of the meeting:

- The report
- The results of any investigation.
- The Initial Review Questionnaire and (if applicable) most recent Continuing Review Questionnaire, updated with any changes.
- The protocol summary.
- The current approved consent document.
- Any other relevant information, e.g., investigator's brochure for drug studies.

The IRB will consider the following actions:

- Modification of protocol
- Modification of information disclosed during consent

- Providing of additional information to past participants
- 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

H. Review of Adverse Event or Safety Reports in Sponsored or Cooperative Group (Multi-center) Projects

The IRB review of such reports is handled in the same manner as internal reports of unanticipated problems or adverse event as detailed in Section VI, RR, 602, G above, unless otherwise stated in the research project and approved by the IRB.

I. Review of Data and Safety Monitoring Board (DSMB) Reports

Data and Safety Monitoring Board Reports should follow the guidelines noted above (G.). The IRB Chairs will perform an initial review of all reports, and take action as needed, based on the nature of the report. If immediate action is not needed, a primary reviewer will be assigned for review at the next IRB meeting, and results will be noted in the IRB minutes.

When DSMBs are used, as indicated on the IRQ, the IRB may rely on a current statement from the DSMB indicating that it has reviewed 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. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its ongoing review is substantive and meaningful.

K. Review of Study Termination Reports

The IRB reviews and acknowledges study termination reports upon receipt from the investigator. Investigators are to submit a notice of study termination to the IRB Coordinator upon completion of the research project. The notice should be submitted on the “Research Project Termination Report” form. However, if at the time the continuing review paperwork is submitted to the IRB, the CRQ indicates that the study is terminated, then it is reviewed as a research project termination.

Premature completion of a research study shall be reported as soon as such completion occurs through a “Research Project Termination Report.”

L. Suspension or Termination of IRB Approval of Research

(38 CFR 16.113)

If the IRB determines there is an unexpected problem involving risk to participants or others or that there is serious or continuing non-compliance after review of reported problems, 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 the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

Where the IRB Chair determines that such action is necessary to ensure the rights and welfare of subjects, the chair 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.

In the event of any suspension or termination of approval of research, the IRB or the IRB Chair (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; or
5. Require continuation of the participant in the research under independent monitoring.

RR 603

Required Criteria for IRB Approval of Research

The IRB shall determine the following during the initial and continuing review and approval of research, as stated in the Department of Veterans Affairs, Department of Health & Human Services, and Food & Drug Administrations regulations.

A. Risks to Subjects

(38 CFR 16.102(i) and 110)

The IRB must consider the overall level of risk to subjects in evaluating proposed research during the initial and continuing review of the research. The IRB identifies the risks to the subject. These risks are 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 regulations require that the IRB distinguish research that is greater than minimal risk from research that is no 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.

The IRB uses the following criteria for determining whether or not the risks to the subjects are minimal: under VA regulations at 38 CFR 16.102(i), “**minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

The IRB must review and approve a data safety monitoring plan to ensure the safety of participants.

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.

B. Risks Minimized (38 CFR 16.111(a)(1))

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

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, including co-investigators, collaborators, and study coordinators. In addition, in all studies that are outside the PI's medical specialty, the PI must designate a co-investigator or collaborator with expertise in the relevant medical specialty being studied. This co-investigator or collaborator will be in charge of all patient 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 patient's electronic medical record.

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

The Research Service staff verifies that individuals listed on the IRQ that will be working on the research project at the VA have completed the appropriate credentialing requirements, consistent with “Credentialing of Personnel Involved in Human Studies Research”

(<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>).

C. Risks Reasonable Relative to Anticipated Benefits (38 CFR 16.111(a)(2))

To approve research, the IRB must determine at the time of initial and continuing review 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 considers the following types of risks: physical, psychological, and social/economic and determines the level of risks of the research. Probable individual and societal benefits of the research are also considered.

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

D. Equitable Selection of Subjects (38 CFR 16.111(a)(3))

The IRB determines by viewing the IRQ, protocol and other research project materials that the 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 person who might benefit from the research.

This is the concept of “Justice” from the Belmont Report. In making this determination, the IRB evaluates: the purposes of the research; setting in which the research occurs; scientific and ethical justification for including 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.

E. 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 (see 38 CFR 16.116), 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 (38CFR16.116). These circumstances are described in Section VIII, IC, 801.

F. Documentation of Informed Consent (38 CFR 16.117)

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. Requirements for informed consent and documentation are described in Section VIII, IC, 801, C.

G. Review of Plans for Data and Safety Monitoring (38 CFR 16.111 (a)(6))

To approve research, the IRB determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. For research in which risks are substantial, the IRB may require a detailed description of the data and safety-monitoring plan to be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting unanticipated problems involving risks to subjects or others (UPRs).

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 has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed.

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.

H. Privacy of Subjects and Confidentiality and Security of Data (38 CFR 17.33(a) and (b))

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.visn20.med.va.gov/portland/research/hrpp/index.htm>). 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 patient information. Individuals must have prior approval by the IRB before receiving individually identifiable patient 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 patient 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 assesses whether adequate provisions exist to protect subject privacy and maintain confidentiality. 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. 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, the Data Security Checklist for Principal Investigators, and/or other submitted materials. The IRB coordinators will assure the Data Security Checklist for Principal Investigators has been reviewed and approved by the Privacy Officer, Information Security Officer, and ACOS/R&D or his designee.

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.

I. Additional Safeguards for Vulnerable Subjects

(38 CFR 16.111(b) and Handbook 1200.5)

For additional information regarding vulnerable subjects, please review Section VI, RR, 605 & 606.

The IRB carefully reviews at its convened meetings studies that include vulnerable subjects. The PVAMC considers the following subjects vulnerable: minors (children), fetuses, prisoners, pregnant women, mentally impaired, or 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.

To approve research, the IRB determines that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence. This includes but is not limited to research with children (45 CFR 46 Subpart D), prisoners (45 CFR 46 Subpart C), pregnant women (45 CFR 46 Subpart B), persons with mental disabilities, or economically or educationally disadvantaged persons. The PVAMC does not conduct research with children, prisoners or fetuses and the PVAMC IRBs do not review research involving these vulnerable populations.

Additional Considerations During IRB Review and Approval of Research

A. 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 patient care. The IRB will decide at initial review whether such a research flag must be activated in the patient's CPRS electronic medical record, and require assurance 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 patient know that they are participating in a research study. 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.

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 and R&D Committee. The VA electronic medical record is programmed such that when patients with electronic record flags make scheduled or unscheduled visits to the medical center and clinics, the patient information display will show a screen with the established type of flag advisory highlighted.

The IRB Coordinators will notify the Principal Investigator and study coordinator when the flag is ready to be applied. As patients are enrolled into the research protocol, the Principal Investigator will obtain a signed informed consent and apply the medical record flag to the patients' electronic medical records. The PI is responsible for activating the research flag immediately following the informed consent process with a patient. 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 patient withdraws or participation ends prior to the termination of the study.

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

B. Criteria for Requiring Review More Often than Annually

(38 CFR 16.103(b)(4)(ii))

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:

12. Probability and magnitude (degree or risk) of anticipated risks to subjects.
13. Likely medical condition of the proposed subjects.
14. Overall qualifications of the principal investigator and other members of the research team.
15. Specific experience of the principal investigator and other members of the research team in conducting similar research.
16. Nature and frequency of adverse events observed in similar research at this and other facilities.

17. Vulnerability of the population being studied.

18. 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.

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

(VHA Handbook 1200.5)

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 that 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.

D. Advertisements

The IRB 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.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (e.g., free health exam).

E. Recruitment Incentives

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.visn20.med.va.gov/portland/research/hrpp/index.htm>).

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

F. Payment to Research Subjects

(VHA Handbook 1200.5, 12)

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 patients in this situation.
2. **Others being paid.** In multi-institution studies, where patients 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 patient 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 patient 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.

G. Compensation for Injury
(38CFR16.116 (a)(6), 17.85)

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.

H. 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. This is rare in VA, however, in such situations the IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC).

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

The IRB may determine that an investigator should request a certificate of confidentiality from the National Institute of Health (NIH) in cases when the information gathered for the research could be held against the research participant in a court of law. An investigator applies for a certificate of confidentiality through the NIH. The NIH will review the application and make a determination as to whether or not a CoC may be granted for the specific research project.

According to the NIH, if an investigator has submitted a CoC application to the NIH, recruitment of research subjects may begin prior to receiving a final determination from the NIH. If the NIH grants a CoC 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>.

I. 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 subjects 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.

J. 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 patient remains minimal.

K. IRB Considerations of Conflict of Interest

Please see the PVAMC “Conflict of Interest in Research” Policy (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>) 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 R&D Committee.

L. Principal Investigator Expertise

Studies which go beyond the individual expertise of the principal investigator into other medical generalist or specialty areas may require that the principal investigator make certain that s/he has identified a qualified co-investigator or collaborator who will be in charge of patient safety. Such patient safety issues here include: making certain that abnormal laboratory/study results are reviewed in a timely fashion, patients are contacted about abnormal laboratory/study results in a timely fashion, and the abnormal laboratory/study results that could result in any patient injury are acted upon in an expedited manner. 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 patient safety of follow-up of abnormal laboratory/study results. The co-investigator and collaborator will also be responsible with making all relevant communication to the patient's primary care provider about any new abnormalities of a moderate or severe nature and recording the same abnormalities in the patient's electronic medical record.

M. Credentialing and Education Verification for New Human Subjects Research Projects

The RACC will verify new human subjects 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 Subjects Research” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>)

N. Participation of Non-Veterans as Research Subjects

(VHA Handbook 1200.5, 16)

According to VHA Handbook 1200.5, non-veterans may be entered into VA approved research studies only when there are insufficient veterans available to complete the study in accordance with 38 CFR 17.45 and 38 CFR 17.92.

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.

O. 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.

In the research plan, the investigator must clearly indicate on the IRQ, whether the research project involves any x-ray or radioactive materials. The PI must indicate the procedures, frequency and purpose. The PI must also determine if the procedures are those which the patient 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:

1. 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.
2. 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.
3. 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.

RR 605

Review of Research Involving Potentially Vulnerable Subject Groups

(VHA Handbook 1200.5 <http://www.research.va.gov/programs/pride/policy/default.cfm>)

A. Vulnerable Populations

Vulnerable populations as listed in the Federal regulations include

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

B. Pregnant Women and Fetuses as Vulnerable Populations

The Department of Health and Human Services (DHHS) regulations at 45 CFR Part 46, Subpart B 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 1200.5, 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 1200.5, 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 VI, RR, 605, F;
2. Determine that adequate provision has been made to monitor the risks to the subject and the fetus.
3. 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
 - i. Any decisions as to the timing, method, and procedures used to terminate the pregnancy;
 - ii. Determining the viability of the fetus at the termination of the pregnancy.
 - iii. 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. Prisoners as a Vulnerable Population in Research

The PVAMC does not conduct research involving prisoners.

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 (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as 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>.

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

The PVAMC does not conduct research involving minors (children).

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 (see 45 CFR Part 46, Subpart D 46.401 – 46.409, Additional Protections for Children Involved as Subjects in Research). **NOTE:** For requirements for requesting a waiver, the Research Office will contact VA Central Office.

E. Mentally Disabled or Those Persons With Impaired Decision Making Capacity as a Vulnerable Population in Research

Policies regarding research involving mentally disabled or those persons with impaired decision making capacity are described in Section VI, RR, 606.

F. Elements to Consider in Reviewing Research Involving Vulnerable Subjects

Department of Veterans Affairs (VA) regulations at 38 CFR 16.111 (b) 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.

RR 606

Review of Research on Human Subjects Likely to Need Surrogate Consent (VHA Handbook 1200.5, 11)

In all cases, the IRB takes special care to consider issues such as the selection of subjects, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human subjects research as set forth in the Belmont Report. Capacity should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. In cases where research involving cognitively impaired individuals is approved, the IRB may require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

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.

A. IRB composition

1. The IRB membership must include at least one member who is an expert in the area of the research. 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, 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. Conditions of Approval

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. **Only incompetent persons are suitable**
Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
2. **Favorable Risk/Benefit Ratio.** The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
3. **Well-Informed Representatives.** Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent

subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

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.

C. IRB Documentation

The IRB must make a determination in writing of each of the criteria listed in Section VI, RR, 606, B. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives as defined below in Section VI, RR, 606, E.

D. 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.

E. Legally Authorized Representative

1. In instances where the subject may not be able to give consent for him/herself, the subject's ability to consent must be 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 page 9-10 of this SOP.

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.

F. Inclusion of subjects who may lack capacity for informed consent:

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.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

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.

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.

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.

G. 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 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. If the PI makes the initial judgment that the potential subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time, then this must be confirmed in consultation with the chief of service or Chief of Staff and must be documented in the person's medical record in a signed and dated progress note. Additionally, if the reason for lack of capacity is because of mental illness, then a psychiatrist or licensed psychologist must confirm this judgment and document in the individual's medical record in a signed and dated progress note.

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. Should the person object to participating, this objection should 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 SOP (see definition of Legally Authorized Representative on page 8). 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.

H. IRB Procedures

The IRB will document that all of the criteria listed in Section VI, RR, 606, B through G, above have been met. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision making capacity in research projects. In considering such studies, it is recommended that the IRB include at least one member who is familiar with the population to be recruited. The IRB is encouraged to utilize ad hoc members as necessary to assure appropriate expertise. The protocol should describe who will conduct the assessment, the method by which prospective subjects' decisional capacity will be evaluated, and the criteria for identifying incapable subjects. Less formal procedures to assess potential subjects' capacity may be permitted if a formal assessment is not feasible. Less formal procedures could include the ways professionals often make judgments about capacity in routine interactions.

The IRB has the authority to require review of the study at earlier intervals, to impose conditions on the use of surrogate consent or prohibit its use entirely, or to require additional reporting by the investigator.

EX 701

Expedited Review of Research (38 CFR 16.110)

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. 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 on the November 9, 1998, DHHS-FDA list of research eligible for expedited IRB review published in the Federal Register, 63 FR 60364-60367 (Section VII, EX, 703) 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.

The Chairs may review the expedited review request and research project or the Chairs may designate a qualified and experienced IRB member to complete the review of the request and research project. The qualified designee to review the request and research project must be a voting member of the IRB and have qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research expeditiously. 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.

EX 702

Expedited Review of Minor Changes in Previously Approved Research (38 CFR 16.110(b)(2))

VA regulations at 38 CFR 16.110, the Common Rule, and FDA regulations permit the IRB Chair or his/her qualified designee(s) to review research through an expedited procedure if minor changes are in previously approved research during the period (of one year or less) for which the approval is authorized. The expedited review and reviewer requirements are stated in Section VII, EX, 701, above. The individuals making this determination cannot be involved in the proposed research.

Approval of a **minor change by expedited review** may not involve the addition of procedures involving more than minimal risk or that do not fall into any of categories 1-7 for expedited procedures, in previously approved research. A minor change is one which, in the judgment of the IRB Chair or qualified designee, makes no substantial alteration in (1) the level of risks to subjects; (2) the research design or methodology; (3) the number of subjects enrolled in the research; (4) the qualifications of the research team; (5) the facilities available to support safe conduct of the research; or (6) any other factor which would warrant review of the proposed changes by the convened IRB.

Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in informed consent documents. The investigator may request an expedited review of minor changes in previously approved research. However, no changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects.

The fully convened IRB will be notified of all minor changes in 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 Service's 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.

EX 703

Expedited Initial and Continuing Review: Permitted Categories

A. Applicability of Expedited Review

Expedited procedures are used for initial and continuing review of research that is no greater than minimal risk **and** falls within the categories published in the November 9, 1998, Federal Register 63 FR 60364-60367. The IRB uses the following criteria for determining whether or not the risks to the subjects are minimal: under VA regulations at 38 CFR 16.102 (i), “minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” The categories for research projects eligible for expedited initial and continuing review are stated below. Even though a proposed research project may fall into the following categories, expedited review will be considered but is not guaranteed.

1. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
2. The categories in this list apply regardless of the age of subjects, except as noted.
3. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subject’s financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
4. The expedited review procedure may not be used for classified research involving human subjects.
5. The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

B. Permitted Categories of Research

All of the below criteria pertain to initial and continuing review of research projects. If a research study is initially approved in the expedited manner, then continuing review may also be expedited as long as the research continues to meet the criteria:

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 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 (a) an investigational device exemption application (21 CFR 812) is not required; or (b) 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.
 - c. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base 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.

3. 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.
4. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (*Note: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects at 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.*)
5. Collection of data from voice, video, digital, or image recordings made for research purposes.
6. 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 DHHS regulations for the protection of human subjects. 45 CFR 46.102(b)(2) and (b)(3). This listing refers only to research that is not exempt.*)
7. 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.
8. Continuing review of research that is **not** conducted under an investigational new drug application or investigational device exemption and where the categories for initial review (1)-(7) and continuing review (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.

IC 801

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 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**.

Informed consent is an ongoing process of information exchange between the prospective research participant and a trained individual conducting the consent process, not simply a signed consent form. The informed consent session must take place with the subject or his/her legally authorized representative **PRIOR** to conducting any procedures, unless the requirements of informed consent are waived by the IRB. 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 a witness. If a potential subject or legally authorized individual 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 patient ample time to consider and make his/her decision. The patient may contact the investigator or representative at a later time to agree to participate in the study and sign the formal document. Throughout the study, the investigator and his/her representatives should encourage the patient to ask questions at any time during procedures or study visits or to contact a research team member or investigator if a question arises between visits.

B. Circumstances of Informed Consent Requirements

(38 CFR 16.111(a)(4) and 38 CFR 16.116)

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 (see 38 CFR 16.116), 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 (38CFR16.116). 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.
 - (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 patients have rested overnight.
 - (d) No informed consent shall be obtained from a legally authorized representative if the patient is expected 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.
- 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. Documentation of Informed Consent

(38 CFR 16.117)

To approve research, the IRB must determine that informed consent shall be appropriately documented, on VA Form 10-1086, properly executed with appropriate signatures of the subject or legally authorized representative, witness, and person obtaining consent, date, time, and social security number as required by the IRB, unless documentation can be waived by the IRB under VA regulations, the Common Rule, or FDA regulations. IRB approval of the wording of the consent must be documented through the use of a stamp on each page of the VA Form 10-1086 that indicates the date of the most recent IRB approval of the document. The witness, except when informed consent is being obtained orally, is only witnessing the signature on the informed consent document and may not be involved in the research project at hand. 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 will be placed under the witness's signature line.

Informed consent must be obtained prior to entering a subject into a study and the conduct of any procedures required by the protocol, unless the informed consent requirement is waived by the IRB.

VA regulations at 38 CFR 16.117, the Common Rule, and FDA regulations provide two methods for documenting informed consent:

1. Written Informed Consent Document

Consent may be documented through use of a written consent document that embodies all of the required elements of informed consent (these elements are discussed in detail in Section VIII, IC 801 N-P). The VA 10-1086 consent document form shall be used and must be signed by the subject (or the subject's legally authorized representative), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated. This form may be read to the potential research participant or his/her legally authorized representative. The potential participant/legally authorized representative must be given adequate time to read the document and make a decision, regarding participation, prior to signing the informed consent document.

2. 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 written summary must embody the basic and required additional elements of disclosure.
- b. The IRB must approve a written summary of what is to be presented orally and the “short form” written consent document;
- c. There must be a witness to the oral presentation; the witness must speak both English and the language of the participant.
- d. The witness must sign both the “short consent form” and the written summary presented to the subject or legally authorized representative;
- e. Only 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.
- f. The person obtaining the informed consent must sign and date the written summary; and
- g. The participant or legally authorized representative must sign and date the informed consent.
- h. A copy of the signed and dated summary and the signed and dated “short form” must be given to the participant or the representative.

PVAMC policy requires the original signed consent documents for VA patients be forwarded to the Research Service within 72 hours of consenting the patient. The Research Service scans the consent form into the patient’s electronic medical record in the Computerized Patient Record System (CPRS). Informed consent forms for non-VA patients or for human subjects other than patients, e.g., caregivers, will not be scanned unless the research team arranges for a CPRS record to be created for those individuals. After the informed consent form is scanned into the patient’s electronic medical record, the original signed consent form will be returned to the Principal Investigator for inclusion in the Principal Investigator’s case history files. A copy must be given to the patient and the patient must initial the original signed consent form acknowledging receipt of a copy of the informed consent form. When applicable, a copy must also be forwarded to the Research Pharmacy, prior to dispensing any investigational drug.

It is the responsibility of the Research Service to assure that this is being done appropriately. Results of internal audits and recommendations for corrective action, if needed, will be reported to the IRB and R&D Committee for deliberation.

D. 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 an individual or individuals who is/are properly trained to inform the prospective subject about all aspects of the research project and conduct the informed consent process.

The Principal Investigator is responsible for ensuring that the individuals s/he authorizes to inform the prospective subject about all aspects of the research project and 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. All authorized individuals must complete the education and credentialing requirements consistent with PVAMC HRPP policies: Education for the Protection of Human Research Participants and Credentialing of Personnel Involved in Human Research (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm#policies>).

E. Observation of the Informed Consent Process

(VHA Handbook 1200.5)

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 gives rise to 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 and overseen through the following mechanisms: 1) the IRB or its designee, which may include the IRB Coordinators and/or Research Office staff, carefully review each signed informed consent form submitted for inclusion into the patient's CPRS record to assure that it was correctly completed and that all required signatures are in place and 2) the Research Assurance and Compliance Coordinator and/or the Quality & Performance Service may conduct audits of informed consent documentation.

F. Assessing a Potential Subject's Capacity to Consent

A subject's capacity to give consent should be evaluated on an individual basis to avoid incorrect assumptions as to the subject's ability to make decisions and to ensure that the subject is able to understand the study procedures and all risks and benefits involved so that the subject may make an informed decision prior to consenting the individual.

In cases where research involving cognitively impaired individuals is approved, the IRB may require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants. The IRB will determine when a subject's capacity to consent is required. This is based on the potential subject population and risks to subjects

More information, regarding assessing a potential subject's capacity to consent, may be found in Section VI, RR, 606.

G. Surrogate Consent

Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent). More information, regarding surrogate consent, may be found in Section VI, RR, 606.

H. Legally Authorized Representative

Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent). More information, regarding surrogate consent, may be found in Section VI, RR, 606, E.

I. Witnesses of Informed Consent Process

The IRB requires that a witness unassociated with the research project for which an individual is consenting be present as follows:

1. 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.
2. During the informed consent process when a "short form" written consent is being used. 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. Ideally, the witness would be a family member or friend of the research participant.

J. Informed Consent Reading Level and Language

(38 CFR 16.116)

VA regulations at 38 CFR 16.116, the Common Rule, and FDA regulations require that informed consent is at the appropriate reading level of the potential patient 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.

K. Exculpatory Language

The IRB prohibits the informed consent, written or oral, from containing 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.

L. Waiver of Documentation of Consent

38 CFR 16.117(c) and 21CFR56.109(c)

An IRB may waive the requirement to obtain written documentation of informed consent based on criteria below. allow such a waiver based only on the second criterion 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

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) (21CFR56.109(c))

IRB minutes shall clearly reflect this waiver provision and the justification for its use. In addition, 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.visn20.med.va.gov/portland/research/hrpp/index.htm>).

(Note: The PVAMC does not conduct research on children, therefore a waiver of parental permission is not applicable.)

M. Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research

VA regulations at 38 CFR 16.116(d) permit the IRB to approve a consent procedure which does not include or which 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 that:

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
3. The research could not practically be carried out without the waiver or alteration.
4. 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 when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB cannot approve such alterations or waivers for FDA-regulated research (21 CFR 50.20).

The waiver or alteration of informed consent requirements for FDA-regulated articles is applicable only for emergency use. (See Section VIII, IC 802, A.)

In addition, 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.visn20.med.va.gov/portland/research/hrpp/index.htm>).

N. Required Elements of Informed Consent Forms

A written consent document embodies the elements of informed consent. 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 the additional elements when appropriate. Depending on the nature of the research an investigator may request elimination of any of the elements.

In accordance with 21 CFR 50.25, 38 CFR 16.116, 45 CFR 46.116 and VA Handbook 1200.5, 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.**

Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. 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 which are currently unforeseeable.

9. Reasonably expected benefits to subjects or others

Informed consent information must describe any benefits to subjects or to others that may reasonably be expected from the research. However, 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

Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject.

11. Extent of privacy and confidentiality

Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained. Research often poses the risk of loss of confidentiality to subjects who participate. 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' private records. In some research, loss of privacy may be the greatest risk of participation. For FDA-regulated studies, consent forms must include a statement that the FDA may inspect research records.

Research projects which will combine the HIPAA Authorization requirements into the informed consent form will require that 9 additional elements be added to the informed consent form. Please refer to the HRPP policy "Health Insurance Portability & Accountability Act (HIPAA)" (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>) regarding the additional elements required if the HIPAA Authorization is included in the informed consent form.

12. Compensation or treatment for injury

Informed consent information for research involving more than minimal risk must include explanations regarding:

- a. Whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and if so, what they consist of or where further information may be obtained.
- b. In accordance with Federal law, a statement that veteran-subjects shall receive medical care and treatment for injuries suffered as a result of participating in a VA research program and whether any medical treatments are available if injury occurs.

13. Contact information

Informed consent information must include details, including telephone numbers, about whom to contact for specific situations:

- 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, Research Assurance and Compliance Coordinator or VA Regional Counsel are appropriate contacts.
- c. In the event of a research-related injury occurs to the subject, the VA Regional Counsel, the Research Assurance and Compliance Coordinator and the Investigators are all appropriate contacts for this information.

- 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 and Compliance Coordinator, and the VA Regional Counsel.

14. **Voluntary participation statement**

It is particularly important in the VA context 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 statements of the following:

- 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.

O. **Additional Elements Where Appropriate**

In accordance with 21 CFR 50.25, 38 CFR 16.116, 45 CFR 46.116 and VA Handbook 1200.5, 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 risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) that are currently unforeseeable.

Explanation: Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant).

2. **Investigator-initiated termination of participation**

The informed consent information must specify the anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

Explanation:

There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research).

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**

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

Explanation:

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 information must provide subjects with knowledge of the consequences

affecting a decision to withdraw. In addition, 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 that do not affect the safety of subjects who have decided to withdraw.

5. Significant new findings

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

Explanation:

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the informed consent information must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.

6. Approximate number of subjects

The approximate number of subjects involved in the study.

7. FDA-regulated studies.

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

8. Payment for participation.

As appropriate, a statement regarding:

- a. information concerning the amount of payment to subjects and
- b. information concerning the schedule of payments to subjects.

Explanation:

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 at 38 CFR 16.116(a)(8), 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. For this reason the informed consent information should be a description of how payment will be prorated and calculated for subjects who withdraw early.

P. Human Biological Specimen Consent Form Requirements

(Memorandum of 03/28/2001, VHA Directive 2000-043, VHA Handbook 1200.5)

If the investigators believe that human biological specimens obtained as part of a research study could be part of, or lead to the development of a commercially valuable product, or if the specimens are to be retained after the end of the 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.

Q. Progress Notes

(VHA Handbook 1200.5 <http://www.research.va.gov/programs/pride/policy/default.cfm>)

A progress note documenting the informed consent process must be placed in the subject's CPRS medical record. The Principal Investigator is responsible for ensuring that the progress notes are assigned appropriately for each individual subject.

1. At a minimum, the progress note 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, and
 - e. A statement that the subject was given the opportunity to ask questions.
2. An entry must also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated.
3. Consent and entry notes may be combined when both occur at the same visit.

IC 802

Exceptions from Informed Consent for Emergency Use of a Test Article (21 CFR 50.23)

A. Waiver of Informed Consent Under Compassionate Use or on an Emergency Basis

Please see also HRPP policy “Investigational Device and Drug Usage in Research & Development Service” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>) **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. [21 CFR 50.23 (a)]

An exception under FDA regulations at 21 CFR 50.23 (a) 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 – see section FD 1001) 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 5 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 5 working days after the use of the test article. The IRB will determine if FDA criteria for emergency use without consent was met and that the activity was not a systematic investigation designed to develop or contribute to generalizable knowledge. Any subsequent use of the test article is subject to IRB review (21 CFR 56.104).

SC 901

Behavioral and Social Sciences Research

This type of research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This section discusses some additional IRB considerations.

A. Social and Psychological Harms

When evaluating behavioral and social science research, the IRB should carefully examine the research to determine the probability of risk of harm to subjects, especially with respect to social or psychological harm. This includes, but is not limited to the following:

1. The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
2. The IRB should also consider the risks of criminal or civil liability or other risks that can 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 being collected on living individuals other than the primary "target" subjects the IRB should consider the risk of harm to those "non-target" individuals, as well. "Non-target" individuals may include members of the subject's family.

To mitigate such risks, the IRB should 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.

B. Privacy and Confidentiality Concerns

The use of confidential information is an essential element of much social and behavioral research. It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do 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. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements.

It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

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.vish20.med.va.gov/portland/research/hrpp/index.htm>). The IRB recognizes the importance of protecting subject confidentiality, and carefully evaluate each protocol for the confidentiality measures taken.

C. Safeguarding Confidentiality

When information linked to individuals will be recorded as part of the research design, the IRB should ensure that adequate precautions should be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with techniques for protecting confidentiality.

D. 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.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The IRB should also make sure that the proposed subject population is suitable.

Deception can 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.

SC 902

Research Using Data

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. These types of studies often use or create data repositories (banks). The following is guidance for the IRB when considering these types of studies.

A. 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 at 38CFR16.101 (b)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated.

B. 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 Department of Veterans Affairs (VA) regulations at 38CFR16.101 (b)(4) 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).

C. 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 they contain individually-identifiable private information about individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

1. 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.
2. If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 38 CFR 16.116(d).
3. 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.

4. 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.

D. Research Utilizing Data Banks (also called Repositories)

Human data repositories collect, store, and distribute individually-identifiable information about individual persons for research purposes.

Data Bank activities involve three components: (a) the **collectors** of data; (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 tissue 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.

SC 903

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 must satisfy itself 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 that is 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 (38 CFR 16.116(d)).

SC 904

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 the VA regulations at 38 CFR 16.102 (f)(2) 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 can consider if informed consent from third parties can 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.

SC 905

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 can 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 subjects that are institutionalized, the subjects' ability to exercise autonomy could be impaired.
3. The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against or over-selected.
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.

SC 906

Research Involving PVAMC Employees, Students and Trainees

The IRB upholds the standards in approving research involving PVAMC employees, students and/or trainees. The IRB takes into consideration undue influence that an employee may experience as being approached for participating in a research project. The IRB ensures that no employees, students, or trainees feel obligated to participate in research in order to avoid loss of employment or privileges. VA employees may participate on IRB-approved studies 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, but they may not use work time to participate in a study.

SC 907

Human Fetal Tissue Transplantation Research

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

SC 908

Research Involving Deceased Persons

In the rare cases that research involving deceased persons is proposed, the IRB will review such research projects by evaluating the nature of the research and determining if consent of family members is necessary, or whether the body may be treated in the same manner as that of donated tissue. The IRB also ensures that appropriate confidentiality measures are in place.

Under HIPAA, investigators who propose research involving decedent's protected health information must complete the "Research on Decedent's Information Application." This application will be reviewed and approved by the IRB Chair(s), since the Common Rule does not cover research involving decedent's information. The investigators will be 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.visn20.med.va.gov/portland/research/hrpp/index.htm>).

FD 1001

Investigational Drugs, Devices, and Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS). The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety while they are in use.

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

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

For information regarding Investigational Devices, please refer to HRPP policy “Investigational Device Usage in Research & Development Service” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>).

The PVAMC Research Pharmacy is responsible for maintaining the written policies and procedures for the Research Pharmacy and the dispensing of investigational drugs.

A. 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 page 8 of this SOP under definition of research and page 11 under definition of human subject.

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” (21CFR312.3(b)) Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.

2. FDA has neither an assurance mechanism nor files of IRB membership. Therefore, FDA does not require the IRB or institution to report changes in membership whereas HHS does require such notification.
3. Conditions for exemption (21 CFR 56.104), exception (21 CFR 50.23), and waiver (45 CFR 46.116(c) & (d) 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.visn20.med.va.gov/portland/research/hrpp/index.htm>)).

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 (Subpart B); prisoners (Subpart C) and children (Subpart D) that are not contained in the VA and Common Rule requirements. In April 2001 FDA issued regulations to protect children in research (20 CFR 50 Subpart D). 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 (21 CFR 312) and devices (21 CFR 812).

B. Additional VA Requirements

VA policy (VHA Handbook 1200.5) 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 and R&D Committee, a Report of Subcommittee on Human Studies (VA Form 10-1223) must be forwarded to the investigator and the Pharmacy Service.

These 2 forms (10-9012 and 10-1223) are sent to the Pharmacy Service (VHA Handbook 1200.5).

C. Research Involving Investigational FDA-regulated Test Articles

Please see also HRPP policy "Investigational Device Usage in Research & Development Service" (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>). Medical products, such as drugs, biologics, and medical devices need to be proven safe and effective before the FDA can approve them for sale to and use by patients. FDA reviews the results of laboratory, animal and human clinical testing to determine if the product to be put on the market is safe and effective. New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

1. The IND is an investigational new drug application and is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." Investigational new drug (or investigational drug) means a new drug or biological drug that is currently unapproved by the FDA for marketing is being used in a clinical investigation. An investigational drug must have an IND before it can be shipped. Criteria for exemption from the requirements for an IND are as follow (21 CFR 312.2):

(b) *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (*a*) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (*b*) it is shipped in compliance with 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (*a*) blood grouping serum; (*b*) reagent red blood cells; and (*c*) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under 50.24 of this chapter is not exempt from the requirements of this part.

2. An approved investigational device exemption (IDE) permits a device not approved by FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE. Criteria for exemption from the requirement of an IDE and criteria for an abbreviated IDE are as follow (21 CFR 812.2):

(c) *Exempted investigations.* This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

(d) *Limit on certain exemptions.* In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(b) *Abbreviated requirements.* The following categories of investigations are considered to have approved applications for IDEs, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).

(iv) Complies with the requirements of 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

D. Investigator and Sponsor Responsibilities

Under FDA regulations, the **investigator** in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include:

2. Obtaining IRB approval for any proposed changes in the research activity all unanticipated problems related to the research;
3. Getting informed consent from each subject;
4. Following the investigational plan;

5. Complying fully with the regulations;
6. Protecting the rights, welfare and safety of the subjects;
7. Supervising the use and disposition of the test article;
8. Maintaining accurate, current and complete records; and
9. Disclosing relevant financial information.

The **sponsor** takes responsibility for initiating the clinical investigation, and holding the IND or IDE, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation. General responsibilities of sponsors include the following: (See 21 CFR 812 online at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812> for detailed responsibilities.)

1. Selecting qualified investigators;
2. Providing investigators with the information they need to conduct the investigation properly;
3. Ensuring proper monitoring of the investigation;
4. Monitoring an effective IND and IDE with respect to an investigator; and
6. Ensuring that the FDA, and all participating investigators are promptly informed of significant new information about an investigation.

E. Necessity of an Investigational New Drug (IND) Number from the FDA

(21 CFR 312.2 (b))

The IRB will take the following information into account when determining whether or not an investigational drug requires an investigational new drug number from the FDA.

A clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of 21 CFR 312.2 if all of the following apply, i.e., does not require an IND Number from the FDA if the following is true:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
2. The drug undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not needed to support a significant change in the advertising for the product.
3. The investigation does not involve a route of administration or dosage or level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

F. **IRB Review of Medical Devices**

Please see HRPP policy “Investigational Device Usage in Research & Development Service” (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>).

G. **Radiology Devices and Radioactive Materials**

All studies involving Radiological devices or procedures are reviewed by the Radiation Safety Officer (RSO), who is a member of one IRB. Studies from the other IRB which include a radiation component are also sent to the RSO for review. The Radiation Safety Officer assures that the use of radioactivity and the conduct of procedures are appropriate.

H. **AEs and Reporting Requirements**

Some requirements for reporting AEs are the same, regardless of what sort of test article is used (e.g., a drug or a device). FDA, VA, and DHHS regulations require **prompt** reporting to the IRB, FDA, OHRP, and the Office of Research Oversight (ORO) of any unanticipated problems involving risks to human subjects and others. See section RR 602, item G of this SOP for precise guidance for reporting to the IRB.

1.

I. **Reporting Requirements – INDs**

FDA IND regulations (for both drugs and biologics) have requirements related to the reporting of adverse events. (21 CFR 312.64) See section RR 602, item G. for guidance in reporting to the IRB.

1. **Investigator Reports to Sponsor:**

- FDA IND regulations require that the investigator report promptly to the sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)).
- The investigator must report progress annually to the sponsor.
- Investigators must report to the sponsor shortly after completion of the investigator's participation in the investigation.
- Investigators must report to the sponsor sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR 54. The investigator must also promptly update any relevant changes during the course of the investigation and for 1 year following study completion.

2. **Sponsor Reports to FDA and Investigators:**

- The sponsor must notify the FDA and all participating investigators of any adverse experience associated with the use of the drug or biologic that is **both serious and** unexpected as soon as possible but in no event later than 15 calendar days after the sponsor determines it to be reportable, 21 CFR 312.32(c)(B).
- The sponsor must notify the FDA of any fatal or life-threatening experience associated with the use of an investigational drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information.
- The sponsor of a clinical study of a marketed drug must only report adverse experiences associated with the use of the drug from the clinical study.
- The sponsor must report any follow-up information to a safety report to the FDA as soon as available.

"Serious adverse drug experience" is defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or

prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect," (21 CFR 312.32(a)).

J. Reporting Requirements – IDEs

FDA IDE (device) reporting requirements are similar but not exactly the same as for drugs and biologics, 21CFR812.150. See section RR 602, item G. for guidance in reporting to the IRB.

1. Investigator to Sponsor: FDA IDE regulations require the following reports:

- (a) Any unanticipated adverse device effect: investigator notify the sponsor as soon as possible and no later than 10 working days of discovery.
- (b) Withdrawal (suspension or termination) of IRB approval: investigator must report to the sponsor within 5 working days.
- (c) Progress: investigator must report to the sponsor no less often than yearly.
- (d) Protocol deviations/violations to protect subjects: investigator must report to the sponsor any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency as soon as possible, no later than 5 working days after occurrence.
- (e) Use of device without informed consent: investigator must report within 5 working days after use occurs.
- (f) Final report: the investigator must report to the sponsor within 3 months of termination or completion of the investigation or the investigator's part of the investigation.
- (g) Other: the investigator shall provide upon request by the FDA accurate, complete, and current information about any aspect of the investigation

2. Sponsor to FDA and Investigator.

- (a) The sponsor must evaluate all unanticipated adverse device effects and report results to the FDA and all participating investigators, no later than 10 working days of the sponsor's receipt of the information.
- (b) The sponsor must report withdrawal (suspension or termination) of any IRB approval to the FDA and all other reviewing IRBs and participating investigators within 5 working days after receiving notification of the withdrawal.
- (c) The sponsor must report to participating investigators of any withdrawal of FDA approval of the investigation within 5 working days of receiving notice.
- (d) The sponsor must submit to the FDA at 6-month intervals, a current list of the names and addresses of all investigators participating in an investigation.
- (e) The sponsor shall submit progress reports to the FDA at least yearly. Sponsors of treatment IDEs must submit semi-annual progress reports to the FDA.
- (f) The sponsor shall report any request and the reason for the request to return, repair, or otherwise dispose of any units of a device to the FDA within 30 working days of receiving request.
- (g) The sponsor shall report to the FDA the completion or termination of an investigation involving a significant risk device within 30 working days and shall submit a final report within 6 months of the completion/termination.
- (h) The sponsor shall submit a copy of any report by an investigator of use of a device without obtaining informed consent within 5 working days of receipt of notice.
- (i) The sponsor shall report to the FDA an IRB's determination that a device is a significant risk device if the sponsor had proposed the IRB consider the device not to be a significant risk device within 5 working days of receiving notification of the IRB's determination.
- (j) The sponsor shall provide upon request by the IRB or the FDA accurate, complete, and current information about any aspect of the investigation

K. "Off-label" (Unapproved) Use of FDA-Regulated Products in Medical Practice

The FDA approves the sale, use, and labeling of a product for specific indications (the reason the product is being used - a disease, condition, as a diagnostic tool, etc.). "Off-label" or unapproved use is when the product is used in a way or on a population different from that for which it was approved. The IND regulations do not apply to the use of marketed drugs for unlabeled indications in the practice of medicine (21 CFR 312.2(d)).

L. **"Off-label" (Unapproved) Use of FDA-regulated Products in Research**

Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

The off-label use of a marketed drug or biologic in **research** does require IRB review, informed consent and, under some circumstances, may require an IND. To be exempt from the requirements of the IND regulations, all of the following must apply (note that this includes the requirement of IRB review and approval and informed consent):

1. The investigation is not intended to support of a new indication for use nor any other significant change in the labeling for the drug;
2. The investigation is not intended to support a significant change in the advertising for the product;
3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. The investigation is conducted in compliance with the requirements for institutional review board review and informed consent; and
5. The investigation is conducted in compliance with the FDA regulations on promoting and charging for investigational drugs (21 CFR 312.7).

Use of an off-label marketed product in research intended to support **a new indication for use, change in labeling or advertising** requires IRB review and approval, informed consent and submission of an IND.

Using an off-label marketed product in research involving a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with its use requires IRB review, informed consent and may also require submission of an IND and IRB review and approval.

M. **Expanded Access to Investigational Drugs**

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval (21 CFR 312.34, 312.35, and 312.83).

1. **Open Label Protocol or Open Protocol IND**

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

2. **Treatment IND**

The treatment IND (21 CFR 312.34 and 312.35) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug. Four requirements must be satisfied before a treatment IND may be issued:

- a. The drug must be intended to treat a serious or immediately life threatening disease;
- b. There must be no satisfactory alternative treatment available;
- c. The drug must already be under investigation or the drug trials must have been completed; and
- d. The trial sponsor must be actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent.

3. **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent.

N. Expanded Access to Investigational Devices

Please see also HRPP policy "Investigational Device Usage in Research & Development Service" (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>). According to statute and FDA regulations, an unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved drug or device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved drugs or devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

1. **Emergency Use** : (21CFR parts 50.24, 56.102, 812.35(a) and "Guidance for the Emergency Use of Unapproved Medical Devices")

The FDA states in 21 CFR 56.102 "(d) *Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval." Any subsequent use of the test article at the institution is subject to IRB review. FDA Guidance Sheet for "Emergency Use of an Investigation Drug or Biologic" states the following: "FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Life-threatening, for the purposes of section 21 CFR 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation

requiring intervention before review at a convened meeting of the IRB is feasible.

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.”

- FDA approval of emergency use of the investigational device is not required prior to use if there is insufficient time and the criteria above are met (21 CFR 56.102). Investigators should use the Checklist for Emergency Use of a Test Article to determine if the use is justifiable. After the device is used a report should be submitted to the FDA. The necessary patient protection measures that must be followed include: 1) independent assessment by an uninvolved doctor; 2) IRB review within five days of use to assure the emergency use followed FDA regulations; 3) institutional clearance from the Chief of Staff or his designee; 4) informed consent. See page 110 for further information regarding informed consent and criteria that must be met to waive informed consent.

2. **Treatment Use/IDE:** (21 CFR 812.36)

Criteria for use under this expanded access mechanism includes that the subject must 1) have a life-threatening condition or serious disease; 2) no alternative available and 3) the device is being used in a controlled clinical trial and 4) the sponsor is pursuing marketing approval. This may be used only during a clinical trial. Access is available widely, depending on the patient and physician needs. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Treatment Investigational Device Exemption (IDE) supplement with: 1) intended use, protocol, and patient selection criteria; 2) rationale for treatment use; 3) methods used to evaluate devices use and minimize risks; 4) monitoring plan; 5) summary of safety and efficacy data; 6) instructions for use and device labeling; 7) commitment to patient protection; 8) investigator agreement; and 9) the price if it will be sold. The necessary patient protection measures that must be followed include 1) IRB approval and 2) informed consent.

3. **Continued Access to Investigational Devices:** (“Continued Access to Investigational Devices During PMA Preparation and Review” and ODE Blue Book IDE Memorandum #D96-1)

This mechanism allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims.

Criteria for use under this continued access mechanism includes that there must be: 1) a public health need for the device and 2) preliminary evidence that the device is effective and there are no significant safety concerns. This may be used only after the completion of a clinical trial. The number of patients that may be treated is the same rate of enrollment as study. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Investigational Device Exemption (IDE) supplement with: 1) justification for extended study; 2) summary of safety and efficacy data and risks posed by the device; 3) proposed enrollment rate; 4) clinical protocol; and 5) progress towards marketing approval. The necessary patient protection measures that must be followed include: 1) IRB approval and 2) informed consent.

4. **Treatment Use:** (21 CFR 812.36(a))

Criteria for use under this expanded access mechanism includes that the subject must have a serious condition/disease with no alternative intervention available. Compassionate use may be used only during the conduct of a clinical trial. Access is limited to an individual patient or a small group of patients. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via an Investigational Device Exemption (IDE) supplement with: 1) explanation of circumstances constituting need for the device; 2) reasons alternatives are not acceptable; 3) deviations from protocol, if any; and 4) patient protection measures. The necessary patient

protection measures that must be followed include: 1) independent assessment by an uninvolved doctor; 2) IRB chair's concurrence; 3) institutional clearance from the Chief of Staff or his designee; 4) informed consent.

O. Gene Transfer Research

Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by both the FDA and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA).

1. FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.
2. DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).
3. While the RAC is advisory to the Director of the NIH, compliance with RACs guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

P. **Emergency Use of a Test Article Without IRB Review** - Please see N.1. above.

Q. "Compassionate" or "Humanitarian" Use of a Test Article

Questions frequently arise regarding "compassionate" or "humanitarian" use of a test article. "Compassionate use" and "humanitarian use" are not terms that appear in the VA, or DHHS regulations or the Common Rule. "Compassionate use" and "humanitarian use" are often meant to refer to the emergency use situations discussed above or to one-time treatment use requiring a Treatment IND.

R. Humanitarian Use Device (HUD)

The FDA defines humanitarian use device as "a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year." U.S. Food and Drug Administration – Center for Devices and Radiological Health, Humanitarian Device Exemption (HDE) Regulation Questions and Answers; Final Guidance for Industry, July 12, 2001.

A HUD requires a Humanitarian Device Exemption (HDE) for the FDA. An HDE is an application that is similar to a pre-market approval (PMA) application, but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

FDA regulations (21 CFR 814.124(a)) require the IRB to conduct a full board review of a HUD prior to its use, except in emergency situations in which the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient. An investigator who would like to use a HUD must forward a letter of request to the IRB. Effective January 2003, the clinician/investigator must also submit the Proposed Project Questionnaire (PPQ), protocol and any other additional information requested. The convened full board IRB will review and make a determination of the use of the HUD at the PVAMC. However, the IRB does not have to approve individual uses of the HUD if it is within the FDA approved indication.

The HDE regulations do not require the use of informed consent because the HDE provides for marketing approval and so use of the HUD does not constitute research or an investigation, which would normally require informed consent. In these cases, the clinician/investigator must provide a copy of the clinical consent to be used to the IRB. However, if the HUD is the subject of a clinical investigation (the HDE holder is collecting safety and effectiveness data to support a PMA under the approved HDE) IRB approval and informed consent are required (21 CFR Parts 56 and 50).

If the IRB approves the use of the HUD, the HUD will be reviewed on an annual basis by the IRB. The continuing review of the HUD may be performed under an expedited process. The HUD will be tracked in the MIRB database.

S. Off-label Emergency Use of a Humanitarian Use Device (HUD)

Reference: Humanitarian Device Exemption (HDE) Regulations: Questions and Answers; Final Guidance for Industry, Issued July 12, 2001. <http://www.fda.gov/cdrh/ode/guidance/1381.html>

HUDs may be used off-label in an emergency situation, but certain patient protection measures should be followed before the use occurs. Because IRB review and approval is required before a HUD is used within its approved labeling, a HUD should not be used outside of its approved labeling without similar restrictions. That is, in an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient, but the physician and HDE holder should follow the emergency use procedures governing such use of unapproved devices. According to this policy, before the device is used, if possible, the physician should obtain the IRB chair's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. In addition, authorization from the HDE holder would be needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder, who would then submit this report as an amendment to the HDE.

The physician should follow the procedures outlined in HRPP policy "Investigational Device Usage in Research & Development Service" (<http://www.visn20.med.va.gov/portland/research/hrpp/index.htm>), section 5.c.

T. Requirements for Planned Emergency Research (21CFR50.24)

The PVAMC may not review and conduct planned emergency research, according to the VA Office of Research Oversight (ORO).

U. FDA Warnings Announced by VA

1. Drug Warnings: Research Pharmacy lists all research drugs.
 - Pharmacy will email FDA warnings to the ACOS/R&D, the Administrative Officer (AO) and the Research Compliance Officer (RCO).
 - The RCO will ask Research Pharmacy to search their database to determine any research studies using the relevant drug(s).
 - Research Pharmacy will email the names of relevant PIs to the ACOS/R&D, the AO and the RCO. No action will be required if no investigator is using the drug.
 - R&D staff will contact the PIs, IRB Chairs, and all IRB members.
 - 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.
 - PIs will notify study participants if directed by the warning (based on level) or by the IRB.
2. Device warnings: The research database, MIRB, allows a report indicating current device investigations
 - When the FDA issues an alert/warning, IRB staff will generate a report. No action will be required if no investigator is using the device.
 - IRB staff will contact the PIs, IRB Chairs, and all IRB members.
 - 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.
 - PIs will notify study participants if directed by the warning (based on level) or by the IRB.