Edward Hines Jr. VA Hospital
and
North Chicago VA Medical Center
INSTITUTIONAL REVIEW BOARD

HUMAN RESEARCH PROTECTION PROGRAM
AND
STANDARD OPERATING PROCEDURES FOR PROTECTION OF HUMAN SUBJECTS IN RESEARCH

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STANDARD OPERATING PROCEDURE
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INTRODUCTION

Preface

The Human Research Protection Program is incorporated by reference.
These Institutional Review Board (IRB) Standard Operating Procedures (SOPs) for protection of human subjects are the current policy and procedures in operation for the combined Edward Hines Jr., VA Hospital (HVAH) and North Chicago VA Medical Center (NCVAMC) IRB. These SOPs are based on the VA's regulations, which are compatible with those of the Department of Health and Human Services (DHS) and the Food and Drug Administration (FDA). This document will be updated as regulations and policies change.

Institutional Authority

Effective August 19, 1991, VA is one of sixteen Federal Departments and Agencies that follow the Federal Policy for the Protection of Human Subjects, generally known as the "Common Rule". This policy is incorporated in 38 CFR 16, 17. With the exception of the categories listed in the exemption section, this policy applies to all research involving human subjects conducted completely or partially in HVAH or NCVAMC, including research funded from external VA sources. The Research and Development Committee is responsible for all research activities conducted under the auspices of Hines VAH and NCVAMC. The IRB is charged by the Research and Development committee to protect the rights and welfare of human research subjects.

Scope of Authority

The Office of Research Compliance and Assurance of the Department of Veterans Affairs (VAHQ-RDO) approves the Federal Wide Assurance under which HVAH and NCVAMC operates all aspects of research involving human studies in accordance with 38 CFR 16 and 45 CFR 46.

Legal Authorities to Protect Human Subjects

1. Statutory provisions for protection of VA patient rights: U.S.C. (United States Code) Sections 7331 through 7334, inclusive.
2. VA regulations pertaining to protection of patients' rights: 38 CFR Sections 17.34 and 17.34a.
3. VA regulations pertaining to rights and welfare of patients participating in research: 38 CFR 16 (Federal Policy for the Protection of Human Subjects).
4. DHHS (Department of Health and Human Services) regulations pertaining to rights and welfare of patients participating in research supported by DHHS: 45 CFR 46.
5. Food and Drug Administration (FDA) regulations pertaining to rights and welfare of patients participating in research involving investigational drugs and devices: 21 CFR parts 50 and 56. The FDA regulations at 21 CFR §50 (Protection of Human Subjects) applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that supports for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content

claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts of the regulations (e.g., parts 312 (drugs) and 812 (devices).

6. VHA HANDBOOK 1200.05, July 31, 2008

DEFINITIONS

Definitions
The following terms defined in 38 CFR 16.12, 21 CFR 50.3 and 45 CFR 45.102 and VHA Handbook 1200.05 are delineated more specifically for the purposes of HVAH/NCVAMC Human Subjects Protection Program policy:

Research. Research is defined as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question. The Common Rule (38 CFR 16) defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. ***NOTE:*** *The FDA definition of research differs according to the applicable regulations; refer to 21 CFR 812.3(h), 21 CFR 50.3(c), 21 CFR 56.102(c), and 21 CFR 312.3(b).*

Human Research Protection Program (HRPP). An HRPP is a comprehensive system to ensure the protection of human subjects participating in research. The HRPP consists of a variety of individuals and committees such as: the Medical Center Director, Associate Chief of Staff (ACOS) for Research and Development (R&D), the Administrative Officer (AO) for R&D, compliance officers, etc., the R&D Committee, the IRB, other committees or subcommittees addressing human subjects protection (e.g., Biosafety, Radiation Safety, Radioactive Drug Research, Conflict of Interest), investigators, IRB staff, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

IRB. An IRB is a board established in accordance with and for the purposes expressed in the Common Rule (38 CFR 16.102(g).) Within VHA, an IRB was formerly known as the Subcommittee on Human Studies. At VA medical centers, the IRB is a subcommittee of the R&D Committee. This committee reviews research involving humans as subjects

Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or need not meet the 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 later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of 21 CFR 58, regarding nonclinical laboratory studies.

Human Subjects: are defined by the federal regulations 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 [45 CFR 46.102(f)]. The definition of human subject provided in the Federal Policy is expanded to include investigators, technicians, and other assisting investigators, when they serve in a “subject” role by being observed, manipulated, or sampled.

1. **"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.
2. **"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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record).
3. Private information must be able to be linked back to the individual (i.e., the identity of the subject is or may be readily ascertained by the investigator [whether an investigator at HVAH/NCVAMC or at another institution] or associated information) to constitute research involving human subjects.
4. When it is not clear whether the research involves human subjects as defined in 45 CFR 46.102, research investigators shall seek assistance from the IRB in making this determination.
5. If the investigator's determination is that the research does involve "human subjects," a complete research proposal must be submitted to the IRB.
6. If the investigator concludes that, although the research involves "human subjects," it is exempt under Section 101(b) of 45 CFR 46, the investigator may submit that conclusion on an Exemption Form for review by the HVAH/North Chicago IRB. Only the IRB may determine that the research is exempt from 45 CFR 46 and 38 CFR 16f, and may not agree with the Investigator's determination.
7. If the IRB determines the submission is exempt from further IRB review, the R&D must still review and approve the project.

Human subject as defined by the FDA (21 CFR 50.3 (g) means a living individual who is or becomes a participant in research, either as a recipient of the test article or as a control, or an individual on whose specimens a medical device was used. A subject may be either a healthy human or a patient.

Adverse event (AE). 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. 1200.05 3a

Serious Adverse Event (SAE). A SAE is defined as death; 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; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes. 1200.05 3a(1)

Unexpected Adverse Event (UAE). An UAE is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator

brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal 1200.05 3a(2)

Unanticipated or Unexpected problems or AE involving risks to participants or others. Unanticipated problems refer to untoward events that are unforeseen in terms of nature, severity or frequency of occurrence involving any aspect of the research study, are events involving anyone, including participants, research staff, or others not directly involved in the research, are always unanticipated by definition, regulations require prompt reporting to the IRB, appropriate institutional officials, ORO and the Department or Agency head, can occur in either clinical or non-clinical research.

Non compliance - means failure to follow the federal regulations governing the protection of human subjects involved in research, facility policies regarding human subjects involved in research (i.e. Investigational drugs and devices, recruitment, Privacy and security) the facility's HRPP, Good Clinical Practice (GCP) guidelines, VHA regulations as set forth in VHA Research Handbook, 1200.05., determinations of the IRB, and/ or the approved research protocol. Non-compliance may involve investigators, research team, IRB members or staff.

Serious non-compliance - means non compliance that requires an intervention and probable reporting to appropriate Institutional Officials and regulatory bodies. Serious non-compliance may include serious protocol deviations, an action that results in increased risk to participants or adversely affects the rights and welfare of research participants. VHA Handbook 1058.01 defines Serious Non-Compliance as the failure to adhere to the laws, regulations or policies governing VA research that:

(1) Results in substantive harm or damage (or risks of substantive harm or damage) to the safety, rights, or welfare of human subjects, research staff or others; or

(2) Substantively compromises the integrity or effectiveness of research protections, either systemically or relative to a particular protocol or project.

Continuing non-compliance – means ongoing non-compliance despite notification, education, or possible other interventions. Continuing non-compliance may be serious, and reflect a willful disregard of research polices or inability to comply with policies or regulations due to inadequate resources. VHA Handbook 1058.01 defines continuing non-compliance as the persistent or repeated failure either in the past or extending into the present, to satisfy VA or other federal research requirements

Expedited Review. Expedited research is research determined by the IRB to present no more than minimal risk to human subjects and involve only procedures in certain specific categories. Minor changes to previously approved research during the period for which approval is authorized may also be approved through the expedited process (38 CFR 16.110(b)).

Exempt Research. Exempt research is research determined by the Institutional Review Board (IRB) to involve human subjects only in one or more of certain minimal risk categories (38 CFR 16.101(b))

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. However, in the VA, an investigational device may be an approved device that is being studied for an unapproved use or efficacy. 1200.05 3(j)

Investigational Drug. 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, in the VA, 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. 1200.05 3(j)

Investigational Device Exemption (IDE). 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. 1200.05 3(l)

Investigational New Drug (IND). An IND 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 1200.05 3(m)

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

Office of Research Oversight (ORO). 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.

Principal Investigator (PI). 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. VHA 1200.05 3(t) The FDA considers a PI and an investigator to be synonymous

Investigator. 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. (VHA 1200.05 3(n) The FDA considers an investigator and a PI to be synonymous

> I**nvestigator** FDA defines the term to be an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (21 CFR 50.3(3))

Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than

an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators.

Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

Test Article. VHA Handbook,1200.05 defines a test article as a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

> **Test article** according to FDA, means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). 21 CFR 50.3

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. 21 CFR 50.3 (k) 45 CFR 102 (j)

Researcher. A researcher is the PI and/or investigator. 1200.05 3(x)

VA-approved Research. VA-approved research is research that has been approved by the VA R&D Committee 1200.05 3(z)

OVERVIEW AND GENERAL PRINCIPLES

Mission of Institutional Review Board (IRB)

The primary purpose of the Institutional Review Board is to protect the rights and welfare of human subjects in research at the HVAH and NCVAMC. The Institutional Review Board is charged with a two-fold mission:

A. It must determine and certify that all projects reviewed by the IRB conform to the regulations and policies set forth by the VA and the Common Rule regarding the health, welfare, safety, rights, and privileges of human subjects.
B. It must assure that HVAH and NCVAMC Research Programs are conducting ethical and scientifically sound research which complies with the applicable regulations in a way that permits accomplishment of the research activity.

Principles That Govern the IRB in Assuring That the Rights and Welfare of Subjects Are Protected

The ***Belmont Report*** of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research articulates three basic ethical principles that guide the conduct of research with human subjects. They are:

- **Respect for Persons:** In consideration of respect for persons, investigators are required to seek voluntary, written informed consent from potential subjects (unless waived). Voluntary informed consent means that subjects are given explicit assurances of the voluntary nature of their participation in terms that are easy to understand and when they are not under duress. The consent form also includes adequate information about the study that will assist subjects in intelligently deciding whether to participate in research. In addition, respect means honoring the privacy of individuals and maintaining their confidentiality. Respect for minors and mentally disabled persons requires taking extra precautions. Individuals who are immature or incapacitated must be protected, perhaps even to the extent of excluding them from the participation in certain research. There are also special rules which apply to prisoners. The extent of the protection depends on the potential risks and benefits of the research to the participant.
- **Beneficence:** The principle of beneficence requires that researchers maximize the potential benefits to the subjects and minimize the potential risks of harm. The benefits should always outweigh risks. Finally, if there are any risks resulting from participation in the research, then there must be benefits, either to the subject, or to humanity or society in general.

- **Justice:** The principle of justice means that subjects are selected fairly and that the risks and benefits of research are distributed equitably. Investigators should take precautions not to systematically select subjects simply because of the subjects' easy availability, their compromised position, or because of racial, sexual, economic, or cultural biases in society. Investigators should base inclusion and exclusion criteria on those factors that most effectively and soundly address the research problem.

Based upon the above, the IRB examines recruitment procedures, proposed remuneration, the informed consent process, and evaluates the risks and potential benefit to participants outlined in each protocol. The review will help ensure that investigators recruit subjects in an equitable,

non-coercive manner, that subjects are fully informed about the risks and benefits entailed in participation and that subjects are not exposed to disproportional risks.

THE AUTHORITY OF THE IRB

A. The IRB is a subcommittee of the Research and Development (R&D) Committee. Though a subcommittee of the R&D, the IRB is independent in its ethics review and oversight function from other committees within the organization, particularly with respect to decision-making regarding the ethics of research involving human participants and will be free from coercion and undue influence. An IRB is a body established under federal regulations to protect the rights and welfare of human research participants.

B. The IRB will determine if a research project meets the definition of involving "human participants" as set forth in the Common Rule [38CFR16.102(f), 45CFR 46.102(f), and FDA 21CFR 50.3(g)] If the research project meets the definition of involving "human participants" the IRB will review such activities and determine if they meet the criteria for approval.

C. The IRB will review, and have authority to approve, require modifications in (to secure approval), or disapprove all research activities for HVAH and the NCVAMC involving human subjects .
All research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research [38 CFR 16, 17; 21 CFR 50, 56; 45 CFR 46] is subject to the authority of the IRB.
The R&D Committee may disapprove a project that has been approved by the IRB, but may not approve a project that has been disapproved by the IRB. The R&D may strengthen requirements and conditions, or add other modifications. These changes must be submitted, reviewed and re-approved by the IRB.

D. The Hines/North Chicago IRB will not review or approve research involving children, prisoners and pregnant women.

E. The IRB has the authority to suspend (put all studies activities on hold for a period of time, until questions, compliance or risk issues have been resolved) or terminate (stop the conduct and approval of the study permanently) a previously approved study when unexpected serious harm to participants has been identified, continued investigator non-compliance, or at any time, at the IRBs discretion or if warranted by findings in the continuing review or monitoring process. On an urgent basis, the Chair, IRB has the authority to cease enrollment, and other study activities to protect the participants. This action will be reported to the next convened IRB where it will be determined if further actions are required, such as suspension or termination of the study. The PI must immediately submit to the IRB Chair, a list of research subjects for whom the suspension/termination of the study would cause harm. The IRB Chair, with appropriate consultation with the investigator and COS, determines if the subject(s) may continue in the research. [21 CFR 56.108(b)(3) and 21 CFR 56.113] [45 CFR46.113]. The IRB approving the suspension or termination, will determine if the subjects are to be notified of the suspension/termination. Any adverse events or outcomes will be reported to the IRB, reviewed, and reported to ORO according to the requirements of VHA Handbook 1058.01.

F. The IRB has the authority to observe, or have a third party observe, the consent process and/or the conduct of the research.

G. The IRB has the authority to place any restrictions on a study that the IRB deems appropriate [21 CFR 56.108(a)(1); 21 CFR 56.109(a); 21 CFR 56.113].

H. Investigator's Educational Requirements and Certification. The IRB must determine that the PI and all other investigators of the proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB must also determine that the investigator(s) is qualified through education, training, and experience to conduct the research.

I. **Auditing Recurring Processes.** The IRB has the authority to:

(1) Conduct audits of recurring processes to be sure that all written procedures are followed,

(2) Review research records and research case histories for compliance with written procedures and regulations contained in this Handbook;

(3) Monitor the informed consent process and the research; and

(4) Consider results of audits conducted by other entities or the Research Compliance Officer (RCO) within the institution

J. No Response to IRB Recommendations: If a new protocol has been reviewed and recommendations made before final approval, the investigator is to respond promptly to the recommendations. If the investigator has not responded within 6 months, the IRB has the authority to terminate and/or withdraw the study. If this occurs, the Investigator will be notified in writing. The protocol must be resubmitted for a full re-review if the Investigator wants to pursue the project.

K. Conflict of Interest. A conflict of interest exists when an individual's personal or financial interests might lead an independent observer to reasonably question whether or not actions or decisions were made for personal or financial benefit. Individuals include investigators and personnel in the study team. Investigators and personnel include spouses and dependent children. The principal investigator has the responsibility for identifying a potential conflict of interest by completing the Request to Conduct Research Form (Part 1) at the time of initial submission. The Administrative Officer (AO) for Research will notify the Institutional Review Board (IRB) of any potential conflicts reported and the review process will follow the Research Service Investigator Conflict of Interest Policy. The review of the research project will not go forward until a report of the resolution of the conflict is provided to the IRB by the Administrative Officer. Once received, the project review process will be continued and the plan for resolution will be considered by the IRB in its deliberations. The Investigator will update the Conflict of Interest reporting at least annually as required as part of the Continuing Review Submission Form. If the Conflict of Interest is brought forward after the project has been approved, the IRB Chair will determine if enrollment should be ceased until the Administrative Officer's review and report is discussed at a convened IRB meeting.

L. **Consulting Legal Counsel:** If a legal opinion is required, the IRB Chair will request an opinion in writing through the ACOS, Research.

IRB RELATIONSHIPS

Administration of the Institution: The HVAH and NCVAMC Research and Development Committee reports to the ACOS for Research and Development and is responsible for all research activities conducted under the medical center auspices. The ACOS for Research and Development reports to the Chiefs of Staff who report to the Director. The hospital administration has the responsibility to provide the IRB with adequate resources.

Other Committees: The IRB is a sub-committee of the Research and Development Committee. The IRB may require projects to be reviewed and approved by the Radiation Safety sub-committee, the bio-hazard sub-committee, or by ad hoc reviewers.
Though a subcommittee of the R&D, the IRB is independent in it ethics review and oversight function from other committees within the organization, particularly with respect to decision-making regarding the ethics of research involving human participants.

Research Investigators: The IRB recognizes one Principal Investigator for each project. The Principal Investigator has ultimate responsibility for his/her research project and all official IRB correspondence is addressed to the Principal Investigator. The investigator must have the appropriate training and be credentialed to conduct research involving human participants by a program that meets all VA requirements. All interventional clinical trials must have a medical physician as the Principal Investigator or at least a collaborator on the study. Co-Investigators communicate with the IRB through the Principal Investigator. Students may not serve as Principal Investigators. The Investigator is the liaison between the IRB and the sponsor.

Other Institutions: The IRB is responsible for the protection of the rights and welfare of human research subjects at HVAH and NCVAMC. The IRB has no authority over or responsibility for research conducted at other institutions. A VA IRB cannot be the IRB of record for a non-VA facility/investigator.

All institutional and non-institutional performance sites for this institution, domestic or foreign, will be obligated by this institution to conform to ethical principles which are at least equivalent to those of this institution.

VA Central IRB: The IRB will adhere to the provisions of the Memorandum of Understanding (MOU) between either HVAH or NCVAMC and the VA Central IRB.

Regulatory Agencies: The IRB is subject to regulation and inspection by all governmental regulatory agencies (e.g., Food and Drug Administration [FDA], General Accounting Office [GAO], Office of Inspector General [OIG], Office of Human Research Protections [OHRP], and the VA Office of Research Oversight (ORO) and Association for the Accreditation of Human research Protection Programs (AAHRPP).

Research Compliance Officer: The Research Compliance Officer reports to the Facility Director and conducts audits and reviews to ensure compliance with all VA and other federal requirements for the conduct of research, including (a) annual audits of all active studies to ensure that informed consent has been properly obtained and documented for each subject accrued since the previous audit, and (b) regulatory compliance audits for all active studies at

least every 3 years. The RCO is a non-voting member of the IRB and will share their expertise with the IRB and make recommendations to the IRB regarding appropriate remediation of noncompliance.

IRB MEMBERSHIP

The IRB is responsible for ascertaining the acceptability of proposed research in terms of medical center commitments and policies, applicable law, scientific merit, sensitivity to community standard and attitudes, as well as standards of professional conduct and practice [21 CFR 46.107(a)] 45 CFR 46.107(a)]. Therefore, the following principles shall be observed in the composition of the IRB**.**

A. A Curriculum Vitae and/or Biosketch (and description of current responsibilities, if available) is reviewed prior to appointment of each member. Membership is selected to assure appropriate experience, expertise and diversity including representation by multiple professions, multiple ethnic backgrounds, both genders, knowledge of institutional commitments, knowledge and experience with vulnerable subjects, inclusion of both scientific and non-scientific members and one member who has no affiliation with HVAH or NCVAMC. [38 CFR 16.103(b)(3) and 16.115(a)(5)] [21 CFR 56.115(a)(5)]

B. The IRB approves recommendations for the Chair and membership to the IRB. These recommendations are forwarded to the R&D Committee. The R&D Committee forwards names for consideration as new IRB members to the Medical Center Director. The Medical Center Directors officially appoint members in writing to the Medical Center's IRB. The length of the appointments will range from one to three years. IRB members may be indefinitely re-appointed without any lapse in time. Terms are staggered to avoid excessive turnover any given year.

C. The IRB Chairperson shall be appointed by the Medical Center Director for a term of 1 year and may be re-appointed without any lapse in time. The IRB Chairperson shall not simultaneously chair the R&D Committee or another subcommittee thereof. Ideally an Associate Chairperson is appointed to assist the Chair in his/her duties and eventually assume the role of Chair. (This position is desired but not required)

    1. The IRB Chair has the primary responsibility for conducting IRB business. He/she directs Board proceedings in accordance with institutional and federal requirements. He/she works with Board members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are protected. He/she functions as a role model and conducts business fairly and impartially. He/she is the signatory official for IRB correspondence.
    2. IRB Chair will: (1) Make determinations whether an activity is human subject's research and falls under the jurisdiction of the IRB. This determination is communicated to the person seeking this decision through written correspondence, including the criteria by which the determination is made. The question of whether an activity represents human research my arise with activities designated as quality improvement, public health, program evaluation, innovative medical care and classroom exercises, among others.
    3. The IRB Chair may be removed by the Research and Development Committee with the concurrence of the Director.

D. The IRB members shall be sufficiently qualified to review the research through their experience, expertise and diversity, including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes. The IRB shall promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; possess the professional competence necessary to review specific research activities.

1. Committee members are responsible for assuring that the rights and welfare of research subjects are protected. Members vote to approve, require modifications, disapprove, or table submissions. These actions apply to: (a) initial reviews; (b) continuing reviews; (c) amendments; (d) HVAH and NCVAMC serious adverse events; (e) sponsor serious adverse events (when indicated by the primary reviewer); (f) unanticipated protocol deviations; (g) advertisements; (h) consent form revisions; (i) investigator brochures; (j) minutes of previous meetings; (k) emergency use of a test article; (l) general policy issues; and (m) non-compliance and other such matters that may be assigned to the IRB by regulation or law. The IRB has the authority to suspend or terminate an investigator's research privileges if it is determined that he/she is non-compliant.
2. The IRB meets twice a month. Several members have alternates (see Membership Listing maintained by the IRB Office. An alternate may only substitute for his/her designated voting member.
3. Alternate members are appointed by the Hospital or Medical Center Director as an alternate member and may substitute for regular members. The IRB's roster identifies the primary member(s) for whom each alternate member may substitute. The alternate member's qualifications are comparable to those of the primary member to be replaced. When an alternate member replaces the primary member, the alternate member receives and reviews the same material that the primary member would have received. In addition, the IRB minutes document when an alternate member replaces a primary member. The number of alternates may be increased as the need dictates. The alternate member may also substitute on a scheduled (shared) basis with the full committee member. Decisions as to who shall attend a designated meeting will be determined by the regular member and his/her alternate. This designation will be communicated to the IRB office at least one week prior to the scheduled meeting. Appropriate meeting materials will be sent to the designated member for that meeting. If the regular member and the alternate attend the meeting, both may fully participate in the meeting. The alternate member however, will have non-voting status when the regular member is present. The voting roster may be modified if the regular member leaves the meeting.
4. The Information Security Officer (ISO) and Privacy Officer (PO) will be appointed to the IRB as non-voting members to ensure compliance with applicable VA and VHA data security and privacy requirements.
5. IRB members will be evaluated by the IRB Chair prior to reappointment. Criteria for evaluation will include attendance, participation, meeting preparedness, and other IRB responsibilities identified in the HRPP. The IRB Chair will also be evaluated prior to reappointment according to HRPP identified responsibilities by the R& D Chair.
6. Members may be removed by the Research and Development Committee with the concurrence of the Hospital Director. IRB members who frequently fail to attend regularly scheduled meetings without notice to the IRB will be removed from the IRB. Failure to attend is defined as unexcused absence by a member or his/her alternate for six or more meetings yearly. A member or alternate attending a meeting counts as attendance.
7. IRB members should be free from coercion or undue influence. A member who

feels they are experiencing coercion or undue influence, may address this issue with the Chair, IRB, Chair, R&D, ACOS for Research. If deemed appropriate, a letter will be sent to the investigator who attempted to unduly influence IRB member(s). The ACOS and/or IRB Chair will then be responsible for taking corrective actions. This same policy will apply to IRB coordinators or staff who may feel coerced or unduly influenced.

E. **Scientific/Nonscientific Members** [21 CFR 56.107(c)] [45 CFR 46.107(c)]

1. The IRB shall include at least one member whose primary expertise is in scientific areas and at least one member whose primary expertise is in nonscientific areas. The non-scientific member must be present and cast a vote on each motion.
2. These members shall be selected primarily to reflect the values of the research community and the community from which the research subjects are drawn with respect to the rights and welfare of human research subjects. One member of the IRB will be (is) a veteran.

F. **Non-VA Members**. The IRB will include at least one member who is not otherwise affiliated with the VA medical center and who is not part of the immediate family of a person who is affiliated with the medical center. This role cannot be filled by a veteran who volunteers at the medical center in any capacity including that of a research subject [21 CFR 56.107(d)] [45 CFR 46.107(d).

G. **Conflict of Interest and IRB members**. All IRB members will be provided with a copy of the Research Service Conflict of Interest policy and be expected to sign an affidavit of understanding and compliance. An IRB member will not participate in the review of any project in which the member, or a member of his/her spouse or dependant children has a financial or non-financial conflict of interest (member of the research team, financial interest, participant of the research study, or otherwise), except to provide information requested by the IRB prior to IRB deliberations. [21 CFR 56.107(e)] [45 CFR 46.107(e)]. Additionally, IRB members will sign such a statement upon entering each IRB meeting. Any pre-identified Conflict of Interest will be documented on the expanded agenda with any additional conflicts of interests identified in the meeting minutes.

Members who have conflicts of interests will absent themselves from deliberations and abstain from voting. The IRB Chair or designated reviewer for an Expedited Review will not have a Conflict of Interest in the research study being reviewed.

H. **Ad Hoc Members**. The IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. Such ad hoc members may not vote with the IRB or contribute to the quorum [21 CFR 56.107(f)] [45 CFR 46.107(f)] Attendance at the meeting and/or written report of assessment will be required.

I. **R&D administration officials** including the ACOS/R&D and the Administrative Officer for Research (AO/R&D), do not serve as voting members of the IRB. The ACOS/R&D and AO/R&D serve as non-voting members and must be sensitive to the occurrence or appearance of conflict of interest.

K.**A quorum** is considered half the full membership plus one member. A quorum may be composed of full committee members present, including the chair, or his/her alternate. The chair has full committee status. All committee actions require a quorum. If a quorum is lost the IRB will not take votes until it is restored. Quorum will be monitored by the IRB coordinators during the meetings. The names and disciplines of all full committee members and alternates are

reported to the Office of Human Research Protections (OHRP). Non-member consultants will not be considered for voting purposes or are not counted towards quorum.

L. Members will be excused and excluded from the meeting during deliberations and voting on their own protocols (such actions will be documented in the minutes). Alternates can be substituted for both quorum and voting during the full committee member's absence.

M. **Compensation**. IRB members who are employees are not compensated.

N. **Liability Coverage**. IRB members are officially carrying out the VA mission and are protected from liability under the US Torts Claims Act. Non-VA employees are registered as WOC (without VA compensation) employees with Human Resources Management Service, HVAH for IRB purposes only. WOC employees are officially carrying out the VA mission and are protected from liability under the Federal Torts Claims Act.

O. Consultants. The IRB is authorized to request or purchase service of ad hoc reviewers when additional expertise is required. Attendance at the meeting and/or written report of assessment will be required. Non-member consultants will not be considered for voting purposes and will not be counted towards quorum. Consultants will be given a copy of the Research Service Conflict on Interest Policy and required to sign an affidavit attesting that they, or their spouse or dependant children, do not have a financial, or non-financial conflict of interest. No consultant will be solicited who has a conflict of interest.

P. Support Staff. The HVAH and NCVAMC employs Coordinators and clerical assistance to meet the workload requirements. IRB coordinators will be recruited in accord with the official position descriptions and appointed by the Research ACOS. The IRB coordinators work collaboratively with the chair in maintaining the human protections program at HVAH and NCVAMCs. The IRB coordinators are responsible for maintaining IRB records, routine correspondence with investigators, preparing materials for IRB meetings, taking minutes at the IRB meeting, writing and distributing minutes to IRB members, updating IRB policies and procedures, providing education for investigators, study staff and IRB members. The clerical assistant is responsible for duties delegated by the IRB coordinators. IRB coordinators and staff will have annual performance evaluations consistent with VA Policy based on their PD responsibilities.

Q. Resources. The Research Conference Room, Building 1, Room C308, at HVAH is reserved for all IRB meetings. The IRB administrative staff has a dedicated office suite, C334, adjacent to the Research Service Administration office where all IRB files are maintained. The IRB staff have access to a high-speed photocopier directly across from the IRB administrative office (C335). The IRB coordinators each have a PC computer with access to IRB database. The IRB Chair and Associate Chair also have access to a PC computer in their office.

R. Videoconferencing: Due to the distance between facilities, videoconferencing with members and guests at North Chicago VAMC may be utilized. In case of equipment failure, a teleconference call would be substituted. For both of these cases the member(s) will have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

VOTING REQUIREMENTS

A. **Quorum Required to Transact Business**: Quorum will be achieved with 50% plus 1 voting members. Quorums can be lost if a member or members leave a meeting early or absent themselves due to conflicts of interest.

B. **Diversity Requirements of Quorum**: At least one licensed physician must be present for review of protocols utilizing FDA regulated test articles and at least one member whose concerns are non-scientific must be present.

C. **Percent Needed to Approve or Disapprove a Study**: Approvals, Contingent Approvals requiring modifications and Tabling/Disapprovals must be by the majority of a quorum. If quorum in not maintained, no voting actions can take place and meeting will be terminated. All pending reviews will be tabled.

D. **Full Voting Rights of all Reviewing Members**: Each member has one vote.

E. **Proxy Votes (written or telephone)**: No proxy votes (written or telephone) are allowed. Videoconferencing with members and guests at North Chicago VAMC may be utilized. In case of equipment failure, a teleconference call would be substituted. For both of these cases the member(s) will have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

F. **Prohibition Against Conflict-Of-Interest Voting**: Members who have conflicts of interests are required to absent themselves from deliberations and abstain from voting. This includes all member investigators and member co-investigators, whose project is being reviewed or members whose family members have conflict-of-interest issues. Conflicts of interest include circumstances where financial or non-financial interests are involved. Non-financial interest may be where the reviewer is the spouse of the principal investigator.

G. **IRB Chair /Associate Chair** each have one vote. Individuals from organizations granting research contracting or research support office do not serve as voting IRB members.

IRB AND INVESTIGATOR EDUCATION

An important aspect of protecting human subjects/good clinical practice in research is an ongoing educational program for all individuals involved in research with human subjects. The following standards will be adhered to by all HVAH and NCVAMC investigators (senior administrators, department heads, principal investigators, co-investigators, research staff, key research personnel and student researchers) who are involved with research with human subjects. Studies which involve cooperation with research staff from other facilities, will submit evidence of education/training that is required by their facility.

Initial Education for Investigators

1. All investigators and key research personnel must have completed the required education for the protection of human subjects prior to submitting any research protocol for Institutional Review Board (IRB) review. All individuals obtaining informed consent from study participants must complete these requirements as well.
2. Any research protocols (initial or continuing review) brought to the IRB for review that do not include documentation that the investigators and key research personnel have met the initial education requirement will not be accepted and will be returned to the investigator.

Initial Education Requirements

All IRB staff, members, investigators and coordinators and other research personnel that will have access to personally identifiable information are required to complete the required education in the protection of an subjects participating in research as mandated by the facility's Assurance, VA ORD, funding institutions and applicable OHRP, and the Hines/NCVA IRB. The IRB must also determine that the investigator(s) is qualified through education, training, and experience to conduct the research.

Additional Requirements for IRB Members and Chair

1. All IRB members will complete the required human subjects protection education prior to participating as a member of the IRB.
2. All new IRB members will receive the following: IRB membership list, IRB meeting dates, Investigator Guidelines, for Preparation of Informed Consent, 21CFR Parts 50 and 56 Food and Drug Administration, Title 45 Code of Federal Regulations Part 45 OHRP Reports, Protection of Human Subjects', June 18, 1991, Department of Veterans Affairs Research Manual, HVAH and NCVAMC Standard Operating Procedures for Protection of Human Subjects in Research and pertinent IRB guidelines and policies (e.g., Scientific Misconduct Policy, Guidelines for Surrogate Consent, etc.), FDA information sheets and OPRR/OHRP IRB Guidebook.
3. All new IRB members will receive an orientation to the IRB processes, manuals and procedures. This orientation will be conducted by one of the IRB coordinators. This orientation will include but will not be limited to an overview of pertinent rules and regulations, an overview of the IRB manual, meeting protocol, procedures for

conducting initial and continuing review, and procedures for reviewing amendments and adverse events.

4. It is expected that IRB members will participate in ongoing education including but not limited to journal article review (pertinent journal articles and policies are distributed regularly at IRB meetings), attending regional and national meetings, developing ongoing educational offerings for investigators.
5. It is strongly encouraged that the IRB chair will attend the PRIMR/ARENA meetings at least every two years.
6. All IRB staff will, at a minimum, complete the requirements for investigators. IRB coordinators will attend regional and national meetings on a regular basis. It is encouraged that at least one IRB coordinator will attend the national PRIM&R and ARENA meeting annually.
7. Educational materials will be distributed at IRB meetings. IRB members are expected to review these materials.

D. Education Documentation

1. The IRB maintains a listing of those individuals who have completed the mandatory education requirement.

PROTOCOL SUBMISSION

A. Requirements for Researchers: Clinical studies may be conducted at HVAH and NCVAMC by HVAH and NCVAMC personnel only. An individual not holding an appointment may conduct research only with the endorsement of a regular staff member who is willing to assume full responsibility for the ethical and scientific conduct of the project. If this is the first research proposal submitted at HVAH or NCVAMC, R&D requirements are that the investigator must also complete an Investigator Data Sheet (VA Form 10-5368). IRB forms and instructions for completion are available in the IRB office—Room 1C334, HVAH or the Research Office, Building 133CA/3D115a, NCVAMC.

B. Preparation of the Protocol

1. Research investigators shall prepare a protocol giving a complete description of the proposed research. In the protocol, research investigators shall make provision for the adequate protection of the rights and welfare of prospective research subjects and ensure that pertinent laws and regulations are observed. This requirement is applicable even in cases where the research is exempt under 45 CFR 46.101.

2. The following items constitute the research project submission packet as they are applicable:

a. Protocol: The requirements for content differ depending on the requirements of the funding agency. At minimum, the following information should be included:

1) A relevant review of the literature
2) Proposed hypotheses
3) Subject sample with inclusion and exclusion criteria (*Note:* Current Federal and VA regulations require that whenever possible and scientifically desirable, researchers should include women and minorities in their research, especially in population-based studies. If these populations are excluded or inadequately represented, the investigator must provide a compelling rationale for the exception. Attention must be paid to issues of research design and sample size related to the composition of the study population by gender and race/ethnic group).
4) Methods, procedures, and the anticipated risks associated with participation
5) Data analysis plans, including methods for maintaining the confidentiality of subjects.
6) References
7) DHHS approved protocol if applicable

b. Administrative Forms

1) *Part I: Request to Review Research Proposal/Project.* Instructions for completion of the form are included. Please note that when a Service Chief is the principal investigator for a project, his/her request must include the signature of the Chief of Staff. Also of note, MESH terms (keywords) requested on this form must be those from the approved VA MESH Term Listing. Copies of the MESH Term Listing are available through the Research Service. The PI must indicate on the submission form that he/she and all staff involved with the project have completed the required education.

2) Abstract. An abstract must be submitted with the form. An abstract is

to include:

i. Background framing the relevance of the work
ii. Testable hypotheses
iii. Specific aims / objectives
iv. Experimental design/methods (includes subject population and procedures)
v. Statistical analyses
vi. Relevance to the VA mission

3) Budget. The budget should be typed on a separate sheet of paper and should follow the request for approval form and abstract. Requirements for budget information are available through the Administrative Officers for Research at HVAH, 708-202-5691 or the Research Liaison at NCVAMC, 847-578-1310

4) Part II: Research Safety -- Facilitates review and approval by the Research Safety Subcommittee as applicable. The Chair, IRB or designee, will verify and document approval of exemption from review by the Research Safety Committee.

5) *Part III: Appendix A-Request for IRB Review*. This form is required for all research proposals submitted to the IRB. By signing Appendix A and the Request for Review of Research Proposal/Project form, the investigator agrees to maintain patient care and/or other interactions with the subject as required by the approved project in a manner consistent with conscientious, ethical practice as described in the Belmont report, the facility FWA and Good Clinical Practice procedures. The investigator also describes the plan for long-term oversight in case of illness or extended leave. The investigator may indicate on Appendix A that they intend to enroll/screen a larger number of subjects than they expect to complete the study (considering screen failures/withdrawals).

6) Additional Appendices (Also listed on the Research Website). When other departments or other institutional support is required, the investigator is to submit the protocol and the completed Appendix form(s) to the support service(s). The original signed Appendix form should be sent to the IRB office (151) and the investigator must maintain a copy. For those services not listed below, a memorandum of agreement must be submitted with the protocol. The approved appendices must accompany the protocol at the time of submission to the IRB and may include, but not limited, to the following:

a) Studies Involving Radioactive Material (Part V)
b) Recombinant DNA or RNA studies (Part II)
c) Diagnostic Radiology Service Agreement
d) Pharmacy Service (For studies involving administration of drugs, Pharmacy Service requires the investigator to complete the following additional forms:
    (1) HVAH Sponsored Research Drug Charges Form;
    (2) VA Form 10-9012, Investigational Drug Record Form, is required for all drugs which have been released by the FDA for investigational use, an approved drug put to a new use, non-standard dosages, levels or routes of administration and those that have been given IND numbers (Investigational New Drug Application Numbers) by the FDA. All the names of potential

drug prescribers are to be listed on the 10-9012. The IND number(s) must be provided on Appendix A and the original form(s) 10-9012, "Investigational Drug Information Record."

e) Laboratory Service Agreement (as required).

f) *Part VI* Research Data Security

7) Studies Involving Investigational Devices: Investigators whose studies involve an investigational device must provide the design and safety data for the device and indicate whether or not the device poses any significant risk to subjects. Those which are determined to be of significant risk require an IDE (Investigational Device Exemption) number from the FDA. The Committee may choose to review the protocol, but final approval will not be granted until the IDE number and FDA comments have been submitted to the IRB. Additional information is available from the IRB office. Documentation of the IDE number must be provided to the IRB prior to review if the device meets or has met the definition of SR prior to initial submission to the IRB.

8) All components of any federal grant applications, the investigator's brochure and case report forms.

9) Informed Consent Form (VA Form 10-1086). A consent form should be prepared according to the HVAH/NCVAMC Guidelines for Preparation of the Informed Consent. DHHS approved sample consent form if applicable

10) Solicitation Flyers and/or Advertisements for Subjects. All advertising and solicitation for subjects must have prior approval of the IRB. Investigators are strongly encouraged to submit all advertising with the original application.

11) Memo for the use of Non-Veterans

12) HIPAA Authorization (or Request for Waiver of HIPAA Authorization as appropriate.)

13) Questionnaires and surveys , participant diaries, other instructional handouts

14) Case Report Forms and/or data collection tools

IRB REVIEW PROCESS
FOR INITIAL SUBMISSIONS

A. The original of the above forms with all signatures on the Request to Conduct Research Proposal / Project (Part I) , Appendix A (Part III), and Appendices must be submitted to the Research Office (HVAH VA, Building 1, Room C337, Mail Route 151) on or before the published deadline. The Research Office will log the protocol in and forward a copy to the IRB office. Meeting dates and deadlines for protocol submission are available on the Research Service web site and from the IRB and/or Research Offices. Generally, the IRB meets on the first and third Mondays of the month. The submission deadline is generally12 working days prior to the meeting. Proposals submitted on the deadline date must be received in the IRB office by close of business (COB).

B. **Once the protocol** is found to be complete, it will be placed on the IRB agenda for the following meeting.

C. Prior to assignment of protocols, the IRB staff will determine which members and/or their alternate will be in attendance at the next meeting. IRB members are encouraged to notify the IRB office if they will be unable to attend a meeting. A primary and secondary reviewer will be assigned to the protocol by the IRB staff. At least one reviewer assignment will be based on clinical or scientific knowledge in the area of study. If there is not at least one IRB member with appropriate scientific expertise the IRB staff after consultation with the chair will identify an appropriate consultant to serve as a primary or secondary reviewer. IRB Coordinators, in collaboration with the Chair, will identify protocols with potential vulnerable populations. These protocols will be assigned reviewers who are knowledgeable or experienced in working with vulnerable participants. This reviewer must be present when the study is reviewed at the IRB meeting.

D. On occasion, only one primary reviewer might be assigned. Each is to be evaluated to determine the appropriate level of review. Examples where this may occur: 1) when a protocol and consent has been approved by the full board for one site (Hines or North Chicago) and is now being submitted for the second site, 2) when Hines/NCVA is serving as the coordinating center or statistical analysis center, 3) when studies of minimal risk where full board discussion is required. IRB staff will assure that no direct conflicts of interest (i.e., the IRB member is a co-investigator on the study) exist. IRB staff will minimize indirect conflicts of interest such as an IRB member reviewing his/her supervisor's protocol.

E. **Complete protocols** (include: DHHS approved protocol and sample consent if applicable, methods, exclusion/inclusion criteria, a listing of risks and plans to minimize risk, procedures, endpoints, statistical analysis, all advertisements, questionnaires, surveys; merit reviews and/or grant applications. The complete protocol along with Part I Application, Appendix A, and Informed Consent Document are assembled and distributed to the primary and secondary reviewers, at least one week prior to the meeting. Additionally, the primary reviewer will receive a copy of the Investigator's Brochure and any submitted adverse event reports, when applicable. It is expected that the primary and secondary reviewer will complete an in-depth review of all pertinent documentation.

F. Members: All other members receive Part I Appendix A, Abstract, protocol summary, the informed consent document, HIPPA Authorization and/or Request for Alteration or Waiver and advertising materials, as applicable. When appropriate, complete packets may be distributed to

all members. It is expected that all IRB members review the distributed materials in enough depth to discuss the information at the convened meeting.

G. Protocols are presented by the primary reviewer and information is supplemented by the secondary reviewer. After both reviewers have presented, the protocol is open for discussion. The principal investigator (PI) and/or other study representative may be invited to the IRB meeting to discuss the study and answer any questions the IRB members may have. After all questions have been answered, the PI and/or other study representatives leave the meeting prior to IRB discussions and voting. If a consultant is being used documentation of key elements will be distributed before or at the meeting if the consultant is unable to be present. If the consultant is able to attend the meeting key elements will be discussed and documented in the minutes. The primary purpose of the IRB review is to protect the rights and welfare of human research subjects. Throughout the discussion, recommendations may be made to improve the scientific or ethical merits of the proposal. After discussion of the pertinent issues is complete and committee members are satisfied with the recommendation(s), a motion is made to approve, approve with modifications, table, or disapprove the project. The motion is seconded and a call for further discussion is made. If there is no discussion a vote taken. IRB members may vote to support the motion (Yea), not support the motion (Nay), or abstain from voting.

H. The IRB determines that all criteria for approval are met: 1. Risks to subjects are minimized 2. Risks to subjects are reasonable in relation to anticipated benefits, 3. Selection of subjects is equitable. The recruitment plan will be reviewed to determine of prospective subjects may be vulnerable. 4. Informed consent is adequate and appropriately documented 5. Securing Informed Consent and Documentation of the Informed Consent Process. Informed consent will be sought from each prospective subject, or if approved, the subject's authorized representative. A person knowledgeable about the consenting process and the research to be conducted will obtain the informed consent. 6. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects 7. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data: and 8. Appropriate safeguards have been included to protected vulnerable data. 9. **Conflict of Interest.** Adequate steps to manage, reduce or eliminate potential or real conflicts of interest (financial, role (investigator/patient relationships), and/or institutional) have been taken. All VA investigators must be aware of and comply with VHA policies and procedures regarding conflict of interest. 10. **Investigator's Educational Requirements and Certification: T**he PI and all other investigators of this proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB has determined that the investigator is qualified through education, training, and experience to conduct the research.

I. The IRB evaluates and determines that each protocol has adequate resources to protect the rights and welfare of participants in terms of:

1. Access to a population that would allow recruitment of the necessary number of participants. This is accomplished by review of the protocol to determine the population being studied, review of Part III, Section " SOURCE OF PARTICIPANTS" and Section "Recruitment Information", which identifies the locations where participants will be recruited. In some cases

the investigator is asked to do a query "preparatory to research" to determine if an adequate population is available for the study.

2. Investigator has adequate time to conduct and complete the research, adequate numbers of qualified staff, adequate facilities. This is determined by the investigator and the Service/Section Chief as demonstrated by the signatures on Part I, Section "Certification of Research Proposal Approval". The IRB also reviews the qualifications, responsibilities and human subjects protection training records to assess and that the research team is qualified. The IRB recommends additional staff, consultants/collaborators or additional training as deemed appropriate.

3. A process to ensure that all persons assisting with the research were adequately informed about the protocol and their research-related duties and functions. This is described in Part I (Appendix A), "Principal Investigator Responsibilities" (4) and demonstrated by the investigator's signature. This document is reviewed prior to the approval of any new research study.

J. Final Approval Process: A letter of final approval will be sent to the Principal Investigator by the R&D Office after approval by the R&D and all appropriate subcommittees.

1. IRB approval documents include: VA Form 10-1223, IRB Approval Letter containing study expiration date and listing of PI responsibilities, stamped consent with approval and expiration date, HIPAA documents, and VA Form 10-9012 (as applicable), supply of the VA Pamphlet, “Volunteering in Research”

   It is the Investigator’s Responsibility to provide the Investigational Drug Pharmacist copies of the IRB and R&D Approval, approved protocol and Investigator’s Brochure, approved consent, and signed 10-9012.

2. If the IRB has given approval with modifications, the investigator will be notified in writing, of those modifications. If the IRB recommends substantive modifications to the protocol or consent, or clarifications to the protocol or informed consent, responses will be brought back to a convened meeting. Minor changes and clarification may be reviewed and approved by the Chair or designee. If changes to the informed consent form are made, the investigator must submit an original consent and a revised consent with the changes highlighted. A clean copy of the revised consent must also be submitted for the purpose of stamping the consent form. The investigator may comply with the recommendations or provide a rationale for not doing so. The adequacy of the investigator’s response is reviewed by the chair of the IRB or an IRB member (often times the primary reviewer) or by the full Committee. The investigator’s response may be accepted (full approval), further modifications may be required, or the project may be tabled or disapproved. If the individual reviewer feels that the project should be tabled or disapproved, it must come before the full convened IRB. If final approval is rendered, the voting procedures outlined in #G are followed.

   If modifications are required but not received within 6 months of the review, the IRB has the authority to administratively terminate approval and close the study. Under these conditions, the protocol will need to be re-submitted for reconsideration. A letter of notification will be sent to the PI.

If the IRB has tabled the protocol, the investigator will be notified that the project was tabled and why. The investigator should address the concerns of the IRB. The investigator may comply with the recommendations or provide a rationale for not doing so. The protocol will then be re-reviewed by the convened IRB.

If a protocol is disapproved, the protocol will be returned to the investigator with an explanation for the disapproval. The protocol must be revised and resubmitted as a new protocol in order to be considered for review.

The period of approval for research starts on the date of the convened meeting at which the IRB approved the protocol or approved the research with or without modifications and conducted, at least, annually. A subsequent continuing review will be based on the IRB approval date. The IRB will determine the frequency of continuing review based on the identified risks. Approval cannot extend beyond 365 days.

K. REMOTE ACCESS to data for research purposes from other VA facilities:
Protocols requesting remote access to data from other VA facilities can be approved as long as there is approval from the IRB of record for that location and the ISO from both facilities. A collaborating PI is not required if both facilities have the same IRB (i.e. Hines/NCVA) If the facility is under a different IRB, then a collaborating PI is required.

A VISN 12 COMPUTER ACCESS REQUEST form must be submitted to the facility's Information Security Officer after concurrence by the ACOS for Research and Research IRM Officer and the IRB of record.

L. If the R&D requires changes to the protocol after the IRB approval, the IRB will receive a copy of the revised protocol at the time it is resubmitted to R&D. The IRB will review the changes to determine if the study still meets the criteria for approval. Some may be reviewed by the expedited process; others may require full board review. The letter of final approval is not sent to the PI until the IRB has approved these additional changes.

IRB REVIEW PROCESS FOR TRAINING GRANTS, PROGRAM PROJECTS, AND CENTER GRANTS

Some funding agencies require that training grants, program projects, and/or center grants certify that IRB approval has been obtained. Often times, individual projects are listed within the body of the total grant.

The IRB may grant overall approval of the grant application. Since the overall grant is expected to fund the subprojects, NO HUMAN SUBJECTS MAY BE ENROLLED IN THE OVERALL GRANT. The approval letter will clearly state that individual projects must be approved by the IRB prior to initiation. Each individual "subproject" will be given an individual IRB number upon submission of the subproject and will be treated as an individual project.

RESEARCH EXEMPT FROM IRB REVIEW

A. Policy: Research activities that fit the criteria as set forth in 45 CFR 46.101 or 21 CFR 56.104 may qualify for an exemption from further IRB review. The determination of exempt status must be determined by the IRB chair or designee based on the criteria. Exemption determinations may not to be made by investigators, IRB members/designees or others who might have an apparent or real conflict of interest regarding the studies.

B. Procedure: An investigator wishing to have a research protocol exempted from IRB review must present a request in writing, along with a research proposal, to the IRB.

C. Exempt Criteria: The reviewer will review and document the specific criterion that is appropriate for exempting the proposal from those listed below:
The exempt categories, as stated in Title 38 Code of Federal Regulations (CFR) 16.101(b), are:

a. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
(1) Research on regular and special education instructional strategies, or
(2) Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

b. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior unless:
(1) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
(2) Any disclosure of the subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation, or *loss of insurability in this category.*

c. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under preceding subparagraph 2b, if:
(1) The subjects are elected or appointed public officials or candidates for public office, or
(2) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information must be maintained throughout the course of research and thereafter.

d. Research involving the use or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects.

- The reviewed materials must already exist at the time the research is proposed and are not prospectively collected.

e. Research and demonstration projects that are conducted by, or subject to, the approval of department or agency heads, and that are designed to study, evaluate, or otherwise examine public benefit or service programs, procedures for obtaining benefits or services under such programs, possible changes in or alternatives to such programs, and possible changes in methods

or levels of payment for benefits or services under such programs. ***NOTE:*** *The determination of exempt status for these research and demonstration projects must be made by the Under Secretary for Health on behalf of the Secretary of Veterans Affairs, after consultation with Office of Research and Development, the Office of Research Oversight, the Office of General Counsel, and other experts, as appropriate.*

- There must be no statutory requirements for IRB review
- The Project must not involve significant physical invasions or intrusions upon the privacy of the participants
- This exemption is for projects conducted by or subject to approval of Federal agencies.

f. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

If the project is subject to FDA regulations, pursuant to 21 CFR 56.104, the following categories of clinical investigations are exempt from the requirements of IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

D. Approval Process: The IRB chair shall review all requests for exemption in a timely manner. If the chair or designee determines that the project meets the criteria for an exemption and fulfills the ethical standards, the project will be reported to the IRB and documented in the minutes and the determination forwarded to the R&D for approval and annual review. The investigator will be notified in writing of the decision of the Chair or designee. The Chair's designee will be the Associate Chair, or a member with appropriate professional education and at least one year experience on the Committee.

EXPEDITED REVIEW OF HUMAN STUDIES

Applicability

A. The following research activities are appropriate for expedited review:

1. Research that presents no more than minimal risk to human subjects, and
2 Research that involves only procedures described below

- The expedited review process may not be used when identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability; or be damaging to the subject's financial standing, employability, insurability, and/or reputation; or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are minimal.
- The expedited review process may not be used for classified research involving human subjects.
- The research categories appropriate for expedited review pertain to both initial and continuing IRB review.

3 Minor changes to the previously approved research within the approval period. A minor change is one that would not change the risk/benefit ratio, would not change the IRB's conditions for approval and would not impact a subject's decision to remain in the research.

4 Waiver or alteration of authorization for the use or disclosure of Protected Health Information (PHI).

B. New Research or Continuing Review: Use of Expedited Criteria for approval of new research: Any of the categories of research listed below, if they are found by the Chair or designee to involve no more than minimal risk, may have expedited review. It is expected that the IRB Chair or designee, as the primary reviewer, consider all pertinent documents and all information that the convened IRB would have reviewed. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only by a convened IRB. The review of new research or continuing review through expedited procedures will be documented by in writing and reported to the convened IRB.

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.
   b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   a. From healthy, nonpregnant adults who weigh at least 100 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[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means

Examples: (1) hair and nail clippings in a nondisfiguring manner; (2) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (3) permanent teeth if routine patient care indicates a need for extraction; (4) excreta and external secretions (including sweat); (5) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying dilute citric solution to the tongue; (6) placenta removed at delivery; (7) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (8) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (9) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (10) sputum collected after saline mist nebulization.

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

Examples: (1) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (2) weighing or testing sensory acuity; (3) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral

history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

8. Use of expedited review may be used for Continuing Review of research originally approved under expedited review criteria or for protocols approved by the convened IRB as follows:

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

9. Use of expedited review may also be used for **Continuing review of research, not conducted under an investigational new drug** application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

C. The IRB determines that all criteria for approval are met: 1. Risks to subjects are minimized **2**. Risks to subjects are reasonable in relation to anticipated benefits, **3.** Selection of subjects is equitable **4**. Informed consent is adequate and appropriately documented, **5**. Securing Informed Consent and Documentation of the Informed Consent Process. Informed consent will be sought from each prospective subject, or if approved, the subject's authorized representative. A person knowledgeable about the consenting process and the research to be conducted will obtain the informed consent. **6.** Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects **7.** There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data: and **8.** Appropriate safeguards have been included to protected vulnerable data. **9**. Conflict of Interest Adequate steps to manage, reduce or eliminate potential or real conflicts of interest (financial, role (investigator/patient relationships), and/or institutional) have been taken. All VA investigators must be aware of and comply with VHA policies and procedures regarding conflict of interest. **10.** Investigator's Educational Requirements and Certification**:** The PI and all other investigators of this proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB has determined that the investigator is qualified through education, training, and experience to conduct the research.

D. Procedures: An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 38 CFR 16.110. A list of approved IRB members that may conduct expedited review for new and continued proposals is maintained in the IRB office. The list is updated regularly by the Chair/Associate Chair. At a minimum, the IRB designee must have one year of experience at as IRB member.

1. The submission of a protocol for expedited review follows the same procedures as full-review protocols. The investigator should indicate, however, if he/she wishes their protocol to be considered for expedited review.
2. The Chair of the IRB or designee will review the documents to determine whether an expedited review is warranted. After careful review of the protocol, if the Chair or designee decides that all requirements for expedited review are met, an approval is issued. The date of approval is the date the protocol is reviewed and approved by the Chair or designee.
3. If the Chair or designee decides that a full review is warranted, then a full review will be required.
4. In reviewing the research, the reviewer may exercise all of the authorities of the IRB except that the reviewer may not disapprove the research. A research activity may be disapproved only after full IRB review in accordance with the non-expedited procedure.
5. Research on marketed drugs that significantly increase the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.
6. The approval of the project will be reported at the next meeting of the IRB and it will be recorded in the minutes [38 CFR 16.110(b)(2)].

CONTINUED REVIEW
(MONITORING ON-GOING PROJECTS)

A. Policy: It is the policy of the HVAH and NCVAMC IRB to conduct Continuing Review as an ongoing process. The IRB conducts formal Continuing Review of nonexempt research involving human subjects at intervals appropriate to the degree of risk, but not less than once per year [21 CFR 56.108(a)(1) and 56.109(e)] [45 CFR 46.109(e)],

B. Purpose: The focus of the continuing review will be:

1. To assure that federally established criteria and conditions of IRB approval are being met and that there are no instances of non-compliance.
2. To assess serious adverse events for commonalities or oddities that may suggest increased risk, reduced potential benefit, investigator error, or evidence that the HVAH and/or NCVAMC population is different than others.
3. To review the current informed consent document to ensure it is still accurate and complete.
4. To determine if any new information regarding the test article requires an amendment or Consent Form revision, or if new information needs to be communicated to research subjects.
5. To ensure prompt reporting to the IRB of changes in research activity has been completed.
6. To approve, require modifications in (to secure approval) or disapprove/table the project.
7. To determine a new Continuing Review date based on the degree of risk
8. To determine any protocol deviations and/or violations.
9. To assess investigator compliance.
10 To process appropriate management of protocols with lapsed approval.
11. To insure that no modifications to the approved research have been implemented without prior IRB approval except to eliminate immediate hazard to the participant(s)

C. Procedures: The review will be carried out by a fully convened IRB or per expedited review by the Chair or designated reviewer.

1. The investigator must submit to the IRB a written progress report that includes:
   a. Brief summary of the research methodology and procedures;
   b. Number of subjects screened, entered and withdrawn (including the reason for withdrawal) for the review period and since the inception of the research project;
   c. The gender and minority status of those entered into the protocol;
   d. Number of subjects considered as members of specific vulnerable populations;
   e. A copy of the proposal and a listing of all approved amendments since the last review;
   f. A copy of the current (stamped) consent document (and one unstamped consent) for the IRB to review to determine whether the information contained in it is still accurate and complete, including whether new information has been obtained during the course of the study;
   g. A copy of the current HIPAA Authorization document, if separate from the informed consent;
   h. A summary of Adverse Events, unanticipated problems involving risks to participants or others and a summary of complaints about the research since the last IRB review.

i. Research findings to date, if available;

j. Summary of the DSMB or DMC meetings (if applicable) or findings based on information collected by the data and safety monitoring plan submitted in the initial proposal;

k. Copies of all monitoring reports (includes FDA, OHRP, ORO, sponsor)

l. An assurance that all SAEs and UAEs have been reported as required; and

n. New scientific findings in the literature, or other relevant findings, that may impact on the research

o. List of all subjects entered into the study since last approval and their veteran/non-veteran status.

p. List of all personnel involved in the study and dates of most current human subject protection education certificates. Also, identification of any personnel who have left the study.

q. A summary of participant benefits.

2. If the continuing review does not occur within the timeframe set by the IRB, the research automatically lapses approval and no more research activities can be conducted until appropriate continuing review is done. The IRB office will promptly notify the PI and the Chief of Staff and Service Line Chief in writing of the lapse of approval.

NOTE: *For research with lapsed approval, enrollment for new subjects cannot occur; continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB or IRB Chair, in consultation with the Chief of Staff (COS), finds that it is in the best interest of individual subjects to do so.*

a. Once notified of the lapse of approval, the PI must immediately submit to the IRB Chair, a list of research subjects for whom lapse of approval of the research would cause harm. The IRB Chair, with appropriate consultation with the COS, determines if the subject may continue in the research.

b. 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.

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

d. Once approval has lapsed, IRB review and re-approval must occur prior to re-initiation of the research.

e. If the investigator continues to do research after being notified of the lapse in approval, this will be considered non-compliance. With continued non-compliance, the IRB will determine the appropriate course if action. This may include, education, or the study may be suspended (put all studies activities on hold for a period of time, until questions, compliance or risk issues have been resolved) or terminated (stop the conduct and approval of the study permanently). The IRB or person approving the suspension or termination, will determine if the subjects are to be notified of the suspension/termination. Any adverse events or outcomes will be reported to the IRB. This suspension or termination is reportable to the R&D Committee, ACOS- Research, Hospital Director, ORD, ORO, OHRP or other Federal agencies, as appropriate. The report documenting the nature of the termination/suspension, IRB action and outcome, will be written by the IRB Staff, approved by the Chair, and routed through the ACOS-Research to the Chief of Staff and Hospital Director to: the Regional Office of ORO, OHRP, and/or FDA , if the study involves a test article or device regulated by the FDA. The sponsor will be notified in

writing if required. This will be written by the Chair of the IRB. Reporting will be done within 5 working days of the IRB determining the suspension or termination as required by VHA Handbook 1058.01

3. The IRB has the authority to consider suspension or termination of a previously approved study if there is unexpected serious harm to participants.

4. On an urgent basis, the Chair, IRB can suspend/terminate the approval of a previously approved study, such as when there is the risk or occurrence of serious harm to a participant, and report the event to the next convened IRB. This action will be reported to ORO within 5 working days through the Director as required by VHA Handbook 1058.01.

D. Review System:

The IRB uses a primary reviewer system for conducting formal Continuing Review (CR). The IRB coordinator conducts an initial audit of the entire file and completes the initial IRB Continuing Review Worksheet. The expectation is that the primary reviewer will perform an in-depth review of all submitted materials. The primary reviewer reviews the entire file and all documents submitted by the investigator for CR, including the protocol, all changes to the protocol within the previous year, all reported adverse events, subject recruitment, enrollment and withdrawal, monitoring reports and the consent document. The IRB members receive the progress report (summary), abstract, most recent Informed Consent and a copy of the audit which includes a summary of adverse events, unanticipated problems, and complaints. This information is derived from the materials submitted by the investigator. The audit or status report worksheet also includes number of subjects, number of subjects withdrawn, status of the project and a summary of amendments with verification that no material changes had occurred since the previous IRB review. Additional information is available to any IRB member who wishes to review it. The expectation is that all IRB members will review the provided materials in enough depth to discuss the information at the convened meeting. The primary reviewer summarizes their review for the Committee. The above aspects of the review are covered. The protocol is then discussed, a recommendation made and a vote taken of the entire Committee. The vote may be to approve, defer for additional information, which may cause a lapse of approval, defer for education, or suspend the project (at which time a decision will be made about the disposition of current and future subjects until specified issues are resolved). The vote may also disapprove the research project. The minutes will reflect YEA, NAY and ABSTENTION votes.

E. Criteria for Approval of Continuing Review:

1. Risks to subjects are minimized 2. Risks to subjects are reasonable in relation to anticipated benefits, 3. Recruitment and Selection of subjects is equitable 4. Informed consent is adequate and appropriately documented 5. Securing Informed Consent and Documentation of the Informed Consent Process. Informed consent will be sought from each prospective subject, or if approved, the subject's authorized representative. A person knowledgeable about the consenting process and the research to be conducted will obtain the informed consent. 6. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects 7. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data: and 8. Appropriate safeguards have been included to protected vulnerable data. 9. Conflict of Interest. Adequate steps to manage, reduce or eliminate potential or real conflicts of interest (financial, role (investigator/patient relationships), and/or institutional) have been taken. All VA investigators must be aware of and comply with VHA policies and procedures regarding

conflict of interest. 10. Investigator's Educational Requirements and Certification: The PI and all other investigators of this proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB has determined that the investigator is qualified through education, training, and experience to conduct the research.

F. Documentation: The discussion and vote of the Continuing Review is reflected in the minutes. The investigator will receive confirmation signed by the IRB Chair or designee and the ACOS/Research.

G. The IRB has the authority to use expedited review procedures for Continuing Reviews when the study was originally approved per expedited criteria, and continues to be minimal risk, or when a study was originally approved by a convened IRB as follows:

1. when (a) the research is permanently closed to the enrollment of new subjects; (b) all subjects have completed all research-related interventions; and (c) the research remains active only for long-term follow-up of subjects; or
2. when no subjects have been enrolled and no additional risks have been identified since the last review; or
3. when the remaining research activities are limited to data analysis.

When a study, previously reviewed by a convened IRB, meets criteria for expedited review, these criteria are documented on the Reviewer Worksheet and in the minutes.

H. The IRB has the authority to increase the frequency of review, or to suspend or terminate an ongoing study if indicated by its review [21 CFR 56.108(b)(2) and 56.113].

Studies which may be considered for more frequent review include:

1. Withdrawal of therapy, whether or not it is replaced by experimental treatment, when there is significant risk of morbidity or mortality;
2. Any invasive surgical procedure, even if the experimental procedure replaces a standard surgical procedure that is thought to involve higher risk;
3. Significant risk of serious impairment;
4. Risks when there is no potential clinical benefit to the subject (e.g., Phase I studies);
5. Vulnerable subjects

I. Data Analysis 3 years or more: Any study which has been in data analysis for 3 years or more, must submit specific justification at the time of continuing review for keeping the study open.

J. Resubmission of Studies if active to enrollment more than 7 years.

1. All projects *actively recruiting subjects for 7 years shall be* resubmitted for full board review. A three month approval period may be granted for the principle investigator to determine the disposition of project. Studies will maintain their initial IRB study

numbers. If the study is not resubmitted, approval will lapse and it will be closed by the IRB.

2. Forms which must be completed (as applicable) for resubmission after 7 years of active to enrollment are to include at least the following:

APPENDIX A "Human Subjects" Section and all other appendices as appropriate, i.e.:

- Updated Protocol
- Consent
- Budget
- Updated references
- Abstract
- Drug forms as appropriate: IND, (H) Pharmacy Approval, H(1) Drug Charges, 10-9012 Form
- Appendices for Radiology / Nuclear Medicine / Laboratory (as applicable).
- Recruitment of Non-Veterans (as applicable).
- Reports of Findings to date

REPORTING IN WRITING, FINDINGS AND ACTIONS OF THE IRB TO THE INVESTIGATOR, THE IRB MEMBERS, R&D COMMITTEE AND THE INSTITUTION

A. The IRB promptly documents in writing to the Principal Investigator all IRB actions. These include written communication from the IRB to the Principal Investigator for additional information, for conveying IRB findings and for acknowledgment of notifications received. The IRB minutes will be completed available for review within 3 weeks of the associated meeting date. The IRB submits reviewed and approved minutes to the HVAH /NCVAMC Research and Development Committee. The Research and Development Committee and IRB minutes are reviewed by the Medical Center Director. IRB records and correspondence are maintained in permanent study files located in the IRB administrative offices, Room C334. Project data information is entered into the national VA Research and Development Information System (PROMISE) and maintained in a designated IRB computerized database

B. Minutes of an IRB Meeting. Proceedings must be written and available for review within 3 weeks of the meeting date. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority. Minutes of IRB meetings must contain sufficient detail to show:

1. The presence of a quorum throughout the meeting including the presence of one member whose primary concern is in a non-scientific area and as possible, one non-affiliated member.
2. Attendance at the meetings including those members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.
3. Alternate members attending the meeting and for whom they are substituting.
4. Actions taken by the IRB including those involving full review. The minutes will reflect separate deliberations and actions taken for each protocol undergoing initial and continuing review. Attendance for each action will be recorded.
5. Documentation in the minutes to notify IRB members of actions taken through expedited review and those studies that have been determined to be exempt from IRB review.

NOTE: *These required notifications may be carried out through other mechanisms.*

6. Documentation of the required findings (38 CFR 16.116 or 16.117) when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent. A justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document that was approved by the IRB will be recorded.
7. The vote on actions including the number of members voting for, against, and abstaining. Votes be recorded in the minutes using the following format: Total = 15; Vote: YEA-14, NAY-0, Abstained-1. The name of the member abstaining will be recorded. In addition, attendance will be kept to document who was present at each vote.

8. A note indicating that when an IRB member has a real or potential conflict of interest relative to the proposal under consideration, the name of the member and that the IRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained).

9. The basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs. Rationale for required modifications or research disapproval will be recorded.

10. A written summary of the discussion of controversial issues and their resolution;

11. Determinations and rationale for significant risk/non-significant risk devices will also be recorded.

12. Review of additional safeguards to protect vulnerable populations if entered as study subjects when this is not otherwise documented in IRB records;

13. The determination of the level of risk, if not recorded elsewhere in IRB records.

14. The frequency of continuing review of each proposal as determined by the IRB if not recorded elsewhere in IRB records.

15. The approval period (dates) for both initial and continuing reviews will be incorporated into the motion. The approval starts on the date of the meeting in which the research was approved by the IRB

16. When a study, previously reviewed by convened IRB, meets criteria for expedited review, these criteria are documented on the Reviewer Worksheet and in the minutes.

17. Documentation of determination required by regulations and protocol specific findings and justifying findings will be recorded for waivers or alterations of the consent process. (as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization.)

18. If the convened IRB approves research contingent on specific minor conditions, the IRB Chair, or another IRB member designated by the Chair, may approve the revised research protocol on behalf of the IRB. The approval by the Chair, or designee, must be documented in the minutes of the first IRB meeting that takes place after the date of the approval.

19. Performance Improvement, Section H in the Minutes will include: Findings, Improvements required, Improvements Implemented and Plan for Follow-up to assess the effectiveness of Improvements.

C. **`:** The IRB will report its activity and any significant issues to the Research and Development Committee. This is accomplished by R&D receipt, review and approval of the IRB minutes, and reports to the R&D Committee by the Chair or Associate Chair at the monthly meetings

D. **Reporting to the Medical Center Director and Chief of Staff**

The IRB will report suspensions, terminations, serious or continuing non-compliance, serious unanticipated problems, or adverse events as required by VA policies,

E. The IRB will report expiration of IRB approval to the Chief of Staff and Service Line Chief

F. The IRB will report or ensure the report, to the **Privacy Officer** any unauthorized use, loss or disclosure of individually identifiable patient information (1200.05.7.d(12)).

G. The IRB will report, or ensures the report of, violations of VA information security requirements to the appropriate VHA Information **Security Officer** (1200.05.7.d(13)).

FUNCTIONS OF THE IRB

The IRB will:

A. **Protect the rights and welfare of all human research subjects at HVAH or NCVAMC.**

B. Determine if the project meets the criteria for "Engaged" or "Not-Engaged" in research based on ORHP guidelines.

C. Determine if the project meets the Common Rule definitions of: 1. Research, 2. Human Participants, 3) the FDA definition of clinical investigation, 4) whether or not the project meets one or both sets of definitions.

D. The IRB reviews and has the authority to approve, require modifications in (to secure approval) or disapprove/table all human research activities conducted under the auspices of HVAH and NCVAMC.

E. Evaluates and determines that each protocol has adequate resources to protect the rights and welfare of participants.

F. Determine if a project meets the federal criteria for exemption from IRB oversight.

G. Determine if a project meets the federal criteria for waiver of consent or waiver/alteration in documentation of informed consent.

H. Determines if devices are Significant Risk or Non-significant Risk.

I. Reviews the design of the protocol and determines whether research was designed to answer the proposed question and the importance of the knowledge reasonably expected to result from the research. The Research and Development (R&D) Committee evaluates whether the research used procedures consistent with sound research design. The R&D Committee's scientific review is communicated to the IRB through the attendance of the chair and IRB coordinators at the monthly meetings. The R&D minutes are also distributed to all R&D meeting attendees. All required modification and responses are forwarded to both the R&D and IRB. The IRB reviews these modifications and determines if they are appropriate for approval. No studies are granted final approval until the R&D and all subcommittees have granted approval.

J. Determine if potential benefits outweigh potential risks and assure that the consent document does not overstate the benefits or understate risk and the risks are reasonable.

K. Determines the study payment should not be contingent upon completion of the entire study but prorated according to the pre-determined periods of participation.

L. Determines that any amount of payment to the participants as a bonus for completion of the study is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

M. Determine which studies need to be reviewed by the IRB more frequently than annually.

N. Determine which studies need verification from sources other than the Principal Investigator(s) that no material changes have occurred since the previous IRB review.

O. Ensure prompt reporting to the IRB of changes in research activities.

P. Ensure that changes in approved research are not initiated without IRB approval, except where necessary to eliminate immediate hazards, or danger to study participants. Such changes are to be reported within 24 hours in writing, to the Chair, IRB.

Q. Ensure reporting to the appropriate institutional officials according to timeframes described in this policy, the FDA, OHRP, Office of Research Oversight (ORO) and ORD (Office of Research and Development), as required by policy or regulations.

R. Insure that DHHS required basic elements of informed consent are stated.

S. Require that additional information be given to subjects if this meaningfully adds to subject protection or subject's desire to continue in the study.

T. Identify Radiation Safety issues and determine the level of review necessary. If required, projects are not approved until radiation safety approval is obtained.

U. Identify vulnerable populations and insure that they are not exploited or being coerced.

V. Assure that IRB members receive all pertinent materials necessary to conduct an appropriate review. (Note: all members have access to complete study documentation in the IRB office.) At minimum these include:

    1. Initial review: (* = to the primary and secondary reviewers, chair) – protocol/grant application*, investigator brochure*, abstract, proposed consent form, surveys and questionnaires, appropriate safety reviews, budget, relevant R&D and IRB applications, advertising intended to be seen or heard by potential subjects.

    2. Continuing review (* = to the primary reviewer only) – protocol including review sheet of previous actions*, list of research subjects signed by the investigator*, continuing review audit form*, continuing review form, abstract, informed consent form, advertising or other correspondence intended to be seen or heard by potential subjects.

W. Require documentation of Informed Consent and approval of the Consent by the IRB, unless a specific waiver is granted by the IRB or unless specific criteria for exception from Informed Consent are met for emergency use of a test article. The IRB may also monitor the consent process routinely or for cause.

X. Convey IRB findings in writing to the Principal Investigator, to the Research and Development Committee, and if required to a sponsor, ORD, ORO or other regulatory agency. In most cases, consent forms are approved at a convened IRB meeting. Instructions to modify the Consent Form will be sent to the investigator and after the

stipulated changes are made and verified, a formal IRB approval letter is issued. If a submission is disapproved or tabled it must be re-submitted for full board review at a convened meeting. All IRB actions and communications are maintained in the IRB computerized database.

Y. Provide to Principal Investigators a VA Informed Consent form 10-1086 template that includes federally required statements. All consent form versions are reviewed and approved by the IRB and filed in the project folder.

Z. Require that new findings potentially impacting subjects' willingness to participate in studies are conveyed to subjects.

AA. Determine which projects may require independent verification that no material changes have occurred between the initial and continuing review periods.

BB. The Committee has the authority to observe the consent process and verify records to insure that only approved research activities are being conducted and [21 CFR 56.108(a)(2)]. Cause for verification may be prompted by:

1. complaints;
2. observations that indicate non-compliance;
3. unanticipated problems; and
4. serious adverse events.

CC. Require that serious deviations from approved protocols are promptly reported to the IRB and that new procedures are not initiated without review and approval except to eliminate apparent immediate hazard to human subjects [21 CFR 56.108(a)(4)]. Any proposed changes to the research that are not minor (e.g., procedures involving increased risk or discomfort), must be reviewed and approved at a convened meeting of the IRB.

DD. Require prompt reporting to the IRB and if required, to the sponsor, FDA, OHRP, ORO, ORD, VA, or other regulatory agency any Serious Adverse Events or Unanticipated problems involving risk to human subjects or others. The IRB will report instances of serious or continuing non-compliance that results in suspension or termination of research privileges to the appropriate institutional and agency officials (i.e. the sponsor, FDA, OHRP, ORO, ORD).

EE. Require that Continuing Review be conducted as previously stated (see Continuing Review Section).

FF. Ensure prompt reporting to the IRB of changes in research activities and ensure that changes in approved research are not initiated without IRB review [21 CFR 56.108(a)(3); 21 CFR 56.108(a)(4) and 56.116(a)(1)].

The IRB Approval Letter contains the following: "…You are granted permission to conduct your study as described in your application effective immediately. The study is subject to continuing review on or before [date], unless closed before that date. Please note that any changes to the study as approved must be promptly reported and

approved. Some changes may be approved by expedited review; others require full board review…"

GG. Ensure prompt reporting of the following to the IRB, appropriate Institutional Officials and FDA , OHRP, ORO, ORD, of:

1. Unanticipated problems involving risks to subjects or others [21 CFR 56.108(b)(1) and 56.115(a)(1)] VHA Handbook 1058.01. (See section on Adverse Events)

2. Serious or continuing noncompliance with 21 CFR Parts 50 and 56 or the Requirements of the IRB [21 CFR 56.108(b)(2)].

   The concerns of the IRB will be conveyed to the Principal Investigator in writing, and a written response addressing the IRB concerns is required from the Principal Investigator. The IRB may vote to restrict, suspend or terminate an investigator's privilege to conduct research at HVAH or NCVAMCs if it finds that research activities are continually (either purposefully or through careless disregard) not being conducted in accordance with federal regulations governing human research. Any suspension or termination of approval to conduct research at HVAH or NCVAMC will be conveyed to the Principal Investigator in writing and will include the reasons for the action. All instances of serious or continuing noncompliance that result in suspension or termination of research will be reported to HVAH and/or NCVAMC officials and to pertinent agency officials (i.e. VA Headquarters, FDA, OHRP, ORO). All correspondence will go through the Chair of the IRB, and ACOS of Research under the signature of the Medical Center Director(s). Suspension or Termination of IRB Approval [21 CFR 56.108(b)(3) and 56.113] [45 CFR 46.113].

   The IRB may vote to suspend or terminate approval of research not being conducted in accordance with IRB or federal requirements or that has been associated with unexpected serious harm to subjects. The PI must immediately submit to the IRB Chair, a list of research subjects for whom suspension or termination of the research would cause harm. The IRB Chair, with appropriate consultation with the COS, determines if the subject may continue in the research. The concerns of the IRB will be conveyed to the Principal Investigator in writing, and a written response addressing IRB concerns is required from the Principal Investigator. Any suspension or termination of approval will be conveyed in writing to the Principal Investigator and will include a statement of the reasons for the IRB's action. The suspension or termination of IRB approval will be reported as required, to appropriate HVAH and/or NCVAMC and agency officials (e.g., VA, ORO, FDA, OHRP). All correspondence will go through the Chair of the IRB, and ACOS of Research under the signature of the Medical Center Director(s).

HH. Determine which device studies pose significant or non-significant risk [21 CFR 812]. (See Investigational Device Section.)

II. If indicated (i.e., for cause), the IRB reserves the right to limit the number of projects conducted by an investigator. Such determinations will be made on an individual basis. Investigators may be asked to document how they maintain adequate supervision over multiple studies.

JJ. Conduct for cause investigations.

KK. Collaborate and cooperate with the Research Compliance Officer (RCO) for routine regulatory and consent audits.

LL. Investigator non-compliance will be tracked and reported to the IRB. Reports of findings will also be forwarded to the R&D Committee and reported as required to appropriate agency officials.

GENERAL OPERATIONS OF THE IRB

The following IRB processes will generally be followed:

A. Meetings are scheduled on the first and third Mondays of the month at noon and as needed. Meetings are held in Room C308 (Research Conference Room) at HVAH. Deviations will be announced to all members. Meetings will be rescheduled for federal holidays, lack of a quorum or for cause at the direction of the Chair.

B. At least one week prior to the meeting, members will receive an agenda and copies of review materials for all proposals and action items to be reviewed at the meeting. The review materials are described in the SOP Chapter *Functions of the IRB*, Letter P.

C. The review process and description of the process ensures that:

1. All members receive appropriate study documentation to review. Review materials are described in Functions of the IRB, Letter P. All study materials are available to all members in the IRB office.
2. Ad hoc reviewers receive personal copies of complete study materials necessary to conduct a thorough review.
3. There are no standing subcommittees of the IRB. Ad hoc subcommittees are appointed as needed.
4. Physicians/investigators must report to the IRB in writing any non-approved emergency use of test articles within five working days. Prospective use of test articles without IRB approval is addressed in the Exemption from Prospective IRB review section.
5. Expedited review procedures are described under the Expedited Review section of these SOPs [21 CFR 56.110(a)(b)] [38 CFR 16,110] [45 CFR 46.110].
6. Changes to the study (amendments/revisions) are reviewed by the IRB Chair or Associate Chair, and include a review of all documents submitted by the investigator. The Chair, Associate Chair, or designee does an in-depth review of all pertinent documents. They serve as primary reviewers and determine if the change requires full board or expedited review. If it is full board, prior to the meeting, the IRB members receive a copy of the amendment request, sufficient information about the proposed modification, which may include a summary of the proposed changes or a complete copy of the revised protocol, and revised consent document, if applicable, to determine whether the modified research continues to fulfill the criteria for approval. The criteria considered for approval of a modification to previously approved research are the same as those for an initial review. When changes require full board review (more than minimal risk), the Chair presents the revisions to a convened IRB for discussion and approval. The changes cannot be initiated without IRB approval except when necessary to eliminate apparent immediate hazards to participants. Changes meeting the criteria for expedited review within the approval period, may be reviewed by the Chair, IRB or designee and reported to the IRB and documented in the IRB minutes.

SECURITY OF IRB RECORDS

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.

Project Files: In order to ensure confidentiality and security of IRB Office Project Files, the following process is to be followed:

A. Access to pull and review IRB Project Files is limited to the Research and Development Administrative Staff, the IRB staff and members and the Chairs of the R&D and Research Safety Committee. Access to files by Regulatory Officials and/ or other personnel will be coordinated with the IRB office staff and this access will be logged.
B. The files will be continuously under surveillance or in a locked room.
C. Other personnel reviewing the IRB Project Files will do so with the permission and oversight of one of the approved staff mentioned above.
D. Permission from the principal investigator will be obtained whenever other staff, not involved in the project, request to review a file and/or if a conflict of interest is identified.
E. When logging access to the files, the log will include the date removed, number of the file, brief description of the title of the file, name of the person removing the file, and the reason for removal and date returned
F. IRB project files may not be destroyed.

CRITERIA FOR IRB APPROVAL

Criteria for conducting reviews include a determination by the IRB or the Chair, or designee (for studies meeting the expedited review criteria) that:

A. **Minimization of Risks:** Risks to subjects are minimized by using procedures that are consistent with sound research design and that do no unnecessarily expose participants to risk, and whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

B. **Reasonable Risk Benefit Ratio:** Risks to subjects are reasonable in relation to anticipated benefits, all known risks are included in the consent form, and sponsors and Principal Investigators have not used language that inappropriately minimizes risks and exaggerates potential benefits. Benefits can take the form of therapy, education, information, resources or empowerment and can be directed at the participant or the community. The IRB should only consider those risks and benefits that may result from the research.

C. **Equitable Selection of subjects:** Selection of subjects is equitable based on the purposes of the research and the research setting.

D. **Review and Approval of the Informed Consent:**

1. Informed consent is adequate, appropriate to the population involved and appropriately documented or if appropriate, the approval of waiver or alteration of the informed consent or the waiver of documentation of informed consent.

2. IRB approval of the wording of the consent is 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. If the consent form is amended during the protocol approval period, the form will bear the approval date of the amendment, rather than the date of the approved protocol.

3. The IRB has reviewed the required language for a valid HIPAA authorization to release health information, or if appropriate, the approval of waiver of HIPAA authorization.

E. Securing Informed Consent and Documentation of the Informed Consent Process. Informed consent will be sought from each prospective subject or, if approved, the subject's authorized representative. A person knowledgeable about the consenting process and the research to be conducted will obtain the informed consent.

F. **Monitoring Safety:** The research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects. The plan includes appropriate procedures for reporting AEs.

G. **Protection of Vulnerable Subjects.** Additional safeguards have been included in the study to protect the welfare of subjects likely to be vulnerable to coercion or undue influence.

H. Certain studies may require special attention including:

1. Withdrawal of therapy, whether or not it is replaced by experimental treatment, when there is significant risk of morbidity or mortality.

2. Any invasive surgical procedure (including arterial catheterization), even if the experimental procedure replaces a standard surgical procedure that is thought to involve higher risk.
3. Significant risk of serious impairment.
4. Risks when there is no potential clinical benefit to the subject. (e.g. Phase I studies).

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

J. **Conflict of Interest.** Adequate steps to manage, reduce or eliminate potential or real conflicts of interest (financial, role (investigator/patient relationships), and/or institutional) have been taken. All VA investigators must be aware of and comply with VHA policies and procedures regarding conflict of interest.

K. **Investigator's Educational Requirements and Certification:** The PI and all other investigators of this proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB has determined that the investigator is qualified through education, training, and experience to conduct the research.

L. Adequate provisions are in place for monitoring at least annually research data collected to ensure the safety of subjects. Continuing Review is scheduled at convened meetings and is based on risk assessment. A Continuing Review reminder is emailed 6 weeks in advance of the due date. If Continuing Review is not submitted in a timely manner approval will lapse. A notice will be sent to the PI and COS and Service Line Chief. All activities will cease until review and approval by the IRB is completed. If subjects are still participating, the PI, Chair IRB and COS will determine what interventions/observations are required to be continued to maintain the safety of the subjects.

APPEAL OF AN IRB DECISION

A. Criteria for Appeal

Appeals of IRB decisions to Disapprove/Table a submission may be addressed to the IRB by re-submission. Re-submissions should be accompanied by a cover letter detailing changes made or a justification of why recommended revisions were not made. Principal Investigators, study coordinators and/or sponsor representatives may be requested to attend an IRB meeting. The protocol may be re-submitted once for review to achieve approval.

Appeals of specific actions taken by the IRB may be submitted via a letter justifying the reason for the appeal.

Appeals of suspension or termination of research privileges must be submitted to the IRB. The convened IRB will vote to sustain or lift privileges.

B. To Whom the Appeal is Addressed

The appeal should be addressed to the Chair of the IRB, Research Service (151), Hines VA Hospital, Hines, IL 60141

C. Resolution of the Appeal (Override of IRB disapprovals by external body/official is prohibited)

The IRB shall approve or disapprove all appeals. All research activities, including any IRB decision regarding an appeal is subject to further review by the Research and Development Committee and Director. Neither the Research and Development Committee, ACOS for Research, Facility Director, or external body or official can override the IRB disapprovals.

IRB RECORDS

IRB Records and Retention: The IRB Coordinator will prepare and maintain adequate documentation of IRB activities, including the following:

A. IRB Membership Roster Showing Qualifications: The IRB membership roster is maintained and includes member names, alternate names, affiliation status, specialty and VA relationship. Individuals with cultural diversity, knowledge of community values, experience with vulnerable populations, medical expertise, and those who are respected by their colleagues are represented in IRB membership. See Appendix B. Curriculum vitas of all IRB members are maintained in the IRB Office.

B. Written Standard Operating Procedures and Guidelines: [21 CFR 56.108(b) and 56.115(a)(6), 38 CFR 16.103(a-b) and 16.108, 46 CFR 103(b)(4) and 103(b)(5) and 46.108]: FDA (21 CFR), VA (38 CFR) and DHHS (46 CFR) require that an Institutional Review Board (IRB) operate according to written Standard Operating Procedures (SOPs) to ensure protection of the rights and welfare of individuals involved as subjects of research. There is significant overlap between FDA, DHHS and VA which at times are addressed individually in these SOPs but the requirements do not differ significantly. SOPs will be reviewed, revised and updated to incorporate new regulations and policies at a minimum every 3 years. Interim changes will be distributed at convened meetings for the IRB members and via e-mail for researchers. Updated Versions of the SOPs will be approved at a convened meeting of the IRB. The updated versions of the IRB SOPs will be summarized by the Chair, IRB at a convened R&D meeting.

C. Minutes of the Meetings: Meeting agendas and minutes are prepared for each convened IRB meeting. The IRB minutes will be completed for review within 3 weeks of the meeting date. . The content of the minutes is described in a previous section titled REPORTING IN WRITING, FINDINGS AND ACTIONS OF THE IRB TO THE INVESTIGATOR AND THE INSTITUTIONS, Letter B.

D.. **Retention of Protocols Reviewed and Approved Consent Documents**: The IRB records will include (Full Board, Expedited, and Exempt Documents) :

- Scientific Evaluations (IRB & R&D Scientific Reviews will be filed in Protocol Files)
- DHHS approved protocol and sample consent form, if applicable
- Approved Informed Consent (Stamped with dates)
    - Statements of significant new findings provided to participants included in Consent Form
- Reports of injuries to participants (Adverse Events)
- Record of continuing review activities.
- Description of action taken by the reviewer (IRB Reviewer Worksheet)
- Determinations required by the regulations along with protocol-specific findings justifying those determinations
- If Expedited or Exempt - specific permissible category

IRB records must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). When appropriate, records will be disposed of in a secure manner (e.g., shredding appropriate documents).

E. Communications to and from the IRB: All communications to and from the IRB are written. Copies are filed in the IRB s investigator project file.

F. **Adverse Reactions Reports and Documentation that the IRB Reviews such Reports**: All SAEs (HVAH and NCVAMC serious adverse events and Sponsor reports) are signed by investigators and submitted to the IRB. Local (HVAH and NCVAMC) SAE and unanticipated problems reports must be completed by the Investigator and forwarded to the IRB within 48 hours of discovery. The IRB will designate qualified members to review these reports within 5 days of receipt, and reports placed on the next IRB agenda for discussion. Prior to the meeting, primary reviewers determine whether sponsor submitted SAEs (non-local only) will be discussed and voted on at the convened meeting. Any member may choose to discuss non-local AEs at the convened meeting. All SAEs will be noted on the prepared agenda for the meeting. Reviews are documented in IRB minutes and filed in the IRB s investigator project file. Written notifications of review and approval or action required are sent to the investigator.

G. **Amendments**: All amendments and actions taken on the amendments will be maintained in the protocol file.

H. Records of Continuing Review: Requirements for Continuing Review are provided to the Principal Investigator with the IRB Approval Letter. The investigator must sign and date his/her Continuing Review. Continuing Reviews are documented in the minutes and filed in the IRB s investigator project file. Records of Continuing Review Activities (for both Full Board and Expedited) are then placed in the research record file.

I. **Budget and Accounting Records**: Budget and accounting records are maintained by the Research Budget Office or the Chicago Association for Research and Education in Science (CARES) Foundation office.

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

K. **Statements of Significant New Findings Provided to Subjects**: The new findings statement is included in the consent form template provided to investigators. The IRB verifies that this statement is included in the approved consent form. The method, and urgency of conveying significant new findings varies depending on safety specifics. For example, if new information indicates that study medication is harmful then subjects will be contacted immediately. In less urgent cases, for example a change in principal investigators, written notification may be appropriate. A phone call, in addition to written information, may be appropriate. A revised consent form and re-consent of all affected subjects may be necessary. All actions will be maintained in the IRB's investigator project file. Those subjects who are presently enrolled and actively participating in the study should be informed of the change if it

might relate to the subjects' willingness to continue their participation in the study. FDA does not requiring of subjects that have completed their active participation in the study, or of subjects who are still actively participating when the change will not affect their participation, for example when the change will be implemented only for subsequently enrolled subjects.

L. **Inspection of Records**: Records are the property and responsibility of the local research office. All records will be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA and other authorized entities at reasonable time and in a reasonable manner.

M. Audits/Investigations: Reports of all audits and investigations of individual projects or the human research protection program will be maintained in the IRB Office. At NCVA, in addition to possible IRB audits, the PIRF Committee may perform individual audits for cause as well as to review compliance to documentation of progress note and consents at the time of continuing review. These audits may be in addition to or in collaboration with the required RCO audits.

INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB

A. Professional Qualifications to do the Research

The IRB must determine that the investigator(s) is qualified through education, training, and experience to conduct the research. The investigator must have the appropriate training and be credentialed to conduct research involving human participants by a program that meets all VA requirements. A medical physician will have oversight for all study-related healthcare decisions for any interventional clinical trial. If the IRB believes that the Principal Investigator does not have the professional qualifications or resources to conduct a research project and to assure that the rights and welfare of subjects are protected then they may disapprove the study. The IRB may consider investigator collaborations with other professionals who have the required expertise and who agree to serve as co-investigators, preceptors or mentors. Students may be co-investigators but cannot be Principal Investigators. Significant faculty supervision is required. A co- principal investigator or a plan for establishing an alternate PI in case of extended leave (expected or unexpected) is to be submitted, in order to provide continuous oversight to the study.

B. Study Protocol which Includes/Addresses

The IRB addresses many complex, overlapping and intermingled issues dealing with the basic proposed research question: "Is there any possible benefit from this study and does the potential gain outweigh the potential risk?" In order to judge if criteria are met the IRB needs detailed information. If a protocol is submitted for review and IRB members believe that there is insufficient information to enable an appropriate review, a written request for additional information may be sent to the Principal Investigator.
The following information should be available for project reviews:

1. Title of the study.
2. Purpose of the study.
3. Sponsor of the study.
4. Results of previous related research.
5. Subject inclusion/exclusion criteria.
6. Justification for use of any special/vulnerable subject populations.
7. Study design.
8. Description of procedures to be performed.
9. Provisions for managing and reporting adverse events, unanticipated events.
10. The circumstances surrounding consent procedures including: setting, subject autonomy concerns, language difficulties, cultural differences, educational capabilities, and vulnerable populations.
11. The procedures for documentation of informed consent, including any procedures for obtaining assent from minors, using witnesses, translators and document storage.
12. Compensation to subjects for their participation and payment terms.
13. Any compensation for injured research subjects.
14. Provisions for confidentiality and the protection of a subject's privacy.

15. Extra costs to subjects for their participation in the study.
16. Extra costs to HVAH or NCVAMC or to third party payers because of subject's participation.
17. HIPAA Authorization and or Request for Waiver or alteration of Authorization to access PHI
18. Waiver of HIPAA Authorization for recruitment purposes (as appropriate)

C. Advertisement Reviews:

In general, the FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded the following items may be included:

1. The name and address of the clinical investigator and/or research facility.
2. The condition under study and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. A brief list of participation benefits, if any (e.g., a no-cost health examination).
5. The time or other commitment required of the subjects.
6. The location of the research and the person or office to contact for further information.

D. Investigational Brochure (when one exists)

The Investigational Brochure will be reproduced and provided to the primary and secondary reviewers, and IRB chair prior to the convened meeting when the relevant protocol is to be reviewed. The Investigational Brochure is available for review by any IRB member in the IRB office.

E. The Case Report Form (when one exists)

F. The Proposed Informed Consent Document

"Enrollment" is the process of obtaining informed consent from a potential research participant, prior to conducting any research procedure. Screening tests done prior to study, randomization or procedures, requires informed consent. Informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research. [21 CFR 50.25(a)(b)] requires that in seeking informed consent basic criteria must be met. The information that should be provided to each subject has been incorporated in the VA FORM 10-1086 informed consent template. The template is distributed to investigators and must be submitted in the prescribed format for review by the IRB. The required elements of informed consent are reviewed in the Informed Consent Section of these SOPs.

Translation of the document is not generally necessary for the HVAH and NCVAMC study population. If translation is required, however, translation services will be provided as identified by the facility.

G. Requests For Changes (Revisions/Amendment) In Study After Initiation [21 CFR 56.108(a)(4) and 56.11 5(a)(3-4)]

Investigators must report to the IRB any changes in research activity. If the amendment involves changes related to biosafety or radiation safety, the appropriate committee or subcommittee must first approve the amendment. A summary of changes and all supporting and/or modified documents should be submitted. Any changes in IRB approved research during the period for which IRB approval has already been given may not be initiated without IRB approval, except modifications to the protocol made to eliminate immediate hazards to subjects. The Chair, IRB have written notification within 24 hours when modifications have been made to eliminate immediate hazards to the subjects. All amendments, advertisements or other changes (including minor consent form changes) are reviewed, findings documented in IRB minutes and written notification provided to the Principal Investigator.

H. Reports Of Unexpected Adverse Events (SAE s) [21 CFR 56.108(a) abd6.115(a)(1 and 4)] [21 CFR 56.108(b)(1), 56.115(a)(3Ä4),56.1 15(b)(1) and 56.113]

Local Reports of Serious Adverse Events or Serious and Unexpected Events (including accidents or errors) must be promptly (within 48 hours) submitted to the IRB for review. Serious Adverse Events or unanticipated problems will be reviewed be a designated reviewer within 5 working days of receipt and reported at the next convened IRB meeting, and findings documented in the minutes. For non-local reports the level and promptness of review depends upon factors such as the seriousness of the event, the health of the subject population, whether the event is felt to be study related. If the sponsor requires immediate changes to the study or consent, requirements of 1058.01 will be followed. The reviewer will also assess the number of occurrences in relation to the size of the study, and whether the event is anticipated and already adequately described in the consent form or other study documents. The IRB scope of responsibilities does not include the evaluation of all risks however it is responsible for considering those risks to subjects that may directly result from the research activity (not a progression of a disease process). The IRB review process involves the following steps:

1. SAE reports are assigned a primary reviewer and entered on an IRB agenda for timely review. During review at the convened meeting, if members require additional information they may review the permanent study file and/or they may request the Principal Investigator or sponsor to submit additional information for further review. Members determine if a consent form revision is required and to what extent re-consenting and/or subject notification about new information is required. The Committee has the authority to suspend a study if it has significant concerns about safety.
2. An acknowledgment letter is sent to the Principal Investigator informing him/her of further action required.

I. Progress Reports - Continuing Review will include a determination by the IRB meets criteria set forth in [FDA 21 CFR 56.111]. These criteria are:

1. Are risks to subjects minimized?
2. Are risks to subjects reasonable in relation to anticipated benefits?
3. Is selection of subjects equitable?
4. Is informed consent adequate and appropriately documented?
5. Where appropriate does the research plan make adequate provision for monitoring the data collected to ensure the safety of subjects?

6. Where appropriate are there adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data?
7. Have appropriate safeguards been included to protect vulnerable subjects?

Continuing Review is scheduled for a convened IRB meeting at the time of Initial Review. The IRB mails a reminder to the Principal Investigator at least six weeks prior to the scheduled Continuing Review.

J. Final Report/ Study Closure: The Continuing Review Form provides the framework for Final Reports. Investigators are required to notify the IRB when their studies are completed. A progress report is required. If the study is being terminated, an explanation is also required (i.e. study not feasible, sponsor closed site). Once a study is closed, no additional identifiable data may be accessed. Investigators are required to keep study records as required by the VA's policy on records destruction, unless the sponsor has separate requirements (beyond VA approved timeframe).

K. Institutional Forms/Reports: VA Form 10-1086 (Consent Form) and VA Form 10-9012 (Investigational Drug Information Record) are utilized. The IRB and Research and Development Information System (RDIS) is linked to the VA Headquarters computerized project reporting system. The IRB has developed multiple forms to assure that investigators provide the information required for review and continuing review activities.

L. Mandatory Education: Investigators must provide documentation that the mandatory education requirements have been completed by all staff involved with the project, current CV, credentialing form, scope of practice and license or verification of license.

SPECIAL CONSIDERATIONS FOR VULNERABLE SUBJECTS

A number of research populations are defined by federal regulations as "vulnerable" or requiring additional consideration or protection. "Vulnerable" or special classes of subjects include children, prisoners, pregnant women, mentally disabled persons and those with impaired decision-making capacity, or economically or educationally disadvantaged persons [45 CFR 46.111].

Vulnerable Subjects who require special considerations: For the purposes of this standard operating procedure Hines VAH/North Chicago VAMC Institutional Review Board will not approve research projects involving children, prisoners, pregnant women, fetuses.

Other subjects who might need special considerations: Other populations that may not be considered "vulnerable", but may require special considerations include: veterans, women and minorities, terminally ill, non-English speaking subjects, students/trainees, employees, homeless and those individuals whose medical records are protected under law due to drug and alcohol use, HIV/AIDS or sickle cell anemia.

CHILDREN

The HVAH and NCVAMC IRB will not be responsible for or approve research involving children

PRISONERS

The HVAH and NCVAMC IRB will not be responsible for or approve research involving prisoners.

If a participant enrolled in a research protocol becomes incarcerated:

- The investigator will promptly notify the IRB.
- All interactions and interventions with obtaining identifiable private information about the now incarcerated participant (prisoner) must cease

PREGNANT WOMEN

The HVAH and NCVAMC IRB will not be responsible for or approve research involving pregnant women.

If a female veteran becomes pregnant during the course of the research study, the June 10, 2009 VACO Pregnancy and VA Research Guidance document will be followed.

FETUSES

The HVAH and NCVAMC IRB will not be responsible for or approve research involving fetuses.

MENTALLY DISABLED PERSONS OR THOSE PERSONS WITH IMPAIRED DECISION MAKING CAPACITY AS A VULNERABLE POPULATION IN RESEARCH

Before an incompetent person or persons with impaired decision-making capacity may be considered for participation in any VA research, the IRB membership must include at least one member who is an expert in the area of the research. [VHA Handbook 1200.05 Appendix D.6.b(1)]. 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. [VHA Handbook 1200.05 Appendix D.6.b(1)] • The IRB may utilize ad hoc members as necessary to ensure appropriate expertise. [VHA Handbook 1200.05 Appendix D.6.b(2)]

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

(1) Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. 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) 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) 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.

No one who is found to lack decision-making capacity may be involved in research without the written consent of an agent designated by a health care power of attorney, or by some other legally authorized representative. Protocols submitted to the IRB should describe how capacity to consent will be determined, by whom it will be done, and what procedures will be in place to

assure that legally effective informed consent is provided for all individuals found to lack decision-making capacity.

The IRB will make a determination in writing of each of the three criteria listed above are 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 on the basis of informed consent from authorized representatives.

The primary consideration when recruiting subjects with severe cognitive or psychiatric disorders is to establish procedures for determining which individuals are able to provide legally valid consent, and which are not. Two physicians, after appropriate medical evaluation may determine that the prospective research participant lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. Because of the importance and implications of such determinations, the IRB generally requires that such determinations be made by someone not otherwise involved in the research and confirmed in writing.

Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research participant lacks decision-making capacity is based on a diagnosis of mental illness. Research involving the withdrawal of psychotherapeutic drugs is required to include provisions for a psychiatrist not otherwise involved in the research to monitor the subjects' mental status on an ongoing basis, and to re-institute drug therapy if the patient/subject does not object and it is clinically indicated. This requirement applies to research involving drugs withheld from control groups, as well as to research involving a drug washout period and research designed to study the symptoms and triggering mechanisms of relapse.

Normally, psychiatric patients should be on an inpatient ward during initial phases of drug withdrawal, and the research protocol should define criteria for: (a) return to outpatient status, (b) continuation of (or return to) inpatient status, (c) reinstitution of drug therapy, and (d) termination from the study.

In addition, consent documents should inform both the subjects and their families (if family members are involved, or it the subjects will be living at home) of the risks of relapse, the possible signs of relapse, and what to do if symptoms of relapse appear. Families should also be told about the subject's right to refuse psychotherapeutic drugs, or hospitalization, except as permitted under federal law.

The consent form is required to clearly explain the patient's right to confidentiality and the extent to which information about the patient/subject will be shared with family members and/or friends participating in the research and vice versa.

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 consenting process with surrogate consent may be necessary. The subject may be re-consented when decision making capacity is restored.

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.

ECONOMICALLY OR EDUCATIONALLY DISADVANTAGED PERSONS

The IRB will attempt to safeguard every subject's rights and welfare by making sure that any possible coercion or undue influence is eliminated (e.g., compensation that is not commensurate with risk, discomfort, or inconvenience involved, or recruiting in institutional settings where voluntary participation might be compromised). Investigators should address these issues specifically when submitting protocol information to the IRB for review.

VETERANS

Due to their propensity to take orders and obey authority, veterans may be more willing to participate in research than non-veterans. When explaining research to veterans, special emphasis must be placed on the veteran's right to refuse participation without loss of VA benefits.

TERMINALLY ILL

Patients with a terminal illness may be willing to "try anything" that might offer hope of either a cure or a slowing of the disease process. Others, aware that nothing further can be done to cure their disease, might fear abandonment by the medical establishment and agree to participate in research as a means of maintaining contact with physicians expert in treating their condition. On the other hand, many terminally ill individuals are willing to submit to considerable discomfort and risk for the possible benefit of future patients suffering from the same condition.

Investigators need to be sensitive to these matters and explain the likelihood (or lack thereof) that research subjects will experience any personal medical benefit from their participation in a particular study.

WOMEN AND MINORITIES

The inclusion of women and minorities in research is important both to ensure that they receive an equal share of the benefits of research and to ensure that they do not bear a disproportionate burden.

Most diseases affect all population groups. In order to contribute to the pool of generalizable knowledge, investigators are required to include the widest possible range of population groups in their research. However, sometimes women and minorities are subject to different risks Other research focuses on characteristics of diseases or effectiveness of therapies in particular populations, and may also concern conditions or disorders that disproportionately affect a certain racial or ethnic group. Exclusion or inappropriate representation of these groups, by design or inadvertence, would be unjust. Further, to the extent that participation in research offers direct benefits to the subjects, under-representation of women and minorities denies them, in a systematic fashion, the opportunity for direct benefit.

Thus, federal regulations require that research design include diverse populations. Investigators submitting protocols for IRB review which do not call for heterogeneous study populations are required to justify, in writing, in their submissions, why a homogeneous study population has been chosen.

NON-ENGLISH SPEAKING

Consent documents must be written in the language that is most easily understood by the subject. A potential subject's inability to read or read English is not an appropriate basis for exclusion for most research. For investigators proposing to use non-English language consent documents, documentation must be provided to demonstrate the translation of the document from English to the second language and then back to English, to ensure that the information is correctly conveyed. The IRB is required to review all non-English consent forms and recruitment materials.

STUDENTS/TRAINEES

Students, residents and fellows often serve as subjects for biomedical and psychosocial research. The obvious concern is that their participation may not be truly voluntary, because of a desire to appear particularly cooperative or highly motivated, or because participation in research is a course requirement. Researchers need to be sensitive to allowing students to participate in their research. When students or trainees are to be involved in research, the following guidelines should be observed: (a) personal solicitations by the investigator should be avoided, (b) advertisements for students/trainees should be broad based (i.e., do not recruit primarily from your own section), and (c) the informed consent document should address potential coercion. Investigators, whether PI, Co-Investigators, or Associate Investigators, are not permitted to recruit any person associated with our VA facilities who is their subordinate.
Subordinates, are permitted to respond to a posted or published advertisement for research subjects even when the PI is in a supervisory position, provided the PI has not made direct request to the would-be volunteer.

EMPLOYEES

Hospital employees, such as office staff, lab technicians, and post-doctoral fellows, are similar to students in that they are vulnerable to perceived, even if not intended, pressures to appear cooperative and supportive of their supervisor's work. Accordingly, many of the same procedures (described above) to reduce the likelihood of coercion in recruiting student volunteers apply equally to hospital employees. It is the IRB policy not to approve recruitment procedures that include employees from the investigator's own lab or office. This policy will be reconsidered on a case by case basis. Employees may passively respond to flyers and/or other recruitment materials.

VETERANS WITH PTSD

The IRB will conduct an additional review of studies involving veterans with PTSD to ensure appropriate sensitivity to this population, consideration of FDA or pharmaceutical company advisories, alerts and warnings, appropriate dissemination of this information to the potential subject, and an additional review of risks associated with medications likely to be used in the PTSD study population. The reviewers and members will be provided with a worksheet with the additional considerations set forth in ORO correspondence dated July 1, 2008. The reviewers will complete this worksheet based on their review and committee discussion.

SPECIAL CONSIDERATIONS FOR NON-VETERAN SUBJECTS

PARTICIPATION OF NON-VETERANS AS RESEARCH SUBJECTS (VHA HANDBOOK 1200.05)

A. 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.

B. All 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.

C. All safeguards and provisions required for veteran subjects are also required for non-veteran subjects.

D. A VA medical record must be initiated for non-veterans enrolled in clinical intervention studies conducted at HVAH or NCVAMC. Subjects must be enrolled in the hospital computerized record system and consent forms filed in the medical record. For these subjects, a copy of the informed consent will be filed in the VA medical record the research office. The original will be kept in the investigators files. A medical record need not be initiated for subjects screened with a history and physical exam and found not to be eligible. For such subjects, the consent documents will be handled as described below.

E. For subjects enrolled in survey research or non-clinical interventional studies, original consent documents for non-veterans will be maintained in the investigator's file and a copy sent to the Research Office. For these subjects, a medical record need not be initiated.

F. All research files will be maintained by the investigator. If non-veterans would like medical information to be sent to their physician, routine release of information procedures will be followed.

G. Guidelines for the use of Non-Veterans are also described in Hospital Policy Memorandum 578-02-151-003, RECRUITMENT OF AND SOLICITATION FOR RESEARCH SUBJECTS

DUAL ENROLLMENT

A. In general, subjects may not be enrolled in more than one interventional or long term observational study at a time.

B. For some studies with long-term follow-up, this may limit a subject's ability to enroll in other research. Thus, investigators may petition the IRB for permission to dual enroll. Both principal investigators must sign a letter of agreement for dual enrollment. These letters may be specific to a patient or a study.

C. For purposes of enrollment only, tissue donation and studies restricted to the medical record shall not restrict dual enrollment.

D. Approvals for dual enrollment may normally be reviewed by the expedited process.

F. On a case by case basis the IRB may review and approve blanket dual enrollment for selected studies which do not increase risk to the subjects, i.e. surveys.

INVESTIGATOR RECORDS

A. Investigators should maintain records to assure the confidentiality and privacy of patient data except when required by law or released with the permission of the patient. Subjects have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and that the confidentiality of private information will be preserved. The more sensitive the research material, the greater care required in obtaining, handling, and storing data.

B. To protect subject confidentiality, the following guidelines should be considered:

1. Limit recording of personal information to that which is absolutely essential to the research.

2. Store personally identifiable data securely, according to current VA Policy, and limit access to the principal investigator and authorized staff.

3. Code data as early as possible in the research process, and plan for the ultimate disposition of the code linking the data to individual subjects.

4. Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available.

5. Subject records should be stored in a locked file cabinet or in a locked office.

C. Investigators should keep copies of all information submitted to and received from the IRB. IRB correspondence should be maintained in an orderly fashion.

D. It is suggested that inclusion and exclusion checklists be developed by investigators.

E. The investigator must maintain the original informed consent signed by each subject enrolled in a research study.

F. The records, including the investigator's research records in accordance with VHA's Records Control Schedule (RCS 10-1), applicable FDA and DHHS regulations, or as required by outside sponsors.

G. Inspection of Records: Records are the property and responsibility of the local research office. All records will be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA and other authorized entities at reasonable time and in a reasonable manner.

IRB AUDITS OF INVESTIGATOR RECORDS

A. Authorized representatives from the IRB may conduct audits of Principal Investigator's research files to assure compliance to local and federal regulations in addition to or in collaboration with the RCO required audits.

B. Audits may be conducted for three reasons:

1. Cause: If there are allegations of misconduct or noncompliance, or there have been previous infractions, an audit of an investigators files may be requested.

2. New Investigator: Audits of new investigator files may be performed if necessary to aid in education and training.

3. Random: Random audits may be performed to reinforce education and to assure investigator compliance.

C. Investigators will be notified in advance of a new investigator or random audit. IRB and RCO checklists will be given to the investigator. Investigators may not be notified for cause audits.

D. An exit interview will be conducted with the study coordinator and principal investigator. This interview will provide a verbal summary of audit findings. A written summary report will follow within one week.

E. The IRB will be notified of the results of the audit at the next scheduled meeting.

F. Investigator audit checklists are available for all investigators in the IRB office. Investigators are encouraged to self-audit their files to assure compliance with the regulations.

G. Investigator audits may include but are not limited to:

1. Inclusion and exclusion criteria are met;

2. All subjects are consented fully prior to conducting any research procedures.

3. The informed consent process is observed;

4. Investigator records are properly maintained.

5. Review of other audits conducted by other internal or external entities.

6. Changes to the protocol have not been made without prior IRB approval unless to prevent immediate hazards to the participant(s)

RISK / BENEFIT ANALYSIS

Investigators submitting research proposals for IRB review should understand that the IRB has the responsibility for assessing the risks vs. anticipated benefit of research as one of its primary functions. In addition, once risks and benefits have been assessed, the IRB is responsible for ensuring that the risks of study participation are minimized to the greatest extent possible while the benefits of study participation are maximized.
The following definitions of risk, minimal risk and benefit will be used by the IRB:

A. **Risk:** The probability of harm (physical, psychological, social or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal risk to significant. The federal regulations only define minimal risk.

B. **Minimal Risk:** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine or psychological examinations or tests [45 CFR 46.102(i)].

C. **Benefit:** A valued or desired outcome; an advantage.

D. **Reasonable Risk Benefit Ratio.** Risks, both physical and non-physical, to human subjects are reasonable in relation to any anticipated benefits (the risk benefit ratio) to subjects, and the importance of the knowledge that may reasonably be expected to result. Validity of research design must be taken into consideration in determining the risk benefit ratio. In evaluating risks and benefits, the IRB needs to consider only those risks and benefits that may result from the research, as distinguished from risks and benefits the subjects would receive even if not participating in the research (38 CFR 16.111(a)(2)). The IRB must consider the risks and benefits related to both biomedical (including genetic) research and non-biomedical research. The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

IRB CONSIDERATIONS

Evaluations of risk and benefit are complex due to the subtle distinctions that exist between therapeutic and research activities and by evaluations of actual risks in the lives of normal and vulnerable subjects.

In evaluating risks and benefits, the IRB must:

A. Consider the validity of the research design.

B. Identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in the study;

C. Determine that the risks will be minimized to the extent possible, such as:

1. using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk;

2. whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

D. Identify the probable benefits to be derived from the research;

E. Determine that the risks are reasonable in relation to the benefit to subjects, if any, and the importance of the knowledge to be gained;

F. Consult with subject matter experts or reviews by such committees or subcommittees as Biosafety, Radiation Safety or Radioactive Drug Research as appropriate.

G. Ensure risks associated with ionizing radiation are addresses and included in the informed consent, e.g. nuclear medicine, radiation therapy, radiology.

H. Assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;

I. Determine intervals of periodic review, and, where appropriate, determine that adequate provisions are in place for monitoring the data collected, and where the subjects are likely to be members of a vulnerable population, determine that additional safeguards are in place to protect the rights and welfare of these subjects.

J. Reviews the plan for data and safety monitoring and determines the plan has adequate protection for participants. For studies that have a Data Safety Monitoring Board (DSMB) the IRB will review the board's plan to determine that they are adequate to insure the safety of participants. If the study does not have or is not required to have a (DSMB) and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, the IRB needs to carefully review the data and safety-monitoring plan.

K. If a DSMB is used, all events must be reported to the DSMB, and a summary of the DSMB findings must be reported to the IRB.

IDENTIFICATION AND ASSESSMENT OF RISK

When considering risks, the IRB considers only those risks associated with the research (i.e., physical, psychological, social, legal, emotional). Risks include immediate risk of study participation, risks of randomization (especially to placebo groups), risks of breach of confidentiality, and risks of long term effects.

For biomedical research, the IRB is required to determine and differentiate between the risks associated with the research and the risks associated with standard diagnostic or therapeutic interventions or therapies subjects would undergo regardless of participation in research. Since the IRB does not establish or determine what constitutes standard of care, it is important for investigators to clearly distinguish procedures which are standard of care from those which are conducted solely for research purposes in the protocol and informed consent form.

A. **Physical Risk:** Some biomedical research presents risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation may result in permanent injury to subjects. For all research with the potential to cause physical harm, investigators need to think through all risk possibilities so that they can be resolved quickly and minimize the harm to subjects. Investigators need to address procedures to minimize physical risk to the greatest extent possible.

B. **Psychological Risk:** Some research has the potential to cause undesired changes in thought processes and emotion including episodes of depression, confusion, hallucination resulting from drugs, feelings of stress, guilt and loss of self-esteem. As is the case with physical risks, these effects are usually transient. For all research with the potential to cause psychological harm, investigators need to think through all risk possibilities so that they can be resolved quickly and minimize the harm to subjects. Investigators need to address procedures to minimize psychological risk to the greatest extent possible.

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

D. **Minimal Risk:** Assignment of research for expedited review, approval of waiver of consent, and the conduct of research involving vulnerable research populations may be dependent upon whether the research places subjects at minimal risk or greater than minimal risk. Note: When risks are unknown, they are considered more than minimal.

BENEFITS

A. **Benefits to the individual:** Research frequently provides subjects with treatment, diagnosis or examination for an illness or abnormal condition. In these cases, the research involves evaluations that may benefit the subjects by improving their condition or provide a better understanding of their disorder. Investigators should detail these potential benefits for the IRB in their application, and for the subjects in the informed consent form, while not overstating these benefits. Investigators should fully describe any benefits to the subject or to others that may reasonably be expected from the research [45CFR46.11(a)] [21CFR50.25(a)].

B. **Benefits to society:** Although research may not always provide a benefit to society, researchers are encouraged to design research projects so that information, in the form of generalizable knowledge, can contribute to societal benefit whenever possible. Investigators should detail these potential benefits for the IRB in their application, and for the subjects in the informed consent form, while not overstating these benefits. Research which does not provide benefit to individuals is required to provide a reasonable likelihood of resulting in benefits for society.

EMERGENCY USE AND EXEMPTION FROM PROSPECTIVE IRB REVIEW

Emergency use is defined as the use of an investigational drug or biological product with 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 [21 CFR 56.102(d)]. FDA regulations allow for one Emergency Use of a test article without prospective IRB review. Subsequent use of a test article is considered a second use if either it is administered to a subject again or it is administered for the first time to another subject and is subject to prior IRB and R&D approval.

In its review of emergency use, if it is anticipated that the test article may be used again, the IRB may request a protocol and consent document so that an approved protocol would be in place when the next need arises. In the 1998 FDA Information Sheets, the 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. In such a case, a physician would discuss the individual case with the Chair of the IRB, the ACOS and the Chief of Staff to determine is a second usage may be permitted.

An Investigator must obtain informed consent from the subject or subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]: must meet the following criteria and be documented:

1. The human subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from the subject.
3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

Physicians are expected to follow as many subject protection procedures as possible. These include:

1. Obtaining an independent assessment by one or more uninvolved physicians (e.g., IRB Chair or member, ACOS for Research and Development or Chief of Staff) prior to the use to determine that the regulatory criteria are met.
2. Obtaining informed consent from the patient or a legal representative.
3. Promptly notifying the ACOS for Research and Development or Chief Staff of any Emergency Use.
4. Notifying the IRB as soon as possible and within 5 working days of any Emergency Use.
5. Submitting to the IRB a complete report.
6. Obtaining authorization from the sponsor if possible.
7. If feasible, contact the FDA for approval prior to treatment.

The 5 day report will be screened by the IRB Staff and forwarded to the Chair for review to assess that the circumstances met the FDA regulations. The full report will be copied for all IRB members and placed on the next IRB agenda.

EMERGENCY USE IND

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23].

EMERGENCY RESEARCH

A. Requests for waiver of informed consent must be submitted to the IRB for review and approval. These exceptions apply to a limited class of research activities who are in need of emergency medical intervention but who cannot give informed consent because of their life threatening medical condition and who do not have a legally authorized person to represent them. Exceptions from the informed consent requirement are conditional upon documented findings by the IRB. FDA requirements are specified in [21 CFR 50.23(a-c) and 50.24 (a-e)]:

1. The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (4) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

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

2. 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 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.
3. The documentation required of this section shall be submitted to the IRB within 5 working days after the use of the test article.
4. All subsequent uses must be submitted to IRB for Full Board Review.

B. Informed consent requirements for planned emergency research [21CFR 50.24 a-e]
(Note: VA requirements: the IRB may not grant a waiver of Informed Consent in planned Emergency Research)

The IRB is responsible for the review, approval, and continuing review of the clinical investigations and may approve the investigation without requiring that informed consent of all research subjects be obtained if the IRB, with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation, finds and documents each of the following:

a. The human subjects are in a life threatening situation, available treatments are unproven or unsatisfactory and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

b. Obtaining informed consent is not feasible because:

1) The subjects will not be able to give their informed consent as a result of their medical condition.
2) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible.
3) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

c. Participation in the research holds out the prospect of direct benefit to the subjects because:
    1) The subjects are facing a life-threatening situation that necessitates intervention.
    2) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects.
    3) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy if any and what is known about the risks and benefits of the proposed intervention or activity.

d. The clinical investigation could not practicably be carried out without the waiver.
e. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence; the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
f. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.
g. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
    1) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.
    2) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.
    3) Public disclosure of sufficient information following completion of the clinical investigation to appraise the community and researchers of the study

including the demographic characteristics of the research population, and its results.

4) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.
5) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator will commit, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
6) The IRB is responsible for ensuring that procedures are in place to inform each subject, at the earliest feasible opportunity, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.
7) The IRB determinations and documentation are to be retained by the IRB for at least 5 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA, and other authorized entities at reasonable times and in a reasonable manner.
8) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments.
9) If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in

writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to the FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

C. The IRB shall promptly notify the investigator and the sponsor in writing when it determines it cannot approve an FDA [50.24] Study (waiver of informed consent requirement due to critical life threatening emergency): If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the physician or Principal Investigator and to the sponsor if requested.
D. The IRB shall provide to the sponsor in writing a copy of the information that has been publicly disclosed under [50.24(a)(7)]: In some types of controversial research involving waiver of informed consent it may be appropriate to consult with community representatives and discuss the investigation. In such circumstances information must be provided to the communities from which the subjects will be drawn prior to study initiation and public disclosure of sufficient information of the demographics of the research populations and the results following completion of the study. Copies of these reports will be provided to sponsors.
E. In Order to Approve an Emergency Research Consent Waiver Study, the IRB must Find and Document:

1. Subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory and collection of scientific evidence is necessary.
2. Obtaining informed consent is not feasible because:

    a. Medical condition precludes consent.
    b. No time is available to get consent from legally authorized representative.
    c. Prospective identification of likely subjects is not reasonable.

3. Prospect of direct benefits to study subjects because:

    a. A life threatening situation exists that necessitates treatment.
    b. Available data supports the potential for direct benefit to individual subjects.
    c. The risk - benefit ratio of both standard and proposed treatments is reasonable.

4. A waiver is needed to carry out study.
5. The plan defines a therapeutic window, during which the investigator will seek consent rather than starting without consent. The Principal Investigator will provide a detailed summary to the IRB.
6. The IRB reviews and approves consent procedures and consent document. The IRB reviews and specifies family member objection procedures as appropriate.
7. Additional protections, including at least:
    a. Consultation with community representatives.
    b. Public disclosure of plans, risk, and expected benefits.

c. Public disclosure of study results.
d. Assure establishment of an independent data monitoring committee is established.
e. Objection of family member summarized for Committee review.

8. The investigator must inform the family at the earliest feasible opportunity of the subject's inclusion in the study, and that his/her participation may be discontinued and that death may or may not occur.
9. Separate IND or IDE required, even for marketed products - emergency research consent exception studies may not begin unless the FDA approves a separate IND or IDE.

10. IRB disapproval must be documented in writing and sent to the clinical investigator and the sponsor of the clinical investigation.

ADVERSE EVENTS and UNANTICIPATED PROBLEMS

Adverse event reporting is to be in compliance with the following documents:

1. VHA Handbook 1050.1, January 30, 2002, VHA National Patient Safety Improvement Handbook;
2. VHA Handbook 1058.01, February 27, 2009, Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight
3. Hines VAH PM 578-01-011-057 (R-2), December 22, 2003, Patient Safety Improvement/Risk Management Program
4. FDA 21 CFR 56.113, 38 CFR 16.113, 45 CFR 46.113

An adverse event is defined in VHA Handbook 1200.05 and VHA Handbook 1058.01 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. A local AE is one occurring at a site for which the VA Investigator's IRB of record is responsible.

Regulations (38 CFR 16.103(b)5, 21 CFR 312.64(b) and 21 CFR 812.150(a)(1), VHA Handbook 1058.01, require prompt reporting of unanticipated events involving risks to subjects and adverse events.

Reporting Requirements:

- All local serious adverse events (SAE) events or unanticipated problems or events must be reported to the IRB within 48 hours of the investigator or staff becoming aware of the event.
- Any unexpected death must be reported to the IRB within 24 hours. IRB has the responsibility to review and report such deaths to ORO pursuant to the requirements set forth in VHA Handbook 1058.01.
- All local unanticipated related adverse events that are not serious, can be reported to the IRB at the time of continuing review. Any local AE directly or indirectly related to the study, such as loss of confidentiality or emotional trauma are reportable.
- Any emergency actions taken to eliminate immediate hazards to subjects must be reported in writing within 24 hours to the IRB Chair.
- Non-Local adverse events are to be reported immediately if there are recommendations for changes to the protocol, investigator brochure, consent, or halts enrollment for safety considerations. Otherwise non-local adverse event reports may be reported at the time of continuing review.
- Protocol violation and serious protocol deviations.
- All unanticipated problems involving risk to participants or others are to be reported within 48 hours to the IRB. These include, but are not limited to: (a) interruptions of enrollment or other research activities due to concerns about the safety rights or welfare of human research subjects, research staff or others, (b) any work related injury to

personnel involved in human research or research related injury to any other person requiring more than minor medical intervention or that leads to serious complications or death, (c) any VA National Pharmacy Benefits management (PBM) Bulletins or Communications (Safety Alerts) relevant to one or more of a local research project, (d) any DMC report describing a safety problem, (VHA Handbook 1058.01)

- Reports of serious protocol deviation that impact on risks to the research subject or integrity of the protocol.
- **DSMB/C (Data Safety Monitoring Board / Committee):** The reports from these committees may be quarterly, semi-annually or annually UNLESS the report describes a safety problem. DSMC reports for safety problems must follow the 48 hour reporting requirements.

Procedures for Reporting Adverse Events

For all serious local adverse events for all studies: An IRB *Adverse Event Reporting Form* must be completed with sufficient information and submitted to the IRB office within **48 hours** of identification of the event.

A qualified, designated IRB reviewer (or convened IRB) will review the submission within 5 days as required by 1058.01.
This reviewer will be assigned to asses the event(s) reported and determine:

1). Seriousness and significance
2). Whether it is unanticipated.
3). Relationship between event(s) and research
4). Risks to local subjects
5). Whether modifications are needed.

They will also document:

- whether Immediate action is required to prevent an immediate hazard to subjects and review by the convened IRB is needed; or
- review by the convened IRB is needed, but immediate action to prevent immediate hazard to subjects is not warranted.

This assessment will be discussed and voted on at the next meeting of the convened IRB.

If the IRB reviewer or convened IRB determines the problem or AE is serious, unanticipated, and related or possibly related to the research, the IRB Chair will report the finding to the Hospital Director within 5 business days.
The convened IRB will also determine if consent modifications are required and if previously enrolled subjects need to be notified and how such notification should take place. These determinations will be documented in the minutes.

The Investigator must follow the SAE to resolution and provide the IRB with periodic updates.

If the event meets the criteria for reporting to ORO as specified in VHA Handbook 1058.01: ORO will be notified, in writing by the Institutional Official within the required timeframe.

The IRB staff will prepare the initial report, which will be reviewed by the IRB Chair, and go through the ACOS to the Hospital Director for transmission to the Central ORO Office, with copies to the Regional ORO Office and VISN Director within the required 5 day reporting period. Copies of minutes from the convened meeting where discussion and action was taken will also be forwarded to ORO if required
This will also be reported to the R&D.

NON-LOCAL ADVERSE EVENT REPORTS

SAEs from Other Sites (External/Non-Local), Provided by the Study Sponsor or Coordinating Center for studies involving multiple sites are summarized on the Adverse Event Reporting form and this form is attached to the reports and forwarded to the IRB at the time of continuing review. This information will be included in the review by the Primary Reviewer and considered with the continuing review information.

If the non-local SAE was unexpected and related, the Investigator must promptly report this to the IRB to be reviewed following the requirements of 1058.01 and reported at a convened meeting prior to continuing review.

The Investigator must also report non-local SAE's following the requirements of 1058.01 if:

- Risks to subjects are increased
- There is a modification to the protocol required to reduce risks
- A change in the consent form is required.

A primary reviewer will be assigned to review the SAE reports and protocol file prior to a convened meeting to determine if there is a change to the risk/benefit ratio and if the project should continue.

The Investigator will be notified in writing of the IRB's determination.

SERIOUS PROTOCOL VIOLATIONS

A protocol violation is defined as non-compliance (by being omitted or committed) of a procedure outlined by the study protocol, standard operating procedures of the medical center, HRPP or IRB. This type of protocol deviation may expose participants to increased risk or compromise the integrity of the study.

Examples of some serious protocol deviations:

- Inclusion/exclusion criteria not fulfilled Enrolling a person in a study before signed consent has been obtained;
- Administering an investigational drug outside protocol, i.e. without a signed approved informed consent
- Administering higher or lower dosages of investigational drug to a subject than is specified in the protocol; and
- Enrolling a person from a satellite study site where IRB approval was not obtained to conduct the study.

Deviations can be deliberate or accidental and be caused by study staff or participants. The investigator does not have the authority to allow any deviation from the research protocol without a waiver by the sponsoring company. Waivers obtained for deviations from the protocol must be submitted to the IRB for review. If the protocol does not have a company sponsor, the Investigator must request permission to deviate from the protocol from the convened IRB.

Serious Protocol Deviation occurring without prior approval from the IRB, must be reported in writing to the IRB using an Adverse Event Form.
Serious Protocol Deviations will be reviewed by the Chair or designee and will be placed on the agenda for discussion and vote by the convened IRB. The IRB will determine, in it's discussions whether or not the deviation is Investigator non-compliance, and determine if, and what further action is required.

G. DSMB (Data Safety Monitoring Board) reports provided by the study sponsor must be submitted to the IRB Office, accompanied by an *Adverse Event Reporting Form* for review by the IRB. For multi-site studies with an active DSMB, a DSMB report may be accepted in lieu of a report of individual non-local SAEs and AEs

DSMB reports provided by the sponsor will be assigned a reviewer who will review the report and study file.
The DSMB report will be summarized on the agenda with the DSMB recommendations, and the reviewer recommendation for discussion and vote by the convened meeting.

F. **Reporting of all unanticipated problem involving risk to participants or others**

Examples of unanticipated events other than adverse events may include:

- An investigator loses a laptop that contains confidential information about participants.
- A principal investigator is charged with a felony.
- Reports from a blood draw or other test (i.e. imaging) performed the previous week were in error, and a participant was enrolled as a result
- Participants in a group counseling session become unexpectedly violent, or confidentiality was breached and there was a negative result.
- A participant unexpectedly becomes pregnant.
- A breach in confidentiality

These unanticipated problems involving risk to participants or others are to be promptly reported to the IRB within 48 hours with sufficient information for the IRB to assess following the requirements of VHA Handbook 1058.01 to determine if what, if any, additional action is required.

OTHER REPORTABLE EVENTS

A. Other events, incidents, and/or noncompliance that *must be reported* include:

1. Problems involving conduct of a study or subject participation (including problems with recruitment and/or the consent process). Example: A report should be written if a person who is contacted (either personally or in writing) about participating in a study becomes upset about the recruitment process.

2. **Modifications to the protocol made to eliminate immediate hazards to subjects**. The Chair, IRB is to have written notification within 24 hours when modifications have been made without IRB approval, to eliminate immediate hazards to the subjects. The notification is to include the potential risk/hazard, follow-up description of the event and outcomes. On an urgent basis, the Chair, IRB can cease enrollment in the study, or other activities as deemed necessary to protect the participants. This event will be reported to the IRB who will determine any further actions required, such as suspension or termination of the project. An amendment is to be submitted if the change is permanent, with supporting documents to be reviewed by the IRB.

B. **OHRP:**

1. **The following will be reported by the IRB through the Directors Office pursuant to** 45 CFR 46.103(a) and (b) (5)**:**

a. Any unanticipated problems involving risks to subjects or others;

b. Any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB;

c. Any suspension or termination of IRB approval.

2. In general, these reporting requirements apply to all nonexempt human subjects research that is:

a. conducted or supported by HHS;

b. conducted or supported by any non-HHS federal department or agency that has adopted the Common Rule and is covered by a Federalwide Assurance (FWA) determined to be appropriate for such research; or

c. covered by an FWA, regardless of funding source.

3. Information to be included in incident reports as described in guidance 5/27/05:

a. Name of institution

b. Title of the research project

c. Name of the principal investigator

d. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

e. A detailed description;

f. Actions the institution is taking or plans to take to address the problem;

4. Time frame for reporting incidents: For a more serious incident, reporting is required within days. For less serious incident, a few weeks may be sufficient. It may be appropriate to send an initial report, and indicate that a follow-up or final report will follow.

5. IRB Procedure: All correspondence goes through the Chair, IRB, ACOS, Research, Hospital Director, to Director, Division of Compliance Oversight, Office for Human Research Protection. Copies will be sent to: AO for Research (578/151), Chair, R&D (151), Regional Office Director, Midwestern ORO (578/10R), VAH, Hines, IL..

C. FDA: The following will be reported by the IRB through the Directors Office

Any unanticipated problems involving risks to human subjects or others, any instance of serious or continuing noncompliance with the regulations or IRB requirements and determinations, and any suspensions or termination of IRB approval.(21 CFR Parts 50, 56, 312 or 812)

IRB Procedure: All correspondence goes through the Chair, IRB, ACOS, Research, Hospital Director, to Director, Division of Compliance Oversight, Office for Human Research Protection. Copies will be sent to: AO for Research (578/151), Chair, R&D (151), ORO Regional Office Director.

E. **Procedure:**

1. The IRB has the authority to suspend (put all studies activities on hold for a period of time, until questions, compliance or risk issues have been resolved) or terminate (stop the conduct and approval of the study permanently) a previously approved study when unexpected serious harm to participants has been identified, continued investigator non-compliance, or at any time, at the IRBs discretion or if warranted by findings in the continuing review or monitoring process. On an urgent basis, the Chair, IRB has the authority to cease enrollment, and other study activities to protect the participants. This action will be reported to the next convened IRB where it will be determined if further actions are required, such as suspension or termination of the study. The PI must immediately submit to the IRB Chair, a list of research subjects for whom the suspension/termination of the study would cause harm. The IRB Chair, with appropriate consultation with the investigator and COS, determines if the subject(s) may continue in the research. [21 CFR 56.108(b)(3) and 21 CFR 56.113] [45 CFR46.113]. The IRB approving the suspension or termination, will determine if the subjects are to be notified of the suspension/termination. Any adverse events or outcomes will be reported to the IRB.

2. **Correspondence:** Correspondence is written by the Chair, IRB. All correspondence goes through the Chair, IRB, ACOS, Research, Hospital Director, to Director, Division of Compliance Oversight, Office for Human Research Protection. Copies will be sent to: AO for Research (578/151), Chair, R&D (151), ORO Regional Office Director.

INVESTIGATIONAL NEW DRUG / DEVICES PROCEDURES

INVESTIGATIONAL DRUGS IN RESEARCH WITH HUMAN SUBJECTS (VHA HANDBOOK 1200.05)

A. **Regulations:** Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA and VA regulations.

The use of drugs in research must be carried out in a responsible manner. The storage and security procedures for drugs used in research must follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations.

B. **Definition:** An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312). Pursuant to these regulations an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or on earlier notification by FDA that the clinical investigation may begin (21 CFR 312.40). In the VA, an investigational drug is also defined as an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

C. **PI Responsibilities:**

1. The PI is responsible for informing Pharmacy Service that IRB and R&D Committee approval has been obtained. This must be through the use of VA Form 10-1223, Report of Findings Institutional Review Board, to be sent to Pharmacy Service. VA Form 10-9012, Investigational Drug Information Record, or superseding forms must be provided to the pharmacy by the PI as required in VHA Manual M-2, Part VII, Chapter 6, or superseding policy document. In addition a signed copy of VA Form 10-1086, must be sent to Pharmacy Service to document each subject's consent to participate in the study.
2. The PI must inform the Chief, Pharmacy Service, IRB and the R&D Committee when a study involving investigational drugs has been terminated.
3. All applicable requirements in M-2, Part VII, Chapter 6, or superseding policy document must be met.

D. FDA regulations provide for exceptions to the general requirements for obtaining informed consent under two specific situations:

1. When the human subject is confronted by a life-threatening situation necessitating the use of the drug, when a legally effective informed consent cannot be obtained from the subject, when time is not sufficient to obtain consent from the subject's legally-authorized representative, and when there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject (21 CFR. § 50.23(a).
2. 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 in 21 CFR § 50.23(a) in advance of using the drug (21 CFR § 50.23(b)).

E. FDA regulations (21 CFR 312.34 and 312.35) address the treatment use of an investigational drug (not approved for marketing, but under clinical investigation for a serious or immediately life-threatening disease condition) in patients for whom no comparable or satisfactory alternative drug or other therapy is available. Use of the investigational drug for this purpose must meet all applicable FDA requirements.

F. FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

G. **Emergency Exemption from Prospective IRB Approval.** FDA defines emergency use as the use of an investigational drug or biological product with 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. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized. Informed consent is required unless the conditions for exemption are met. The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review.

H. Definitions

1. An **investigational drug or device** for clinical use is one for which a sponsor has filed, respectively, an IND (Investigational New Drug) or IDE (Investigational Device Exemption) application with, and which has been approved by, the FDA. An investigational drug may be a new chemical compound which has not been released by the FDA for general use, or it may be an approved drug but not FDA approved for a new application or use.

2. Investigational Device Exemption (IDE). 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.*

3. Treatment IND Use is where the FDA has granted approval for an investigational drug to be used by a qualified investigator in a patient with a serious or life-threatening illness.

I. Policy

1. The use of drugs and devices in research must be carried out in a responsible manner.
2. The use of controlled substances, such as narcotics and barbiturates, requires even more stringent monitoring.
3. The use of an investigational drug or device in clinical research must be conducted according to a protocol approved by the IRB as well as the R&D Committee.
4. The storage and security procedures for drugs used in research shall follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations.

5. All new investigational brochures relating to ongoing research must be submitted to the IRB for review.
6. Any unanticipated problems involving risks to human subjects or others involving the use of investigational drugs must be reported in accordance to the previously described timetable (see Adverse Events). In addition, investigators must comply with reporting requirements to sponsors and the FDA.

J. Determination of the Need to Obtain an IND: The IRB will not approve a study if a drug/biologic is *NOT* FDA approved unless an IND has been secured. An IND is also required if the drug/biologic is FDA approved in the following circumstances:

1. The trial is intended as a well-controlled study in support of a new indication or intended to support any other significant change in the labeling of the drug;
2. The research is intended to support a significant change in the current advertising for an approved product;
3. The research involves a route of administration, dosage level, use in a subject population, or other factor that significantly increases the risk (or decreases the acceptability of the risks) associated with the use of an approved product.

The Investigator will provide documentation of the valid IND to the IRB at the time of submission. This may be in the form of sponsor documents, or, if investigator initiated, correspondence from the FDA.

If the investigator is acting as the sponsor, the investigator will be invited to the IRB meeting. During the discussions, the IRB will determine that the investigator is knowledgeable about the additional FDA regulatory requirements and is able to adhere to them.

K. **INVESTIGATIONAL DEVICES IN RESEARCH WITH HUMAN SUBJECTS (VHA Handbook 1200.05)**

1. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, other applicable FDA regulations, and applicable VHA regulations.

2. If the study of the device is not exempt (21 CFR 812.2(c)), the device must be characterized as "significant risk" (SR) or "non-significant risk" (NSR) by the IRB. The IRB will determine and document if the device represents SR or NSR based on information provided by the Investigator and pursuant to the regulations and *FDA Information Sheets, 2006.*

3. The IRB must review the research in accordance with these requirements and needs to use the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).

4. NSR device studies may commence immediately following IRB and R&D Committee approval, if no changes are required by either committee. *NSR devices may represent greater than minimal risk depending upon the research study.* NSR device studies do not require submission of an IDE application, but must be conducted in accordance with the "abbreviated requirements" of the IDE regulations (21 CFR 812.2(b)). Unless otherwise notified by the FDA, a NSR study is considered to have an approved IDE if all abbreviated requirements are fulfilled.

5. SR device studies must be conducted in accordance with the full IDE requirements (21 CFR Part 812).
The IRB will verify the existence of the IDE if applicable. The investigator must include a copy of the FDA's correspondence to go forward prior to review of the protocol. An investigation may begin 30 days after FDA receives the application (unless FDA provides notification that the investigation may not begin), or after the FDA approves, by order, an IDE for the investigation (21 CFR 812.30). In addition, the investigator must have approvals from the IRB and R&D committee. The FDA considers all SR studies to be greater than minimal risk.
6. The PI is responsible for compliance with all applicable FDA regulations.
7. Emergency use of un-approved devices must follow FDA guidance.
8. The VA facility must have procedures for receipt, control, custody, and dispensing of the investigational devices.

L. **The IRB must** assure that the investigator obtains an IDE if a proposed device is determined by the IRB to be of significant risk. The risk determination will be based on the proposed use of a device in an investigation, and not on the device alone. If the subject must undergo a procedure as part of the research e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

M. **A device will be considered to be of serious risk if it**:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health, and represents a potential for serious risk to the health, safety, welfare of a subject;
4. Otherwise presents a potential for serious risk to the health safety, or welfare of a subject;
5. Is a custom device being tested for safety or effectiveness.

N. **Examples of Significant Risk Devices** and Non-Significant Risk Devices are listed on the FDA Information Sheets and are included in the IRB Standard Operating Procedures Appendix.

Questions or concerns whether a device is deemed "significant risk" or "non-significant risk" may be discussed with the FDA staff.

O. **If the IRB disagrees** with the sponsor or Principal Investigator regarding risk designation, written notification will be provided to the Principal Investigator and the sponsor. The sponsor or investigator may provide additional information. The Investigator may attend an IRB meeting to discuss concerns pertaining to his/her project. The IRB may consider any device study for initial review. If the IRB determines that the device is a Significant Risk Device, study approval will be deferred until the IDE number and FDA correspondence, and any required changes to the study have been received and. brought to the convened IRB for review.

INVESTIGATIONAL NEW DRUG PHARMACY PROCEDURES

PHARMACY RESPONSIBILITIES

A. Pharmacy Service will be responsible for the receipt, custody, storage and dispensing of all drugs in clinical stages of evaluation, or used under investigational protocols. Investigational drugs will be stored in an appropriate storage area under custody and control of the Chief of Pharmacy Service.
B. Pharmacy Service will be responsible for maintaining files of investigational protocols of pending, approved and closed studies. Records of closed studies will be maintained for a period of five years following closure.
C. Pharmacy Service will be responsible for obtaining a copy of the Informed Consent (VA Form 10-1086) prior to dispensing the drug.
D. Pharmacy Service will be responsible for maintaining a log of all transactions involving receipt, dispensing and disposition of unused stocks of investigational drugs.
E. The Principal Investigator will supply to the Pharmacy Service information on each patient receiving an investigational drug, with emphasis on documentation of allergies, toxicities, or adverse drug reactions related to the investigational drug and other drug therapy.

RECEIPT, CONTROL, CUSTODY, DISPENSING

A. Regardless of source, all investigational drugs will be delivered to the pharmacy for receipt, storage and distribution. All investigational drugs will remain under the control and in the custody of the Pharmacy Service until the time of dispensing. The Investigational Drug Information Record (VA Form 10-9012), listing all physicians authorized to prescribe, will be provided to Pharmacy.
B. Investigational drugs will not be obtained from other facilities or principal investigators except as noted under humanitarian or treatment IND use.
C. Investigational drug stocks will be kept separate from other drugs and dispensed only on the properly written order of the practitioner authorized to use the drug.
D. For each new patient added to the protocol, the practitioner authorized to use the investigational drug will provide pharmacy with a direct copy of the signed informed consent document with the first written order for the investigational drug.
E. In addition to the customary prescription label data and appropriate auxiliary, caution, or warning labels, all investigational drugs labels will include the following legend, "INVESTIGATIONAL DRUG NOT FOR GENERAL USE."
F. An investigational drug log will be maintained containing the following information where applicable.
    1. Name of the drug
    2. manufacturer or other source
    3. Date of receipt of the drug
    4. Quantity received
    5. Expiration date
    6. Control number
    7. date protocol approved
    8. Name of authorized practitioner signing the prescription

9. Name of patient receiving the medication
10. Serial number of the Prescription
11. Quantity dispensed
12. Balance remaining after transaction
13. Signed initial of the dispensing pharmacist
14. A final entry will be made when the use of the investigational drug is discontinued. This entry will document the date of termination of the use of the drug, the quantity remaining, and the action taken to dispose of the balance on hand.

HUMANITARIAN USE OF AN INVESTIGATIONAL DRUG

A. Occasionally it may become necessary to treat a patient with an investigational drug that was given while undergoing treatment at another facility or as a compassionate treatment. In those cases, the following steps should be taken:
   1. The responsible staff practitioner should communicate with the Chief of Staff, the pharmacist responsible for the investigational drug use, the IRB, and the Research and Development Committee. Initial communication within the facility may be telephonic to expedite patient care.
   2. After the responsible staff practitioner obtains tentative approval for use of the drug, the request should be submitted in writing and include:
      a. A brief case report including patient data and diagnosis
      b. The reason for requesting approval to use the drug
      c. Literature or reference material to support the request
      d. The name of the PI and the local practitioner responsible for care of the patients.

B. The Chief of Staff of the requesting facility will communicate to VA Headquarters and the Executive Committee on Therapeutic Agents all essential data listed above requesting priority approval. A copy of the written approval will be forwarded to the Pharmacy Service.

C. The requesting practitioner will provide Pharmacy Service with a copy of the drug protocol, signed Agreement to Participate in Research By or Under the Direction of the VA Form 10-1086, and an Investigational Drug Information Record Form 10-9012, and a properly completed order for the drug prior to administration. All supplies of the drug must be delivered to the pharmacy as with any other investigational drug.

D. The practitioner must prepare a preliminary report to the local Pharmacy and Therapeutics Committee within 90 days of initiation of therapy, and a final summary report upon termination of the drug. The local Pharmacy and Therapeutics Committee will forward the report(s) to VA Headquarters.

E. All documentation of use of drugs obtained for humanitarian or compassionate use will be the same as for other investigational drugs.

PAYMENT OF SUBJECTS

Policy: VA policy prohibits paying patients to participate in research when the research is an integral part of a patient's medical care and when it makes no special demands on the patient beyond those of medical care. Payment may be permitted, with prior approval of the IRB, in the following circumstances [M3 Part 1 Chapter 9.13]:

A. There is 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.
B. 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 rate proposed.
C. Comparable situations. In other comparable situations in which in the opinion of the IRB, payment of patient volunteers is appropriate.
D. Transportation Expenses. When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism. (Handbook 1200.05)
E. Any amount of payment to the participants as a bonus for completion of the study is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

Procedure:

A. Principal Investigators who wish to pay research subjects must indicate in their proposal the justification for such payment.
B. Principal Investigators must substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject.
C. State the terms of the subject participation agreement and the amount of payment in the Informed Consent form. The entire payment should not be contingent upon completion of the entire study but prorated according to the pre-determined periods of participation.
D. 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 or continue in the research study.
E. The IRB will review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of the above policies.
F. The facility research office is responsible for ensuring that IRB-approved payment to subjects is made from a VA approved funding source for research activities. (Handbook 1200.05)

INFORMED CONSENT POLICY

Policy: Investigators wishing to involve human beings as subjects in research will obtain legally effective informed consent of the subject or the subject's legally authorized representative. Individuals who may obtain informed consent include the investigator and/or designated study personnel who have completed the required Human Subjects Protection education and possess a thorough knowledge of the protocol in order to explain the study to the participants and sufficiently answer any questions. Patient enrollment into the study begins with the process of obtaining informed consent from prospective participants. The IRB has the authority to observe the consent process. The IRB will review the consent document and determine the elements of informed consent will be disclosed to the subject or subject's legally authorized representative: The basic elements of informed consent are:
(References: [45 CFR 46.116(a)] [21 CFR 50.25(a) and VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research, dated July 31, 2008.)

A. A statement that the study involves research.
B. An explanation of the purposes of the research and the expected duration of the subject's participation.
C. A description of the procedures to be followed.
D. Identification of any procedures which are experimental in relationship to standard care.
E. A description of any reasonably foreseeable risks or discomforts to the subject.
F. A description of any benefits to the subject or to others which may reasonably be expected from the research.
G. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
H. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
I. For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
J. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research related injury to the subject.
K. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
L. A statement that a veteran-subject will not be required to pay for treatment received as a subject in a VA research program. Investigators should note, however, that veterans in the "discretionary work load" category are subject to making a co-payment if so indicated by a means test (M1. Pt. 1, Ch. 4, par. 4.30), for any procedure that is not considered research The veteran subject will receive medical care and treatment for injuries suffered as a result of participating in a VA research program in accordance with Federal law.
M. The VA statement regarding Research-Related Injuries The VA will provide necessary medical treatment to a research subject injured by participation in a research project. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. The Department of Veterans Affairs does not

normally provide any other form of compensation for injury. You have not released this institution from liability for negligence.

N. The VA statement regarding Research-Subject Costs: You will not be required to pay for medical care or services received as a participant in a VA research project except as follows: some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

When appropriate, the IRB will determine that one or more of the following elements of information will also be provided to each subject:

1 A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2 Anticipated circumstances under which the subject's participation may be terminated by the investigator without the subject's consent.
3 Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.
4 An explanation that a subject's decision to withdraw from the research and procedures in no way jeopardizes their ability to receive future care or any other rights and privileges.
5 A statement indicating 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 subjects.
6 The approximate number of subjects involved in the study.
7 A statement on the signature page: "I authorize the use of my bodily fluids, substances, or tissues." This is required if the researcher believes that bodily fluids, substances or tissues of a research subject could be part of, or lead to, the development of a commercially valuable product.
8 A statement regarding any payment the subject is to receive and at what periods during the study.
9 A statement describing the extent to which confidentiality of records identifying the subject will be maintained. If appropriate, a statement that Federal agencies such as the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP) and the Government Accounting Office (GAO) may have access to the records. If an FDA-regulated test article is involved, the FDA requires a statement that the FDA may choose to inspect research records that include the subject's individual medical records.
10 These informed consent requirements are not intended to pre-empt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

Exculpatory Language: No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. 45 CFR 46.116

Examples of Exculpatory Language:

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

Exceptions to the Requirement for Some or All of the Elements of Informed Consent:
If the research is subject to FDA, except as provided in 21 CFR 50.23 and 21 CFR 50.24, the IRB may not waive the requirements for informed consent.

As defined in 38 CFR 16.116(c) the IRB may approve a consent procedure which does not include**,** or which alters some or all of the elements of informed consent (unless subject to FDA regulations) provided the IRB document that:

A. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
   1. Public benefit of service programs;
   2. Procedures for obtaining benefits or services under those programs;
   3. Possible changes in or alternatives to those programs or procedures; or
   4. Possible changes in methods or levels of payment for benefits or services under those programs.

B. The research could not practicably be carried out without the waiver or alteration when the following also apply:
   1. The research involves no more than minimal risk to the subjects;
   2. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
   3. Whenever appropriate, the subjects shall be provided with additional pertinent information after participation.

Exceptions to the Requirement for W*ritten* Informed Consent:
In the following situations, even though informed consent of the subject may be required, its documentation in writing through a consent form is not required:

A. The only record linking the subject and the research would be the consent document and the principal risk would be a potentially harmful breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
B. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the nature and scope of research.

In these cases, the IRB must review a written summary of what is to be said to the subject or the representative.
Whenever appropriate, the subjects shall be provided with additional pertinent information after participation in the research study.

INFORMED CONSENT PROCEDURES

A. Documenting Informed Consent

Respect for persons (Belmont Report) is the underlying concept for obtaining informed consent. The Informed Consent is an ongoing process that starts with the initial presentation of a research activity to a prospective subject by the investigator, and continues through the research activity until the subject ends his/her participation, or the study closes. The project must be presented to the participant or his/her legally authorized representative, in a language that is understandable, without coercion or undue influence, and must allow adequate time for the participant to review and ask questions. Informed consent must be obtained prior to entering a subject into a study and/or conducting any research procedures. Except in the circumstances described above, informed consent must be documented by the use of a written consent form and signed and dated by the subject or the subject's legally authorized representative. All pages of the consent must be initialed by the subject or legal representative. The consent form must be dated and signed by a witness who is unrelated to the study. In this case, the witness role is to witness the subject's or legally-authorized representative's signature. If the IRB or sponsor requires a witness to both the consent process and signature, and one individual is witness to both, a note will be written under the witness line indicating that the witness served in both capacities. A study investigator must review, sign and date the consent form within a reasonable timeframe. The original signed consent form must remain with the principal investigator in the subjects' case history. Copies (1) must be filed in the subject's medical record and (2) made available to the IRB which will review them. A copy of the signed and dated consent document must be given to the person signing the consent

B. The Principal Investigator may delegate the duty of obtaining informed consent to other study personnel provided: 1) Those duties fall within the scope of practice for which the individual is licensed or certified, and has been awarded clinical privileges by the institution. 2) The individual is familiar with the purposes, methods, and procedures of the protocol, 3) The individual has been so designated within the project and approval for the individual's responsibilities have been obtained from the IRB. This approval may be obtained through an amendment or at initiation of the project as designated in the Staff Responsibilities Section of Part III (Appendix A).

C. A progress note documenting the informed consent process (when applicable) must be placed in the subject's medical record. (VHA HANDBOOK 1200.05) and the Medical Record may be Flagged.

PROGRESS NOTE:

1. A progress note should be added to the Medical Record documenting the patient's agreement to participation in the research study.
2. The progress note should include the following:
   - date subject was entered into the study, and date participation began.
   - title of research study
   - name of Principal Investigator

- A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,
- A statement that the study was explained to the subject, and
- name of person obtaining informed consent. If the written informed consent requirement has been waived by the IRB, the note must document this.
- A statement that the research study was explained to the subject and the subject was given the opportunity to ask questions.
- If the study involves a FDA regulated test article (investigational drug or device), then the case history must document informed consent was obtained before participation began in the study.
- An entry must also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated. *NOTE: Consent and entry notes can be combined when both occur at the same visit.*

D. FLAG ALERT IN THE MEDICAL RECORD

The IRB needs to determine if the patient's medical record (electronic or paper) must be flagged to protect the subject's safety by indicating the subject's participation in the study, and the source of more information on the study. The IRB may not want to require the medical record to be flagged if:

1. The subject's participation in the study involves:

   a. Only one encounter, interview, focus group, etc.
   b. Only the use of a questionnaire, or
   c. The use of previously collected biological specimens.

2. The identification of the patient as a subject in a particular study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk.

EXAMPLE OF A FLAG ALERT IN THE MEDICAL RECORD

Patient Name:
This patient is enrolled in a RESEARCH STUDY.
<title>
Principal Investigator:
Call 708-123-4567----- if there are questions
Enrollment date: MM/DD/YYYY
Consent signed on: MM/DD/YYYY

E. Nature of the Consent Process

Documentation of the consent process may be either of the following:
Written consent document: A written consent document that embodies the elements of informed consent described above. VA Form 10-1086, VA Research Consent Form shall be used to meet these requirements. The consent form document may be read to the subject or the subject's legally authorized representative, but in any event the investigator will give either the subject or the representative adequate opportunity to read it before it is signed; or

Verbal Consent: Documented by a short form written consent form stating that the required elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there will be a witness, conversant in both English and the language of the participant, to the oral presentation who is not a study team member. This process includes the following [45 CFR 46.117(c)] [21 CFR 50.27(2)]

1. The IRB will approve a written summary of what is to be said to the subject or the representative.
2. Only the short form itself is to be signed and dated by the subject or the representative.
3. The witness will sign both the short form and a copy of the summary, and the person actually obtaining consent will sign and date a copy of the summary.
4. A copy of the summary will be given to the subject or the representative, in addition to a copy of the signed and dated short form.

F. Surrogate Consent

1. Policy: Under appropriate conditions, investigators may obtain informed consent from the legally authorized representative (LAR) of the participant. According to VHA Handbook 1200.05 11(a). a Surrogate Consent may be obtained from: a health care agent appointed by the person in a DPAHC or similar document; court-appointed guardians of the person, or from next-of-kin in the following order of priority, unless otherwise specified by applicable state law: spouse, adult child (18 years or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older). ***NOTE:*** *The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes.*

Such consent may be requested and accepted only when the prospective research participant is incompetent as determined by the practitioner in consultation with the chief of service or Chief of Staff, after appropriate medical evaluation, and there is little or no likelihood that the patient will regain competence within a reasonable period of time; or as established by a legal determination.

This policy is designed to protect patients from exploitation and harm and, at the same time, to make it possible to conduct essential research on problems that are unique to incompetent patients (e.g., a study of treatment options for comatose patients can only be done with incompetent subjects).

2. Criteria for IRB approval: Before incompetent persons may be considered for participation in any study, the IRB must find that the proposed research meets all of the following conditions:

• Only incompetent persons or persons with impaired decision making capacity are suitable as research participants. [VHA Handbook 1200.05 Appendix D.6.c(1)]
• Competent persons are not suitable for the proposed research. [VHA Handbook 1200.05 Appendix D.6.c(1)]
• 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 participants. [VHA Handbook 1200.05 Appendix D.6.c(1)]]
• Such consent (surrogate consent) may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note [VHA Handbook 1200.05 Appendix

• Incompetent persons or persons with impaired decision-making capacity must not be participants in research simply because they are readily available. [VHA Handbook 1200.05 11 (3)]
• If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study. [VHA Handbook 1200.05 11 (3)(d)]

3. Favorable risk/benefit ratio: The proposed research entails no significant risks, or if the research presents some probability of harm there must be at least a greater probability of direct benefit to the participant. [VHA Handbook 1200.05 Appendix D.6.c(2)] Incompetent people will not be subjects of research that imposes a risk of injury unless that research is intended to benefit the subject and the probability of benefit is greater than the probability of harm. VHA Handbook 1200.05 Appendix D.6.c(2)] In placebo studies, special care must be taken to be sure that subjects know that they may not receive the study drug and careful monitoring must be in place to assure patient safety.

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

5. Well informed representatives: Procedures have been devised to assure that participants' representatives are well informed regarding their roles and obligations to protect incompetent subjects. Health care agents (appointed under Durable Powers of Attorney for Health Care [DPAHCs]) and next of kin or guardians must be given descriptions of both proposed research studies and the obligations of patients' 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 interests. [VHA Handbook 1200.05 Appendix D.6.c(3)]

6. IRB Procedure: The IRB will make a determination in writing of each of these criteria. If these criteria are met, the IRB may approve the inclusion of incompetent subjects in research projects on the basis of informed consent from authorized representatives or next of kin. [VHA Handbook 1200.05 Appendix D.6.d]

G. Procedure for observation of the Consent Process: The IRB has the authority to observe, or have a third party observe, the consent process and/or the conduct of the research as a method to protect participants and observe investigator compliance.

1. The IRB may observe the consent process if:
   a. Cause: If there are allegations of misconduct or noncompliance, or there have been previous infractions, an audit of an investigators files and/or observation of the informed consent process may be requested.
   b. Concerns: If there are concerns about the conduct of the study or the process for obtaining consent, as part of adequate oversight of the study, an audit/consent observation.
   c. New Investigator: Audits of the informed consent process and/or new investigator files will be completed to aid in education and training.
   d. Random: Random audits and/or observation of the consent process may be performed to reinforce education and to assure investigator compliance.
   e. Research involving adults with potentially limited decision-making capacity.
2. The observation of the consent process may be performed by the IRB Chair, or designated member, IRB Coordinators, or by a third part hired by the investigator or sponsor.

3. When an audit or observation of the consent process is to occur, the investigator is notified of a date and time, or the investigator will notify the designated observer, when a consent process is going to take place. The observer will then be present during the consenting process and observe for appropriateness, such as:

a. Investigator / person obtaining consent is knowledgeable about the protocol and consent and able to answer questions.

b. An Adequate timeframe is allowed for the potential participant to review the consent.

c. Adequate time is allowed for the potential participant to ask questions.

d. An assessment was made of the potential participant's understanding of the study by having them restate some of the major purposes, procedures, risks and participant time commitment.

e. Observe for any coercion or false promises or minimization of the identified risks.

f. The consent was completed with appropriate signatures and dates.

4. Upon completion of the observation, if the participant agrees to participate and signs the Informed Consent, the person observing the consent process can sign as witness to the signature, but also must make a note that he/she also witnessed the consent process.

5. Upon completion of the audit or observations, a report is written and summarized to the IRB and in the IRB minutes.

COMPLAINTS AND ALLEGATIONS

A. Policy: All research participants and others are encouraged to ask questions or to voice concerns or complaints. The IRB will respond to complaints and allegations of noncompliance with institutional policies. The process includes the following factors:

1. Ensuring a response to each question, concern or complaint.
2. Investigating complaints and allegations.
3. Taking remedial action for, and consequences of findings of, noncompliance with HRPP and IRB policies.
4. Identifying individuals who have responsibility for responding to questions, concerns or complaints regarding an individual's rights as a research subject.

B. Procedure:

1. All research consents will include the contact numbers of the principle investigator and the Chair of the IRB, which is 708-202-5701 to encourage all participants to express concerns and questions.

2. All inquiries and/or complaints regarding any research involving human subjects, will be referred to one of the IRB Coordinators who will screen the call/complaint. If there is a serious complaint of non-compliance or dissatisfaction, it will be referred to the Chair of the IRB

3. Investigation regarding complaints or allegations of non-compliance will be initiated immediately and a brief summary documented in the study file.

4. As appropriate, the investigator files will be audited by one of the IRB Coordinators and a written report summarized for the IRB and a summary of the findings, discussion and recommendations documented in the minutes. If a plan of action is required, it will be considered and voted on by the IRB membership. All findings and correspondence will be filed in the study file and a summary sent to the investigator.

5. Inquiries and/or complaints may also be referred to the Research Compliance Officer who will collaborate with the IRB Chair and/or IRB Office staff for resolution.

6. Any identified misconduct will follow the Research Misconduct Policy, dated December 6, 2000 and the memo dated 7/6/01 from the Chief, Research and Development Officer (12).

7. Complaints are also evaluated as part of the Request for Continuing Review, which is submitted at least annually. During this process, the principle investigator and the peer reviewer will evaluate participant complaints, as summarized on the application, as well as, reasons why participants withdrew or were withdrawn from the study to identify any improprieties or trends.

8. The IRB will monitor the timeliness of responses to questions and complaints and the satisfaction with the responses through review of the minutes, investigator files and IRB study files and the Continuing Review process.

9. Individuals have the right to file a complaint regarding VHA privacy practices. The complaint does not have to be in writing, though it is recommended.

Complaints should be made to the VHA Privacy Officer, or the VA health care facility Privacy Officer, or designee. All privacy complaints must be investigated and a written response provided to the complainant. In addition the Privacy Officer must enter the complaint into the Privacy Violation Tracking System (PVTS).

NON COMPLIANCE

A. Policy: Reports or findings of non-compliance will be evaluated and appropriate action taken.

Reports of non-compliance may be identified through internal or external audits, monitoring reports, reports of protocol deviations or violations, or reported concerns by an individual. Reports and allegations of Non-compliance will be reported promptly to the IRB by any individual who has knowledge or a concern of non-compliance.

B. Procedures:

- Non compliance may be minor, continuing or serious.
- When reports are received, an evaluation may be made by the IRB staff if the non-compliance is minor, continuing or serious. The Chair will also be consulted for the determination.
- Minor issues of non-compliance may be handled by the IRB staff and results reported to the IRB on the agenda.
- Reports of non-compliance or protocol deviations may be reported by the Investigator or study coordinator, study monitor, RCO or IRB member performing an investigator audit, or any other individual who believes there is non-compliance. All sponsor monitors must sign in with the Research Office. Any potential or serious findings conveyed to the study staff (investigator, coordinator), must be reported to the ACOS and/or AO. All findings of serious non-compliance must also be reported to the IRB for appropriate action within 5 days of becoming aware of possible serious or continuing non-compliance according to the requirements of VHA Handbook 1058.
- Reports may be made either to an IRB staff member, IRB Chair, RCO, ACOS or AO.
- Reports will be reviewed and evaluated by the Chair. The event will be described and recommendations put the meeting agenda. As appropriate, the IRB may require additional information and follow-up by the Investigator. If the report is serious, and affects risks to the participants, the Chair has the authority to halt further enrollment until the matter is further evaluated. Any such action will be reported to the convened IRB and R&D.
- If the IRB determines that the possible non-compliance is or was serious and continuing, the IRB Chair will report the non-compliance to the ACOS/R and Hospital Director and the R&D within 5 days of determination by the IRB.
- Reports of protocol deviations will be evaluated by a Primary Reviewer to determine if the deviation is non-compliance, if it is serious and/or continuing, and refer to convened Committee for further action as appropriate.
- Reports of Investigator non-compliance identified by an audit by a regulatory oversight body (i.e. OHRP, FDA, ORO), are sent to the Director. Copies will be forwarded to the ACOS and IRB. The report will reviewed and evaluated by the Chair and placed on the next agenda for review and appropriate evaluation and action. IRB members will receive copies of the letters to facilitate necessary actions. As necessary, additional information

will be gathered by Chair or IRB staff. This additional information will be provided to the IRB members either in summary on the agenda or copies of documents.

- Other issues of non-compliance are reviewed by the Chair for further action. The Chair may direct the staff or assign IRB member(s), or request the RCO to investigate or audit, results of which will be reported to the convened IRB for determination of necessary action.
- Depending on the circumstances, the IRB may take any or all of the following actions: stop enrollment, require education, require the Investigator to provide an action plan for resolution and steps to assure the non-compliance will not occur again, terminate approval, require more frequent reviews or frequent reporting to the IRB.
- If the convened IRB determines that the study must be suspended, the PI must immediately submit to the IRB Chair, a list of research subjects for whom suspension/termination of the research would cause harm. The IRB Chair, with appropriate consultation with the COS, determines if the subject may continue in the research, or a plan to safely discontinue the subject from the study.
- Continuing non-compliance will be evaluated on a case by case basis. Once identified, the Chair will determine what action is appropriate based on the type of repeated non-compliance (i.e. late continuing review submissions, adverse event reports, protocol deviations, conducting research procedures prior to consent or conducting research without approval) The Chair may discuss the issue directly with the Investigator, or assign staff or members to obtain additional information. The findings will be brought forward to the IRB for determination of necessary action. The IRB may take any or all of the following actions: suspend the research, cease new enrollment, require additional education, require the Investigator to provide an action plan for resolution and steps to assure the non-compliance will not occur again, terminate approval, require more frequent reviews or frequent reporting to the IRB, or suspension of research privileges. Reporting of such cases will be in compliance with VHA Handbook 1058.01
- More than minor changes in approved research made in response to serious or continuing non compliance must be reviewed and approved by the convened IRB
- If the continued non-compliance is serious, as necessary, the IRB Chair will involve the R&D Chair, ACOS, Department Head, and Chief of Staff or Hospital Director for potential disciplinary action.
- As necessary, incidences of serious or continued non-compliance will be reported to the R&D Committee by the IRB Chair at a convened meeting. Reports including the nature of the non-compliance, action and outcome, will be in writing, approved by the Chair, and routed through the ACOS to the Chief of Staff and Hospital Director to: the Regional Office of ORO, OHRP, FDA , if the study involves a test article or device regulated by the FDA, and VA Central Office. If a sponsor is required to be notified, a written report or letter will be sent through the Office of the ACOS.

PRIVACY AND THE HEALTH PORTABILITY AND ACCOUNTABILITY ACT HIPAA

A. USE OF VA RECORDS FOR RESEARCH AND DEVELOPMENT (VHA HANDBOOK 1200.05)

1. VA personnel are bound by all legal and ethical requirements to protect the rights of human subjects, including the confidentiality of information that can be identified with a person.
2. Obtaining and using medical, technical, and administrative records from other VA facilities or VA databases (national, regional, or subject specific) for R&D purposes must be in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information (45 CFR Parts 160 and 164). Obtaining and disclosing individually-identifiable patient records must be in compliance with all applicable and confidential statues and regulations including those discussed in subparagraph 7a(7).
3. **Persons not employed by VA can be given access to medical and other VA records for R&D purposes only within the legal restrictions imposed by such laws as the Privacy Act of 1974 and 38 U.S.C. Requests for such use must be submitted to the CRADO in VA Central Office at least 60 days before access is desired**. Requests for information filed pursuant to the Freedom of Information Act ordinarily requires a response within 10 working days. VA guidelines and policy must be followed when making such requests to allow for a timely reply.

This does not apply to those individuals having access for the purpose of monitoring the research. Obtaining and using the records must be in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information (45 CFR Parts 160 and 164).

B. PRIVACY AND CONFIDENTIALITY

The privacy and confidentiality of the research participant must be protected. Privacy and confidentiality are not the same. For the purposes of research involving human subjects, privacy related to the *person*, confidentiality relates to the *data*.

Privacy and Confidentiality regulations and statutes are referenced in 1200.05 7a(7) and in VHA Handbook 1605.01.

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

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

Confidentiality
The IRB must assure there are adequate provisions to protect the confidentiality of identifiable data. This is evaluated on a continuing basis.

The IRB will evaluate the Investigator's plan for handling, managing, storage, and sharing of identifiable information, this also includes recruitment and obtaining consent, and how information in obtained or about the participant

In Part III (Appendix A), the section regarding maintaining the confidentiality of participant information must be fully completed. Methods used to collect information about participants, and provisions for protecting the confidentiality of the research data must be identified.

The VA Privacy Act and VA Privacy Handbook 1605.1 provides more complete explanation of the regulations covering veteran's data. Section 13 refers to research uses.
http://www1.va.gov/vhapublications/publications.cfm?pub=2

Compliance for Researchers is guided by the following documents:

1. VHA HANDBOOK 1605.1 **Privacy and Release of Privacy Information**
2. Website - http://www.research.va.gov/programs/pride/policy/default.cfm
3. Website: http://www.research.va.gov/safeguarding_vets.cfm
4. Website: http://www.research.va.gov/resources/data-security/default.cfm

C. Procedure for HIPAA Authorization Documentation for Hines/NCVA.

1. In compliance with VHA /ORD guidelines, the ORD supplied *HIPAA Authorization template (Appendix 0(1))* and is available on the Research website.

2. Investigators who are actively enrolling participants are to complete one HIPAA Authorization per protocol, using the approved template.

3. Once the protocol specific Authorization Form is completed:
   a. A copy of the protocol specific HIPAA Authorization template is to be sent to the IRB for review and filing into the Protocol File.
   b. Though the IRB staff may review and give recommendations regarding the protocol specific HIPAA Authorization, IRB formal approval of the completed template is not required and will not be provided.

c. The Privacy Officer will review the Authorization as part of the PO responsibilities

d. The protocol specific HIPAA Authorization is to be reviewed and signed by the newly enrolled participant in addition to the Informed Consent, not in place of.

e. A copy of the signed HIPAA Authorization (along with the signed Informed Consent) will be submitted to the IRB office for review and placement into the protocol file.

D. Verbal HIPAA Authorization Documentation

If approved, verbal authorization may be obtained over the telephone and in the presence of a witness. The witness signs the consent as confirming the consent and authorization process. For Verbal HIPAA Authorization, the HIPAA Authorization Form will have two places for signature: 1) Person obtaining authorization and 2) witness.

The consent process and HIPAA Authorization could also be taped, with a copy given to the participant. This process must also be witnessed, unless a waiver is granted by the IRB.

E. Surrogate Authorization: HIPAA Authorization in situations where the participant is deemed mentally disabled, a legally authorized representative may sign the authorization

F. Procedure for HIPAA Waiver of Authorization

1. If the investigator requires a waiver or alteration of the HIPAA Authorization, the investigator must provide the IRB with information sufficient for the IRB to find that such waiver or alteration is necessary. The IRB must document its decision in its minutes.

NOTE: *The elements of such documentation are listed below and may be used by an investigator to determine what information needs to be provided to the IRB with a request.*

2. Recruitment: For screening of medical records and other documents linked with identifiable information, for the purposes of recruiting /enrolling participants, prior to obtaining consent and HIPAA authorization, the investigator is to complete a ***Request for Waiver of Authorization (Appendix 0(2))*** available on the Research website.

3. Retrospective chart reviews/database reviews: A Request for Waiver of Authorization (Appendix 0(2))

4. Once approved, the investigator will receive an approval memo : Approval of Waiver of HIPAA Authorization , signed and dated by the Chair, IRB

5. This process may be either through full board review or expedited review by the Chair,IRB.

6. Element of Documentation Required for Waiver of Authorization, Per VA HANDBOOK 1200.05, July 31, 2008, Appendix E:

a. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule requires that, if an IRB grants a waiver or alteration of the HIPAA Authorization, the Institutional Review Board (IRB) document the findings on which it based its decision. A request from an investigator to waive or alter the HIPAA authorization must be accompanied by information sufficient to make the required findings listed in the following.

b. The documentation must include <u>all</u> of the following:

1). Identification of the IRB

2) Date of IRB approval of waiver of authorization

3) Statement that alteration or waiver of authorization satisfies the following criteria:

(a) The use or disclosure of the requested information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:

(b) An adequate plan to protect the identifiers from improper use and disclosure

(c) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and

(d) Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;

(e) The research could not practicably be conducted without the waiver or alteration; and

(f) The research could not practicably be conducted without access to and use of the requested information.

4) A brief description of the Protected Health Information (PHI) for which the IRB has determined use or disclosure to be necessary

5) Identification of the review procedure used to approve the waiver of authorization (either normal review procedures (38 CFR 16.108(b) or expedited review procedures (38 CFR 16.110)).

6) Signature of Chair of the IRB, or member designated by the Chair, to approve the waiver of authorization.

G. Procedure for Revocation of Authorization for Release of Protected Health Information for Research Purposes

Appendix O(3) Revocation of Authorization: A template form for a revocation of authorization that can be given to a subject who expresses a desire to revoke a previously granted authorization. This form is available through the Privacy Office.

H. Reviews Preparatory to Research

The HIPAA Privacy Rule and VHA policy allow for the access to PHI without an authorization from the individual or a waiver from an IRB or Privacy Board when a VHA researcher is preparing a protocol. However, the researcher must represent that access is only for the purpose of preparing a protocol. The representations necessary for preparatory access are 1) the access is only to prepare a protocol, 2) no protected health information will be removed from the VHA and 3) the protected health information accessed is necessary to the research proposed. This is the only instance of access allowed without authorization or IRB approval. This access is granted only to VHA researchers, non-VHA researchers may not access VHA data for reviews preparatory to research.

USE OF DATA AND DATA REPOSITORIES IN VHA RESEARCH

Requirements of VAH Handbook 1200.12 dated 3/9/09 are hereby incorporated by reference.

Background

The Department of Veteran's Affairs (VA) data repositories developed for health care, administration for VA Programs, or research are valuable resources for researchers. Use of these resources must be consistent with the mission of the VA including relevance to the health of veterans, protecting the privacy of the individuals from whom the data are collected and complying with all applicable ethical and legal standards.

A research data repository is created when data obtained from implementing a research protocol are placed in a data repository. The protocol may be a primary research project designed to prove or disprove a specific hypothesis, or it may be a protocol specifically designed to collect data that will be placed in a research data repository for future use. A research data repository can be created only after a research repository protocol is developed and approved by the IRB (if human research is involved) and the R&D Committee

Policy

The VA research data repository must be physically located within space owned or leased by HVAH or NCVAMC. The local ISO and VA Police Service must determine that the security for the data repository and the location where the data repository is to be located meet applicable VA security requirements prior to data being placed in the space.

All applicable VA Privacy Rule and data security requirements are expected to be followed.

If the Research Repository is located at HVAH or NCVAMC, the IRB will:

1. Comply with all requirements in VHA Handbook 1200.05, and Conflict of Interest policies. The Investigator must comply with the Research Service COI Policy. The IRB will determine if potential research subjects are required to be advised about any commercial ties to the repository and how to manage the conflict.
2. Review and approve the creation and operation of the research data repository, consulting with individuals regarding data security as necessary
3. Conduct a review of the Repository's activities at least once a year. The IRB must receive at least the following information as referenced in VHA Handbook 1200.12:
    a. Sources of data being added to the research repository and the protocol(s) under which they were collected
    b. Type of data released to others for use and the protocol(s) under which they were used.
    c. Summary of any events involving risk to subjects or others, (i.e. breach of privacy or confidentiality)

d. Findings linking a negative impact on the health status of individuals in the data repository with identified causal factors, including whether there may be a clinical intervention

e. All reporting requirements for active protocols (i.e. continuing review, adverse event/unanticipated problem reporting, protocol violations, termination or protocols). Risks to institutions will also be reported.

4. All privacy and security incidents regarding the data repository must also be reported in according to VA policies.

For HVAH or NCVAMC investigator(s) for individual research protocols

The IRB must review and subsequently approve the individual research protocol prior to any access to data.

The IRB is also responsible for:

(1) Complying with all requirements of VHA Handbook 1200.05, including provisions for initial and continuing review of the research protocol which includes

(a) Sufficient information from the investigator to adequately assess the request including if the data to be used are reasonable and necessary to conduct the research.

(b) The source of the data and the purpose for which the data were originally collected, including whether they were collected for research purposes.

1. If the data were collected for other research projects, whether the reuse is consistent with the consent under which they were collected.

2. If the data were collected for administrative or clinical reasons whether the guidelines under which they were collected allow for storage in a specific data repository and reuse for research purposes.

3. If the data is to be obtained from an administrative or clinical data repository, whether the administrative policies and procedures for the data repository allow for use of the data for research purposes, and if so, whether they allow for it as identified, de-identified, or coded.

(c) A description of the data including if they are identified, de-identified, or coded. If the data are identified or coded, a justification for use of this type of data is required.

(d) A justification for the use of real SSNs, if they are requested.

(e) Information on data storage and security including:

1. All locations where the data is to be stored, accessed, or used including servers, desktop personal computers, laptops, non-VA locations, or portable media.

2. Information on the need and mechanism for copying data from a secure VA server and transmitting or transporting data to other locations.

3. Plans for the destruction of data if they are not to be placed in a data repository after the protocol is completed and the retention period has expired.

(f) Information on any plans to contact, re-contact, or recruit the patients or individuals for further information, or to recruit them for any other research project.

(g) How the privacy and confidentiality of subjects associated with the data is to be maintained.

(h) Information on any plans to use the current data and the data obtained from the proposed project for future research. If data is to be retained for future research, the protocol must describe the repository in which they are to be maintained, its location, and its security measures. ***NOTE:*** *If the data are retained for future research, the data repository must be established and maintained.*

(i) If any data is going to be released outside VA. If this is the case, a discussion regarding why this release is consistent with the VHA policy, the Privacy Act, and HIPAA must occur and reviewed by the ISO and PO.

(j) Information on the PI's ability to finish the protocol.

(k) Documentation that all research team members are to be working within their scope of practice, privileges, or functional statements.

(2) Determining whether or not the project is research as defined by the Common Rule as found in 38 CFR 16.102(d).

(3) Determining, if the research activity is human subjects research, if it is exempt from review by the IRB in accordance with 38 CFR 16.101(b). If the facility does not have an FWA or IRB of record, non-exempt human subjects research cannot be conducted at the facility.

(4) Approving or exempting the protocol from IRB review.

(5) Waiving informed consent and HIPAA authorization if the appropriate criteria are met.

(6) Ensuring that if the data were collected during the conduct of a previous research protocol, the reuse in the new protocol is consistent with the original informed consent. If it is not, or the original informed consent did not address the reuse of the data, the IRB must specifically approve the proposed reuse. ***NOTE:*** *If the informed consent states specifically that the data will not be used for other purposes, it cannot be reused.* Review for the reuse will be subject ot the provisions of VHA Handbook 1200.12 14, 8 a-d).

(7) Performing continuing review, unless the protocol is determined to be exempt.

(8) Ensuring the data accessed from the data repository are required by the approved protocol and used only for the purposes defined in the approved protocol

(9) Approving research. To approve the research, the IRB must make all determinations required by 38 CFR 16.111. In addition, the IRB must determine if the use of the data is allowed by and is consistent with both the Privacy Act of 1974 and the HIPAA Privacy Rule.

(10) When acting as a PB, ensuring that all HIPAA Privacy Rule requirements have been fulfilled.

(11) Obtaining, as needed, the assistance of ad hoc reviewers or consultants including the Privacy Officer and ISO.

Once data (identifiable or de-identified) have been transferred from HAVAH or NCVAMC, IRB is no longer responsible for reviewing and approving research protocols accessing those data, if no part of the research is to be conducted either at or using the resources of HVAH or NCVAMC

CERTIFICATES OF CONFIDENTIALITY

A. Background: OHRP (Office of Human Research Protections) and DHHS (Department of Health and Human Services) released a publication dated February 25, 2003 regarding The Public Health Service Act.

§301(d), 42 U.S.C. §241(d), "Protection of privacy of individuals who are research subjects," states:

> The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.

The privacy of the research subjects referred to in §301(d) is protected through the issuance of Certificates of Confidentiality (COC). These certificates of Confidentiality provide protection against compelled disclosure of identifying information about subjects enrolled in sensitive biomedical, behavioral, clinical, or other research. This protection is not limited to federally supported research.

B. Guidance: Certificates of Confidentiality are issued by the National Institutes of Health (NIH) and other HHS agencies to protect identifiable research information from forced or compelled disclosure. The IRB may determine that at COC is required for projects involve participants in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. Certificates of Confidentiality may be requested for studies collecting information that, if disclosed, could have adverse consequences for subjects, such as damage to their financial standing, employability, insurability, or reputation. The IRB will also review other appropriate mechanisms and procedures that are in place to protect the confidentiality of the identifiable private information to be obtained in the proposed research.

ENGAGEMENT OF INSTITUTIONS IN RESEARCH

DHHS GUIDELINES

Department of Health and Human Services (HHS): Regulations at 45 CFR 46.103(a) requires that each institution "engaged" in human subjects research provide OHRP with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b).

In general, an institution is considered *engaged* in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research [45 CFR 46.102(d),(f)].

An institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award.

Examples

A. Institutions would be considered "engaged" in human subjects research (and would need an Assurance) if their nonexempt involvement includes the following:

1. Institutions whose employees or agents intervene with living individuals by performing invasive or noninvasive procedures for research purposes (e.g., drawing blood; collecting other biological samples; dispensing drugs; administering other treatments; employing medical technologies; utilizing physical sensors; utilizing other measurement procedures).

2. Institutions whose employees or agents intervene with living individuals by manipulating the environment for research purposes (e.g., controlling environmental light, sound, or temperature; presenting sensory stimuli; orchestrating environmental events or social interactions; making voice, digital, or image recordings).

3. Institutions whose employees or agents interact with living individuals for research purposes (e.g., engaging in protocol-dictated communication or interpersonal contact; conducting research interviews; obtaining informed consent). (See Example (B)(3) below for certain informational activities that do not constitute "**engagement**" in research and do not require an Assurance.)

4. Institutions whose employees or agents release individually identifiable private information, or permit investigators to obtain individually identifiable private information, without subjects' explicit written permission (e.g., releasing patient names to investigators for solicitation as research subjects; permitting investigators to record private information from medical records in individually identifiable form). (However, see Example (B)(5) regarding release of such information with subjects' prior, written permission, and Example (B)(6) regarding release of such information to State Health Departments.)

5. Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for research purposes (e.g., obtaining private information from medical records in an individually identifiable form). (However, see Examples (B)(7) and B(8) for certain activities involving the release of information and/or specimens to investigators in non-identifiable form.)

6. **Statistical Centers:** Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for the purpose of maintaining "statistical centers" for multi-site collaborative research. Where institutional activities involve no interaction or intervention with subjects, and the principal risk associated with institutional activities is limited to the potential harm resulting from breach of confidentiality, the Institutional Review Board (IRB) need not review each collaborative protocol. However, the IRB should determine and document that the statistical center has sufficient mechanisms in place to ensure that :

a. the privacy of subjects and the confidentiality of data are adequately maintained, given the sensitivity of the data involved;

b. each collaborating institution holds an applicable OHRP -approved Assurance (FWA) ;

c. each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and

d. informed consent is obtained from each subject in compliance with HHS regulations.

7 **Coordinating Centers:** Institutions whose employees or agents maintain "operations centers" or "coordinating centers" for multi-site collaborative research. Where institutional activities involve no interaction or intervention with subjects, the IRB need not review each collaborative protocol. However, the IRB should determine and document that the operations or coordinating center has sufficient mechanisms in place to ensure that

a. management, data analysis, and Data Safety and Monitoring (DSM) systems are adequate, given the nature of the research involved;

b. sample protocols and informed consent documents are developed and distributed to each collaborating institution;

c. each collaborating institution holds an applicable OHRP-approved Assurance (FWA);

d. each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects;

e. any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and

f. informed consent is obtained from each subject in compliance with HHS regulations.

8. Institutions receiving a direct HHS award to conduct human subjects research, even where all activities involving human subjects are carried out by a subcontractor or collaborator (e.g., a small business receives a HHS award to design a medical device at its own facility and contract with a medical clinic to test the device with human subjects; a foundation receives a HHS award on behalf of an affiliated institution that will actually conduct the human subjects research).

B. **Institutions would <u>not</u> be considered "engaged"** in human subjects research (and would <u>not</u> need an Assurance) if their involvement is limited to the following:

1. Institutions whose employees or agents act as consultants on research but at no time obtain, receive, or possess identifiable private information (e.g., a consultant analyzes data that cannot be linked to individual subjects, either directly or indirectly through coding systems, by any member of the research team).

a. Should a consultant access or utilize individually identifiable private information while visiting the research team's institution, the consultant's activities become subject to the oversight of the research team's Institutional Review Board (IRB). However, the consultant's institution is not considered to be "engaged" in the research and would not need an Assurance.

b. Should a consultant obtain "coded" data for analysis at the consultant's institution, the consultant's institution is considered "engaged" in human subjects research, and would need an Assurance, unless a written agreement unequivocally prohibits release of identifying codes to the consultant.

2. Institutions whose employees or agents (i) perform commercial services for the investigators (or perform other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), and (ii) adhere to commonly recognized professional standards for maintaining privacy and confidentiality (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis).

3. Institutions whose employees or agents (i) inform prospective subjects about the availability of research; (ii) provide prospective subjects with written information about research (which may include a copy of the relevant informed consent document and other IRB-approved materials) but do not obtain subjects' consent or act as authoritative representatives of the investigators; (iii) provide prospective subjects with information about contacting investigators for information or enrollment; or (iv) obtain and appropriately document prospective subjects' permission for investigators to contact them (e.g., a clinician provides patients with literature about a research study, including a copy of the informed consent document, and tells them how to contact the investigator if they want to enroll; a clinician provides investigators with contact information about potential subjects after receiving explicit permission from each potential subject).

4. Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by research investigators (e.g., a school permits investigators to test students whose parents have provided written permission for their participation; a business permits investigators to solicit research volunteers at the worksite).

5. Institutions whose employees or agents release identifiable private information to investigators with the prior written permission of the subject (e.g., with written permission of the subject, a clinician releases the subject's medical record to investigators).

6. Institutions whose employees or agents release identifiable private information or specimens to a State or Local Health Department or its agent for legitimate public health purposes within the recognized authority of that Department. However, utilization of such information or specimens by Department investigators for research purposes would constitute **engagement** in research, and would require an Assurance from the Department.

7. Institutions whose employees or agents release information and/or specimens to investigators in non-identifiable (i.e., non-linkable) form, where such information/specimens have been obtained by the institution for purposes other than the investigators' research (e.g., nursing home employees provide investigators with a data set containing medical record information, but the data set contains no direct or indirect identifiers through which the identity

of individual subjects could be ascertained, either by the investigators or by nursing home personnel; a hospital pathology department releases excess tissue specimens and relevant medical record information to investigators, but these materials include no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by investigators or by hospital personnel, including the pathology department; consistent with applicable law or recognized authority, local hospitals or health departments permit State or Local Health Department investigators to access information for research purposes, but the investigators record no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by the investigators or by local hospital or health department personnel.)

8. Institutions whose employees or agents receive information or specimens for research from established repositories operating in accordance with (i) an applicable OHRP-approved Assurance; (ii)OHRP guidance and (iii) written agreements unequivocally prohibiting of release of identifying information to recipient investigators.

9. Institutions (or private practitioners) whose clinical staff provide protocol-related care and/or follow-up to subjects enrolled at distant sites by clinical trial investigators in OHRP-recognized Cooperative Protocol Research Programs (CPRPs). In such cases, (i) the CPRP clinical trial investigator (consistent with a registered investigator as defined in Section 14.1 of the NCI Investigator's Handbook) retains responsibility for oversight of protocol related activities; (ii) clinical staff may not accrue subjects or obtain informed consent for research participation; (iii) clinical staff may only provide data to the investigator in accord with the terms of informed consent; and (iv) the informed consent document should state that such data are to be provided by clinical staff as directed by the investigator.

C. **Assurance Coordinators within the Division of Human Subject Protections (DHSP)** retain the authority to determine whether institutions are "engaged" in human subjects research consistent with the above guidelines. The DHSP Director and the Assurance Branch Chief should be consulted should Coordinators require assistance in applying these guidelines to specific situations.

MULTI-SITE STUDIES, COORDINATING CENTERS AND DATA ANALYSIS CENTERS

A. POLICY

A VA IRB cannot serve as the IRB of record for a non-VA institution nor can it engage the services of a non-VA centralized IRB. It is the policy of this VA facility to assure that all facilities participating in a human subjects study receive adequate documentation about the study in order to protect the interests of study participants. Before a study can begin, it must be approved by the IRB of record for the coordinating facility, the IRBs of record for each participating facility, and all applicable Research and Development (R&D) Committees.

B. DEFINITIONS

a. **Agent.** An individual on contract with the VA facility who is authorized to act on its behalf.
b. **Coordinating facility.** The VA facility is considered a coordinating facility when an investigator from the facility is responsible for the oversight of more than one participating facility.
c. **Engagement in research.** The participating facility is engaged in human subjects research if its employees or agents intervene or interact with living individuals for research purposes or obtain release or access to individually identifiable private information for the purpose of research. A facility is not considered engaged in human subjects research when, for example, a VA investigator from another facility is conducting database research or telephone survey research.
d. **IRB of record.** An IRB is a board established in accordance with and for the purposes expressed in the Common Rule. The IRB of record assumes responsibility for the conduct of a study at VA facilities where the specific research activities will occur. The IRB of record must be designated to do so through an approved Federalwide Assurance (FWA) with the Office for Human Research Protections (OHRP).
e. **Local research context.** Local research context means the consideration of the acceptability of the proposed research in terms of local institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes.
f. **Multi-site human research.** Multi-site human research means research where different components of a research study are conducted at different institutions that are not under the control of a single VA facility. .
g. **Participating facility.** The facility is considered a participating facility when it is engaged in the research study and an investigator from another VA facility is responsible for the oversight of the study.

C. RESPONSIBILITIES

1. Investigator responsibilities when the VA facility is the coordinating facility

If this VA facility is the coordinating facility the investigator must document how the important human subject protection information will be communicated to the other participating facilities engaged in the research study. The investigator is responsible for serving as the single liaison with outside regulatory agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The investigator is responsible for obtaining IRB review and approval from the coordinating facility's IRB of record. The investigator is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all protocol modifications in a timely fashion. The investigator is responsible for ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating facility and at the participating facilities (e.g. VA Research and Development Committee approval) prior to enrollment of participants.

2. Investigator responsibilities when the VA facility is a participating facility

The investigator has overall responsibility for the conduct of the study at their VA facility (refer to Investigator's Manual on investigator responsibilities).

3. IRB committee responsibilities when the VA facility is the coordinating facility

If this VA facility is the coordinating facility for a multi-site research study, the VA IRB is responsible for reviewing the study protocol and confirming documentation of FWA status from each participating facility and IRB review and approval from each participating facility's IRB of record.

4. IRB committee responsibilities when the VA facility is a participating facility

If this VA facility is a participating facility for a multi-site research study, the VA IRB is responsible for reviewing the study protocol for its facility only.

5. VA Research and Development (R&D)Committees

The VA R&D committees at both the coordinating facility and all participating facilities are responsible for reviewing their IRB's recommendations for the study. The study cannot be initiated without approval from the Research and Development Committees.

D. PROCEDURES

1. Investigator Procedures when the VA institution is the Coordinating Site

- During the initial IRB submission of the multi-site study, the investigator indicates in writing on the application form or in an application letter that the VA facility is the coordinating facility of a multi-site study.
- The investigator submits the following information in their IRB application materials:
    - Whether research activities at participating institutions are defined as engagement
    - Name of each participating facility
    - Confirmation that each participating facility has an FWA (including FWA number)
    - Contact name and information for investigator at each participating facility
    - Contact name and information for IRB of record at each participating facility

- Method for assuring all participating facilities have the most current version of the protocol
- Method for confirming that all amendments and modifications in the protocol have been communicated to participating sites
- Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others
- Method of communicating regularly with participating sites about study events

- The investigator submits approval letters from all the IRB of record for all participating facilities and all R&D committees.
- The investigator maintains documentation of all correspondence between participating facilities and their IRBs of record.

E. REFERENCES

- Title 21 Code of Federal Regulations (CFR) Part 56
- Title 38 Code of Federal Regulations (CFR) Part 16
- Title 45 Code of Federal Regulations (CFR) Part 46
- VHA Handbook 1200.05
- OHRP Guidance, Engagement of Institutions in Research, http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm

F. IRB REVIEW FOR COORDINATING CENTERS AND DATA ANALYSIS CENTERS

1. **Engaged –** Center is engaged in human studies research if the center is receiving identifiable information and /or links to identifiable information.
   a. **Peer Review**: In most cases, full board approval is not required. Review and approval will be done by the Chair, and reported to the IRB. If the study involves highly sensitive data, or complex issues, full board review and vote may be requested.

   b. Chair will complete 10-1223 Approval Form and the gold IRB Reviewer Worksheet – Coordinating Centers and Statistical Analysis Centers engaged in Research (Not Exempt).

   c. Risk – is based on the activities performed by the center, and the risk of potential loss of confidentiality/privacy, not on the protocol.

   d. Annual Review: If identifiable information is involved, annual review will be required.

   e. **Interim Amendments and Adverse Event reports** will be reviewed by the IRB as they are submitted by the investigator.

TISSUE BANKING

TISSUE BANKING:

A human biological specimen is any material derived from a human subject-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 biological specimens collected and stored for future research purposes that are beyond the scope of work described in the original protocol and informed consent or those collected under a protocol designed for banking of specimens are considered **"banked"** human biological specimens.

A waiver is not needed if human biological specimens are banked at a VA site.

Human biological specimens may be banked at a non-profit or academic institution, if a waiver is obtained from the Office of Research and Development (ORD) **before** the specimens are banked.

Human biological specimens **cannot** be banked at, or on behalf of, a for-profit institution.

Human biological specimens collected under a VA-approved protocol are considered to be **"non-banked"** specimens if they are only used for the specific purposes defined in the protocol and are destroyed either when the specific testing/use is completed or at the end of the protocol.

If the protocol is 5 years or longer and the specimens are stored off-site at a non-profit institution until the end of the protocol, then the investigator must obtain a waiver from ORD.

If the specimens are stored off-site at a for-profit institution for **greater than 3 months**, a waiver must be obtained from ORD. With a waiver the specimens may be stored for up to 1 year after the study completion date, **to perform batch analyses or to repeat analyses that are described in the protocol and informed consent**

For VA approved, or VA sponsored tissue bank, the consent form must clearly state:

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

TISSUE BANKING ADDENDUM TO THE INFORMED CONSENT MUST INCLUDE:
(Only if bank is approved by Central Office)

1. If the specimen will be used for future research and allow the participant the choice of how the specimen will be used (any research, research by the PI or other researchers, genetic analysis, research related to a specific area.)
2. If the research results of reuse of the specimen will be conveyed to the participant
3. If the participant is re-contacted after the original study is completed

4. If the participant requests, the specimen and all links to the clinical data will be destroyed

EXAMPLE:
By signing this form, you are agreeing to the following:

1. Your blood and tissue samples(s) may be kept by the _____ for use later in research to learn about, prevent and or treat _____.

Yes_____ No_____ Initials _____ Date _____

2. Your blood and tissue sample(s) may be kept for research about other health problems (for example_____).

Yes_____ No_____ Initials _____ Date _____

3. Your study doctor (or someone from _____ group) may contact you in the future to ask you to take part in more research.

Yes_____ No_____ Initials _____ Date _____

NON-SIGNIFICANT AND SIGNIFICANT RISK DEVICES

NON-SIGNIFICANT RISK DEVICES (FDA Information Sheets 2006)

Low Power Lasers for treatment of pain
Caries Removal Solution
Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting rinsing and storage solutions)
Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/re-wetting solutions) using active ingredients or preservation system with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use
Conventional Gastroenterology and Urology Endoscopes and/or Accessories
Conventional General Hospital Catheters (longÄterm percutaneous, implanted, subcutaneous and intravascular)
Conventional implantable Vascular Access Devices (Ports)
Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
Dental Filling Materials, Cushions or Pads made from traditional materials and designs
Denture Repair Kits and Realigners
Digital Mammography (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application)
Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)
Externally Worn Monitors for Insulin Reactions
Functional Electrical Neuromuscular Stimulators
General Biliarv Catheters
General Urological Catheters (e.g., Foley and diagnostic catheters)
Jaundice Monitors for Infants
Magnetic Resonance Imaging (MRI) Devices within FDA specified parameter
Manual Image Guided Surgery
Menstrual Pads (Cotton or Rayon, only)
Menstrual Tampons (Cotton or Rayon, only)
Nonimplantable Electrical Incontinence Devices
Nonimplantable Male Reproductive Aids with no components that enter vagina
Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment pain
Wound Dressings, excluding absorbable hemostatic devices and dressing
(also excluding Interactive Wound and Burn Dressings)

SIGNIFICANT RISK DEVICES (FDA Information Sheets 1998)

GENERAL MEDICAL USE

Catheters:
Urology Ä urologic with anti-infective coatings
General Hospital - except for conventional long-term percutaneous, implanted, subcutaneous and intravascular
Neurological - cerebrovascular, occlusion balloon
Cardiology - transluminal coronary angioplasty; intra-aortic balloon with control system
Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery; urological and dental applications

Surgical Lasers for use in various medical specialties
Tissue Adhesives for use in neurosurgery; gastroenterology, ophthalmology general and plastic surgery; and cardiology
ANESTHESIOLOGY
Breathing Gas Mixers
Bronchial Tubes
Electroanesthesia Apparatus
Epidural and Spinal Catheters
Epidural and Spinal Needles
Esophageal Obturators
Gas Machines for anesthesia or analgesia
High Frequency Jet Ventilators greater than 150 BPM
Rebreathing Devices
Respiratory Ventilators
Tracheal Tubes

CARDIOVASCULAR
Aortic and Mitral Valvuloplasty Catheters
Arterial Embolization Devices
Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty, devices, intra-aortic balloon pumps, ventricular assist devices
Cardiac Bypass Devices: oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices
Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable
Cardiopulmonary Resuscitation(CPR) Devices
Cardiovascular/Intravascular Filters
Coronary Artery Retroperfusion Systems
Coronary Occluders for ductus arteriosus, atrial and septal defects
Coronary and peripheral Arthrectomy Devices
Extracorporeal Membrane Oxygenators (ECMO)
Implantable Cardioverters/Defibrillators
Laser Coronary and Peripheral Angioplasty Devices
Myoplasty Laser Catheters
Organ Storage/Transport Units
Pacing Leads
Percutaneous Conduction Tissue Ablation Electrodes
Peripheral, Coronary; Pulmonary, Renal, Vena Caval and Peripheral Stents
Replacement Heart Valves
RF Catheter Ablation and Mapping Systems
Ultrasonic Angioplasty Catheters
Vascular and Arterial Graft Prostheses
Vascular Hemostasis Devices

DENTAL
Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications

Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
Dental Lasers for hard tissue applications
Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
Subperiosteal Implants
Temporomandibular Joint (TMJ) Prostheses

EAR, NOSE AND THROAT
Auditory Brainstem Implants
Cochlear Implants
Laryngeal Implants
Total Ossicular Prosthesis Replacements

GASTROENTEROLOGY AND UROLOGY
Anastomosis Devices
Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
Biliary Stents
Components of Water Treatment Systems for Hemodialysis
Dialysis Delivery Systems
Electrical Stimulation Devices for sperm collection
Embolization Devices for general urlogical use
Extracorporeal Circulation Systems
Extracorporeal Hyperthermia Systems
Extracorporeal Photopheresis Systems
Femoral, Jugular and Subclavian Catheters
Hemodialyzers
Hemofilters
Implantable Electrical Urinarv Incontinence Systems
Implantable Penile Prostheses
Injectable Bulking Agents for incontinence
Lithotripters (e.g. electrohydraulic extracorporeal shock-wave, laser powered mechanical, ultrasonic)
Mechanical/Hydraulic Urinary Incontinence Devices
Penetrating External Penile Rigidity Devices with components that enter the vagina
Peritoneal Dialysis Devices
Peritoneal Shunt
Plasmapheresis Systems
Prostatic Hyperthermia Devices
Urethral Occlusion Devices
Urethral Sphincter Prostheses
Urological Stents (e.g., ureteral, prostate)

GENERAL AND PLASTIC SURGERY
Absorbable Adhesion Barrier Devices
Absorbable Hemostatic Agents
Artificial Skin and Interactive Wound and Burn Dressings
Injectable Collagen

Implantable Craniofacial Prostheses
Repeat Access Devices for surgical procedures
Sutures

GENERAL HOSPITAL
Implantable Vascular Access Devices (Ports) if new routes of administration or new design
Infusion Pumps (implantable and closed-loop Ä depending on the infused drug)
NEUROLOGICAL
Electroconvulsive Therapy (ECT) Devices
Hydrocephalus Shunts
Implanted Intracerebral/Subcortical Stimulators
Implanted Intracranial Pressure Monitors
Implanted Spinal Cord and Nerve Stimulators and Electrodes

OBSTETRICS AND GYNECOLOGY
Antepartum Home Monitors for Non-Stress Tests
Antepartum Home Uterine Activity Monitors
Catheters for Chorionic Villus Sampling (CVS)
Catheters Introduced into the Fallopian Tubes
Cervical Dilation Devices
Contraceptive Devices:
Cervical Caps
Condoms (for men) made from new materials (e.g. polyurethane)
Contraceptive In Vitro Diagnostics (IVDs)
Diaphragms
Female Condoms
Intrauterine Devices (IUDs)
New Electrosurgical Instruments for Tubal Coagulation
New Devices for Occlusion of the Vas Deferens
Sponges
Tubal Occlusion Devices (Bands or Clips)
Devices to Prevent Post-op Pelvic Adhesions
Embryoscopes and Devices intended for fetal surgery
Falloposcopes and Falloposcopic Delivery Systems
Intrapartum Fetal Monitors using new physiological markers
New Devices to Facilitate Assisted Vaginal Delivery
Thermal Systems for Endometrial Ablation

OPHTHALMICS
Class III Ophthalmic Users
Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use
Corneal Implants
Corned Storage Media
Epikeratophakia Lenticules
Extended Wear Contact Lens

Eye Valve Implants (glaucoma implant)
Intraocular Lenses (lOLs) (21 CER part 813]
Keratoprostheses
Retinal Reattachment Systems: fluids, gases, perfluorocarbons, perfluoropropane, silicone oil, sulfur hexafluoride, tacks
Viscosurgical Fluids
ORTHOPEDICS AND RESTORATIVE
Bone Growth Stimulators
Calcium Tri-Phosphate Hydroxyapatite Ceramics
Collagen and Bone Morphogenic Protein Meniscus Replacements
Implantable Prostheses (ligament, tendon, hip, knee, finger)
Computer Guided Robotic Surgery

RADIOLOGY
Boron Neutron Capture Therapy
Hyperthermia Systems and Applicators

RECORDS RETENTION 4/2009

A technical correct to Handbook 1200.05 "Protection of Human Subjects in Research" has been made. The change is in Paragraph 7j and this paragraph now reads:

j. Record Retention. The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1).

(1) All records must be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA and other authorized entities at reasonable times and in a reasonable manner.

(2) Records are the property and the responsibility of the local research office. The medical center must designate where the records will be maintained and/or stored.

(3) Complete (non-redacted) minutes, whether from the VA or affiliate IRB reviewing VA research, must be submitted to the R&D Committee and maintained in the facility research office. The R&D Committee must review and act upon all IRB minutes regardless whether the IRB is established at the medical center or at the affiliate university.

Until a schedule for local research records is published, ALL records including identifiers must be retained. Consent forms and HIPAA authorization forms should not include a timeframe for destruction. If there is language in the consent or authorization about destruction, it must only say "in accordance with the record control schedule." ORO is working with the Privacy Office and ORD to get this situation resolved as soon as possible.

Edward Hines Jr. VA Hospital and North Chicago VA Medical Center
INSTITUTIONAL REVIEW BOARD

HUMAN RESEARCH PROTECTION PROGRAM
AND
STANDARD OPERATING PROCEDURES FOR PROTECTION OF HUMAN SUBJECTS IN RESEARCH

Summary of Amendments

10/30/09: References updated to reflect current VHA Handbook: 1200.5 to 1200.05