REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

1. REASON FOR ISSUE: This Veterans Health Administration (VHA) Handbook prescribes procedures for the protection of human subjects in Department of Veterans Affairs (VA) research.

2. SUMMARY OF MAJOR CHANGES: There are no changes in this Handbook. Although this Handbook will be revised, the revisions will not be completed by the last working day in July 2008, therefore this Handbook is being recertified until December, 2008. VA is one of the seventeen Federal departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects (Common Rule), effective June 18, 1991 (56 Federal Register (FR) 28001). This policy is incorporated in Title 38 Code of Federal Regulations (CFR) Part 16. This Handbook defines the procedures implementing 38 CFR 16.

3. RELATED ISSUES: VHA Directive 1200.

4. RESPONSIBLE OFFICIALS: The Office of Research and Development (12) is responsible for the contents of this Handbook. Questions may be addressed to (202) 254-0183.

5. RESCISSIONS: VHA Handbook 2000.5 dated July 15, 2003.

6. RECERTIFICATION: This document is scheduled for recertification on or before the last working day of December 2008.

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REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

1. PURPOSE

The Department of Veterans Affairs (VA) is one of the seventeen Federal departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects (Common Rule), effective June 18, 1991 (56 Federal Register (FR) 28001). This policy is incorporated in Title 38 Code of Federal Regulations (CFR) Part 16. This Veterans Health Administration (VHA) Handbook defines the procedures implementing 38 CFR Part 16.

2. AUTHORITY

a. Statutory provisions for protection of VA patient rights Title 38 United States Code (U.S.C.) Sections 501, 7331, and 7334.

b. VA regulations pertaining to protection of patient rights; 38 CFR 17.33a and 17.34.

c. VA regulations pertaining to rights and welfare of human subjects participating in research: 38 CFR 16 (Federal Policy for the Protection of Human Subjects).

d. VA regulations pertaining to research related injuries: 38 CFR 17.85.

e. Statutes and regulations pertaining to the release of patient information: 5 U.S.C. § 552a; 38 U.S.C. §§ 5701a, 7332; 45 C.F.R. Parts 160-164.

f. VA regulations pertaining to hospital care for research purposes and outpatient care for research purposes: 38 CFR 17.45, 17.92.

g. Department of Health and Human Services (DHHS) regulations pertaining to rights and welfare of human subjects participating in research supported by DHHS: 45 CFR 46.

h. Food and Drug Administration (FDA) regulations pertaining to rights and welfare of human subjects participating in research involving investigational drugs and devices: 21 CFR Parts 11, 50, 54, 56, 312, 360.1, 600, 812, and 814.

i. Nuclear Regulatory Commission (NRC) regulations pertaining to medical use of byproduct material and protection of human subjects: 10 CFR Parts 20 (Standards for Protection Against Radiation) and 35 (Medical Use of Byproduct Material).

j. VA confidentiality of medical quality assurance records statue: 38 U.S.C. 5705.

3. DEFINITIONS

The following terms, some of which are found in 38 CFR 16.102 and 21 CFR Parts 50, 54, 56, 312, 314, 812, and 814, are defined more specifically for purposes of this Handbook.

a. **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.

(1) **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.

(2) **Unexpected Adverse Event (UAE).** An UAE is any adverse event 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.

b. **Assurance.** An Assurance is also called an Assurance of Compliance, or a Federal-wide Assurance (FWA). It is a written commitment by an institution to protect human subjects participating in research. Under federal regulations, any institution conducting or engaged in federally supported research involving human subjects must obtain an Assurance in accordance with 38 CFR 16.103. ***NOTE****: All research conducted under VA auspices is considered to be Federally-supported.* This requirement also applies to any collaborating "performance site" institutions. Under 38 CFR 16.102(f), an institution is engaged in human subject research whenever its employees or agents: intervene or interact with living individuals for research purposes; or obtain, release, or access individually-identifiable private information for research purposes. Assurances are filed through the VA Office of Research Oversight (ORO) with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP). The FWA replaces previous types of OHRP and VA assurances.

c. **Blinded.** A study design comparing two or more interventions in which the investigators, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects; it is sometimes called a masked study design.

d. **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)). ***NOTE:*** *Refer to Appendix A for a detailed description of the minimal risk categories.*

e. **Expedited Review Procedures for Research.** 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)). ***NOTE:*** *Refer to Appendix B for a detailed description of expedited research categories.*

f. **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.

g. **Human Subject.** A human subject is a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information (38 CFR 16.102(f)). The definition provided in the Common Rule includes investigators, technicians, and others assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled. As required by 38 CFR 16.102(f) an intervention includes all physical procedures by which data are gathered and all physical, psychological, or environmental manipulations that are performed for research purposes.

NOTE: *The FDA definition of human subject differs according to the applicable regulation. See 21 CFR 812.3(p), 21 CFR 50.3(g), 312.3(b,) and 56.102(e).*

h. **Institution.** In the context of this VHA Handbook, an institution is a VA medical center or integrated VA health care system and its satellite facilities including Community-Based Outpatient Clinics.

i. **Institutional Official (IO).** The IO is the Medical Center Director or Chief Executive Officer (CEO). The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The IO is the point of contact for correspondence addressing human subjects research with OHRP, FDA, and VA Central Office.

j. **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, for the purposes of this VHA Handbook, an investigational device may be an approved device that is being studied for an unapproved use or efficacy.

k. **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, for purposes of this VHA Handbook, 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.

l. **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.*

m. **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."

NOTE: *See 21 CFR 312.2(a)-(b) for applicability and exemptions.*

n. **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. The FDA considers an investigator and a PI to be synonymous.

o. **Ionizing Radiation.** Ionizing radiation is particles or rays with sufficient energy to cause the ejection of orbital electrons from absorber atoms. Ionizing radiation should be addressed within the protocol and the informed consent when its use is part of the research study. Ionizing radiation includes diagnostic and therapeutic procedures done for research purposes. Sources of radiation include: nuclear medicine, radiation therapy, and radiology.

p. **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.

q. **Legally Authorized Representative.** A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this Handbook**,** a legally authorized representative includes not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court appointed guardian of the person, but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

r. **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. ***NOTE:*** *The Research Integrity Development and Education Program (PRIDE) is the program within ORD that is responsible for training, education, and policy development related to human subjects protection.*

s. **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.

t. **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. The FDA considers a PI and an investigator to be synonymous.

u. **Quorum.** A quorum is defined as a majority of the voting members as listed on the IRB membership. In the case of the IRB, a quorum must include at least one member whose primary concerns are in non-scientific areas. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

v. **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; see 21 CFR 812.3(h), 21 CFR 50.3(c), 21 CFR 56.102(c), and 21 CFR 312.3(b).*

w. **Research Records.** Research records consist of IRB records as well as case histories (also referred to as investigator's research records) or any data gathered for research purposes.

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

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

x. **Researcher.** A researcher is the PI and/or investigator.

y. **Test Article.** For purposes of this VHA Handbook, a test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

z. **VA-approved Research.** VA-approved research is research that has been approved by the VA R&D Committee.

4. SCOPE

a. VA is guided by the ethical principles regarding all research involving humans as subjects, as set forth in the Belmont report "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," regardless of who conducts the research or the source of support. VA is one of the seventeen Federal departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects (Common Rule), effective June 18, 1991, (see 56 Federal Register (FR) 28001). ***NOTE:*** *This policy is incorporated in 38 CFR Part 16.*

b. With the exception of categories listed in Appendix A, the provisions of this Handbook apply to all research involving human subjects that is conducted completely or partially in VA facilities, conducted in approved off-site locations, facilities, and/or conducted by VA researchers while on official VA duty time. The research may be VA funded, funded from extra-VA sources, or conducted without direct funding.

NOTE: *For policy and guidelines regarding off-site research, refer to VHA Handbook 1200.16, "Off-Site Research."*

c. Investigators receiving support from other Federal agencies, such as the National Institutes of Health (NIH), must meet requirements for the protection of human subjects of the funding source in addition to those of VA.

d. Where FDA-regulated test articles are used, the FDA regulations apply regardless of funding source (21 CFR Parts 11, 50, 54, 56, 312, 314, 600, 812, and 814).

e. It is imperative that human research subjects receive the highest level of protection possible and that any questions or any legal or ethical ambiguities always be resolved in favor of the human research subject.

5. MEDICAL CENTER DIRECTOR RESPONSIBILITIES

a. Every Medical Center Director is responsible for ensuring that:

(1) Each VA medical center conducting research involving human subjects has a systematic and comprehensive approach to ensure the protection of human subjects participating in VA-approved research. This system, also known as the HRPP, is composed of a number of individuals, offices, committees and/or subcommittees. The exact composition of the HRPP is dependent on the specific facility, the resources of the facility, and the size and complexity of the

research program at the facility. The medical center Director must ensure effective coordination by and among the various individuals, offices, and committees that comprise the HRPP.

(2) Every VA medical center conducting research involving human subjects or human biological specimens applies through ORO to DHHS, OHRP for an Assurance of Compliance which must obtain prior to conducting any such research.

(3) Every VA medical center conducting research involving human subjects has an established or designated IRB. The medical center may secure the services of an OHRP registered IRB associated with another VA facility or VA regional IRB; or secure the services of an OHRP registered IRB established by an affiliated medical or dental school. Under exceptional circumstances, a medical center may request a waiver from the Chief Research and Development Officer (CRADO) to utilize the services of an IRB within another Federal agency that is signatory to the Common Rule. The established or designated IRB of the VA facility is to be known as the IRB of record. If the IRB is established by the VA facility, it is a subcommittee of the R&D Committee.

(a) If the medical center chooses to use the services of an affiliated university IRB, or receives a waiver to use the IRB of another Federal agency, the VA's facility's interest must be adequately represented by the inclusion of two or more VA employees as voting members of the IRB on each IRB that reviews VA research. At least one of these members must have scientific expertise. The VA members must serve as full members of the IRB; this includes reviewing non-VA research matters coming before the IRB. At least one of the VA members of the IRB must be present during the review of VA research. ***NOTE:*** *Consideration needs to be given to the inclusion of a veteran or a representative of a legally-recognized veterans' organization, where appropriate.* If the university has more than one IRB, this provision applies only to the IRB(s) designated to review VA research.

(b) An IRB established by an affiliated medical or dental school that is serving as an IRB of record for a VA facility must agree to comply with the provisions of 38 CFR Part 16, and the provisions of this Handbook when reviewing VA research. The provision of services by the IRB must be established through a Memorandum of Understanding (MOU) or other written agreement that outlines the responsibilities of the VA and the affiliate.

(c) As part of its oversight responsibilities, the VA R&D Committee must have access to all IRB records and must review all minutes of the IRB(s) reviewing protocols of that VA facility. In addition when the affiliate university IRB is the IRB of record, at its discretion the research office may develop a file for each approved protocol and maintain a copy of the proposal with all amendments, copies of IRB communications, and the original consent form template in the file.

(d) If an IRB of another VA medical center is used, the R&D Committee of each VA must have access to all records of the IRB reviewing its protocols and must review all of the IRB's minutes. If the requesting VA medical center does not have an R&D Committee, the R&D Committee of the other VA medical center must agree to serve in that capacity and must also approve the protocols. The provisions of this agreement need to be established through an MOU or other written agreement that outlines the responsibilities of both VA medical centers.

(e) A VA facility may not engage the services of another IRB for the purposes of avoiding the rulings of the IRB of record.

(f) Each facility, including its IRB of record, must undergo an HRPP accreditation process by an organization approved by ORD to perform this function.

(g) The use of a commercial IRB is prohibited.

(4) Adequate administrative support, including personnel and space sufficient to provide privacy for conducting sensitive duties and storage of records, is provided for IRB activities. The VA medical center must also provide appropriate educational opportunities for IRB members and staff, and for researchers.

(5) Developing and monitoring procedures to ensure the safety of subjects in research either directly or by delegating the responsibility to other qualified VA staff.

(6) The local research office maintains accurate, up-to-date records regarding the mandatory training and credentialing of investigators and other appropriate research staff in the protection of human research subjects. ***NOTE:*** *This is required by ORD.*

b. The Director of every VA medical center conducting research involving human subjects is responsible for:

(1) Oversight of both the IRB and all VA investigators (compensated, WOC, or IPA);

(2) Assurance that IRB members and investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and all applicable regulations; and

(3) Development and implementation of an educational plan for IRB members, staff and investigators.

c. The Medical Center Director must be the IO for all assurances and must fulfill all educational requirements mandated by VA ORD, the facility's assurance, funding institutions, and OHRP.

6. IRB COMPOSITION

a. The IRB is responsible for ascertaining the acceptability of proposed research in terms of medical center commitments and policies, applicable law, validity of study design as it relates to risks and benefits, sensitivity to community standards and attitudes, as well as standards of professional conduct and practice. ***NOTE:*** *The IRB's composition plays a pivotal role in its ability to fulfill its role.*

b. Each IRB, whether that of the VA or the affiliate, must have at least five members with varied backgrounds to promote complete and adequate review of research activities commonly conducted by the institutions (VA and affiliate) for which it reviews research. The IRB members must 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 must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities (38 CFR 16.107(a)).

c. In the appointment of IRB members, equal consideration must be given to qualified persons of both genders. No appointment to the IRB will be made solely on the basis of gender. Every non-discriminatory effort will be made to ensure that the IRB membership does not consist entirely of men or entirely of women (38 CFR 16.107(b)).

d. No IRB may consist entirely of members of one profession (38 CFR 16.107(b)).

e. Each IRB must include at least one member whose primary expertise is in scientific areas and at least one member whose primary expertise is in non-scientific areas (38 CFR 16.107(c)). These members are to 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.

f. Each IRB must 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 (38 CFR 16.107(d)). Members of the community such as clergy persons, teachers, attorneys, veterans, or representatives of legally-recognized veterans organizations, and practicing physicians need to be considered for appointments to the IRB.

g. No IRB may have a member participate in the review of any project in which the member has a conflict of interest, except to provide information requested by the IRB (38 CFR 107(e)).

h. An 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. These individuals may not vote with the IRB (38 CFR 16.107(f)).

i. R&D administration officials including, but not limited to the ACOS for R&D and the AO for R&D, may not serve as voting members of the IRB. The ACOS for R&D, AO for R&D and/or a Research Compliance Officer may serve as non-voting members and must be sensitive to the occurrence or appearance of conflict of interest.

j. Alternate members may be formally appointed to the IRB. The IRB's written procedures must describe the appointment and function of alternate members, and the IRB roster must identify the primary member(s) for whom each alternate member may substitute. The alternate member's qualifications must be comparable to those of the primary member to be replaced. When an alternate member replaces the primary member, the alternate member must receive and review the same material that the primary member received. In addition, the IRB minutes must document instances in which an alternate member replaces a primary member.

k. IRB members and R&D Committee members need to forward names for consideration for new IRB members to the Medical Center Director. Other VA personnel may submit names to

the IRB or R&D committee to be forwarded to the Medical Center Director for consideration. The Medical Center Director must officially appoint members in writing.

l. Members of VA IRBs and VA representatives to affiliate IRBs must be appointed by the Medical Center Director for a period of 3 years and may be re-appointed indefinitely.

m. The IRB Chair of a VA IRB must be appointed by the Medical Center Director for a term of 1 year and may be re-appointed indefinitely.

7. IRB RESPONSIBILITIES AND AUTHORITY

All research involving human subjects must be reviewed either through full or expedited review. Research meeting the criteria for exempt research may be ruled exempt (see App. A). In all cases, each research proposal to be submitted to VA, other Federal agencies, or other sponsors for funding must first be approved by both the R&D Committee and the IRB, unless exempt from IRB review.

a. **IRB Authority and Review Criteria**. The IRB has the responsibility and authority to approve, require modifications (in order to secure approval), or disapprove all research activities covered by this Handbook regardless of whether the research is funded or non-funded. In order to approve research governed by this Handbook, the IRB must review the full proposal, the consent form and all supplemental information such as but not limited to the investigator's brochure and recruiting information. The IRB must determine that all of the following requirements are satisfied:

(1) **Minimization of Risks.** Risks, both physical and non-physical, to human subjects are minimized by: using procedures that are consistent with sound research design; that do not unnecessarily expose subjects to risk; and, whenever appropriate, using procedures already being performed on the subjects for diagnostic or treatment purposes. ***NOTE:*** *Consultation with subject matter experts and review by such committees or subcommittees as Biosafety, Radiation Safety and/or Radioactive Drug Research may be necessary to ensure risks to human subjects are minimized.*

(2) **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.

(3) **Equitable Selection of Subjects.** In assessing whether selection of subjects is equitable, the IRB needs to take into account the purposes of the research and the research setting. The

IRB needs to be particularly cognizant of the special problems of research involving vulnerable populations such as: children, prisoners, pregnant women, mentally disabled persons or persons with impaired decision-making capacity, and economically or educationally disadvantaged persons (see App. D).

(4) **Review and Approval of the Informed Consent Form**

(a) The IRB is responsible for the review and approval of the informed consent form prepared by the investigator; VA Form 10-1086, Research Consent Form, must be used. The wording on VA Form 10-1086 must contain all of the required elements and meet all other requirements outlined in Appendix C. If the wording of the informed consent has been initially prepared by an entity (e.g., a pharmaceutical company or a cooperative study group including National Cancer Institute (NCI) groups) other than the VA PI, the IRB needs to ensure that the wording of the consent meets all the requirements of, or has been reviewed by, the appropriate VA committees and subcommittees such as the Subcommittee on Research Safety and the Radiation Safety Committee. IRB approval of the wording of the consent must be documented through the use of a stamp on each page of the VA Form 10-1086 that indicates the date of the most recent IRB approval of the document. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment rather than the date of the approved protocol.

(b) The IRB needs to ensure that the required language for a valid authorization to release health information (Health Insurance Portability and Accountability Act (HIPAA) Authorization) is included in the informed consent document. The IRB may waive the requirement for an authorization or may alter the form or content of the authorization only in accordance with and as permitted by the HIPAA Privacy Rule (45 CFR 164.508). Such actions and the justification for them must be fully documented in the minutes of the IRB meeting where the action was taken or reported (if approved by expedited review). ***NOTE:*** *See VHA Handbook 1605.1, regarding Privacy.*

(5) **Securing Informed Consent and Documentation of the Informed Consent Process.** Informed consent must be sought from each prospective subject or the subject's authorized representative, in accordance with, and to the extent required by Appendix C. A person knowledgeable about the consenting process and the research to be conducted must obtain the informed consent. If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity. It is the responsibility of the IRB to ensure that the informed consent process is appropriately documented. ***NOTE:*** *For detailed information regarding documentation requirements, refer to Appendix C.*

(6) **Monitoring Safety.** The research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects (38 CFR 16.111(a)(6)). The plan may include establishing a Data Safety and Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) as required by DHHS or FDA policy, and a plan for reporting DSMB or DMC findings to the IRB. The IRB must review the data and safety-monitoring plan in the protocol developed by the investigator. In addition, for studies that do not have or are not required to have a DSMB or DMC 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. The plan needs to include procedures for reporting AEs.

(7) **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.

(8) **Protection of Vulnerable Subjects.** The IRB must ensure that additional safeguards have been included in each study to protect the welfare of vulnerable subjects. The IRB needs to consider inclusion, as regular or ad hoc members, of one or more individuals who are knowledgeable about and experienced in working with these vulnerable subjects. ***NOTE:*** *Appendix D contains further information and requirements on the protection of vulnerable subjects.*

(9) **Conflict of Interest.** The IRB must ensure that 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 comply with VHA policies and procedures regarding conflict of interest.

(10) **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.

b. **Initiation of Research Projects.** All proposed research involving human subjects must be reviewed and approved by the IRB and the R&D Committee prior to initiation of the research project. The date of continuing review will be based on the date of IRB approval. ***NOTE:*** *The R&D committee may not approve the research until all other appropriate subcommittees of the R&D committee and other committees (e.g., Biosafety, Radiation Safety) have reviewed the research.*

(1) If the IRB approves research contingent upon substantive modifications or clarifications to the protocol and/or the informed consent, IRB approval of the proposed research must not occur until subsequent review by the convened IRB of the material the PI submitted.

(2) 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 date of approval is the date the fully-convened IRB approved the protocol rather than the date that the minor changes were approved by the IRB Chair, or

designee. The research may not begin until the IRB Chair, or designee, has approved the changes and the R&D Committee has approved the research. 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.

c. **Communication with Investigators**

(1) An IRB must notify the PI and the R&D Committee in writing of its decision to approve or disapprove a proposed research activity, or of modifications required to secure IRB approval. An IRB-approved research activity may be disapproved by the R&D Committee, the medical Center Director, or the ORD. If a research activity is disapproved by the IRB, the decision cannot be overruled by the R&D Committee, or any higher authority. The R&D Committee and higher authority may strengthen requirements and/or conditions, or add other modifications to secure R&D approval or approval by a higher authority. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications.

(2) Along with written notification of approval, a copy of the approved consent form containing the stamped approval and date of the approval on each sheet must be sent to the investigator and must be filed in the protocol files maintained by the IRB or the facility research office.

(3) If the IRB disapproves a research activity, it must include a statement of the reasons for its decision in its written notification to the investigator and give the investigator an opportunity to respond in person or in writing.

(4) If the IRB conducts or receives a report of any internal audits of an investigator's research files, the IRB must notify the investigator of any findings that require changes.

d. **Maintaining Written Procedures for Operations**. The IRB must establish written procedures for, but not limited to:

(1) Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the R&D Committee.

(2) Determining which projects require review more often than annually and which projects need verification from sources, other than the investigator, that no material changes have occurred since previous IRB review.

(3) Ensuring that investigators promptly report proposed changes in a research activity including amendments to the protocol, or the consent form, to the IRB, and ensuring that such changes in approved research are not initiated without the IRB's review and approval, except when necessary to eliminate apparent immediate hazard to the subject.

(4) Reporting promptly to the IRB regarding non-compliance by study personnel.

(5) Notifying medical center officials and VA Central Office of any AEs that cause harm or risk of harm to human subjects or groups as required by this Handbook, other VA policies, or Federal regulations; any instance of serious or continuing noncompliance with this Handbook or the requirements of determinations of the IRB; and suspension or termination of IRB approval.

(6) Reporting any AE as required by VA and Federal policy and regulations.

(7) Termination and/or suspension of IRB approval.

(8) Observing the informed consent process when the IRB determines it to be appropriate.

(9) Conducting audits of protocols and other IRB activities.

(10) Ensuring that initial and continuing education requirements for the IRB Chair, IRB members, and IRB alternate members are met.

(11) Notifying members of expedited reviews and decisions about exemptions.

(12) Reporting to the Privacy Officer any unauthorized use, loss, or disclosure of individually-identifiable patient information.

(13) Reporting violations of VA information security requirements to the appropriate VHA Information Security Officer.

e. **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 within the institution.

f. **Obtaining a Quorum for Review.** Except when an expedited review procedure is used (see App. B), the IRB must review proposed research at convened meetings at which a quorum is present, including at least one member whose primary concern is in a non-scientific area. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

(1) A quorum must be maintained for each vote to occur. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. If a quorum is not maintained, the proposal must be tabled or the meeting must be terminated.

(2) It is strongly recommended that IRB members be physically present at the meeting. If physical presence is not possible, a member may be considered present if participating through

teleconferencing or videoconferencing. In this case the member must have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

g. **Monitoring On-going Projects.** An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB has the authority to observe or have a third party observe the consent process.

(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 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 all approved amendments;

(f) A copy of the current consent document for the IRB to review;

(g) A copy of the current HIPAA Authorization document, if separate from the informed consent;

(h) Information that may impact on the risk benefit ratio such as AEs, unanticipated problems, and complaints regarding the research;

(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) An assurance that all SAEs and UAEs have been reported as required; and

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

(2) If the continuing review does not occur within the timeframe set by the IRB, the research is automatically suspended. The local research office is responsible for promptly notifying the PI of the suspension.

NOTE: *For suspended research, 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 suspension, the PI must immediately submit to the IRB Chair, a list of research subjects for whom suspension 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 suspended, IRB review and re-approval must occur prior to re-initiation of the research.

h. **Amendments.** All amendments to the project or changes in the informed consent must be reviewed and approved by the IRB prior to initiating the changes, except when necessary to eliminate immediate hazard(s) to the subject(s). If the amendment addresses an issue related to biosafety or radiation safety, the appropriate committee or subcommittee must first approve the amendment.

i. **IRB Records.** The IRB must prepare and maintain adequate documentation of the IRB's activities including, but not limited to the following:

(1) Copies of all items reviewed, including, but not limited to: research proposals, investigators' brochures and recruitment materials; scientific evaluations (if any) that accompany the proposals; approved consent documents; approved HIPAA Authorization document, if separate from the informed consent, any proposed amendments and the IRB action on each amendment; progress reports submitted by investigators; reports of injuries to subjects and serious and unexpected adverse events; documentation of protocol violations; and documentation of non-compliance with applicable regulations.

(2) 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:

(a) The presence of a quorum throughout the meeting including the presence of one member whose primary concern is in a non-scientific area.

(b) 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.

(c) Alternate members attending the meeting and for whom they are substituting.

(d) Actions taken by the IRB including those involving full review. The IRB may choose to use 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.*

(e) Documentation of the four required findings (36 CFR 16.116(d)) 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.

(f) The vote on actions including the number of members voting for, against, and abstaining.

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

(h) The basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs.

(i) A written summary of the discussion of controverted issues and their resolution.

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

(k) The determination of the level of risk, if not recorded elsewhere in IRB records.

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

(m) Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and investigators, and the R&D Committee.

(5) A membership list of IRB members must be maintained; it needs to identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list needs to contain information such as a member’s name, earned degrees, affiliated or non-affiliated status, status as scientist (physician-scientist, other scientist, non-scientist or social behavioral scientist); voting status, alternate status, or status as chairperson. A resume for each IRB member needs to be maintained.

(6) Statements of significant new findings provided to subjects (as required by App. C) must be maintained with the related research proposal and, when reviewed at an IRB meeting, must be documented in the minutes.

j. **Record Retention.** The required records, including the investigator's research records, must be retained for a minimum of 5 years after the completion of the study and in accordance with VHA's Records Control Schedule (RCS 10-1), applicable FDA and DHHS regulations, or as required by outside sponsors.

(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.

8. RESEARCH EXEMPT FROM THE PROVISIONS OF THIS HANDBOOK

a. **Exempt Categories.** Research activities in which the only involvement of human subjects will be in one or more of the minimal risk categories listed in Appendix A are exempt from the provisions of this Handbook.

b. **Approval of Exempt Category.** Investigators must submit the proposed research and the request for exemption to the IRB. The IRB Chair, or an IRB member designated by the Chair, must review all requests for exemption in a timely manner, make a determination based on 38 CFR 16.101, and record the decision. The decision must be communicated in writing to the investigator and the IRB. Documentation must include the specific categories justifying the exemption**.** Projects that are exempt from IRB review must be reviewed by the R&D Committee prior to initiation and then they must be included in its annual review of research projects.

9. EXPEDITED REVIEW

a. **Circumstances for Expedited Review.** An IRB may use the expedited review process to review:

(1) Any of the categories of research described in Appendix B and found by the reviewer(s) to involve no more than minimal risk.

(2) Minor changes in previously approved research during the period for which approval is authorized. If approved, the continuing review date does not change, but remains the same as determined at the most recent review. ***NOTE:*** *If the change involves biosafety or ionizing radiation, the appropriate committee must be consulted prior to approving the change; the consultation with these committees must be documented in the IRB file.*

(3) Waiver or alteration of authorization for the use and/or disclosure of Protected Health Information (PHI) (see HIPAA Authorization).

b. **Procedures for Expedited Review.** In the expedited review process, the IRB Chair may carry out the review or delegate the review to one or more experienced reviewers from among IRB members.

(1) In reviewing the research, the reviewer(s) may exercise all of the authorities of the IRB except that the reviewer(s) may not disapprove the research. A research activity may be disapproved only after review in accordance with the full-review procedure.

(2) If a proposal has been initially approved through the full-review procedure, the continuing review may not be done by the expedited review procedure. ***NOTE:*** *Exceptions may be found in Appendix B, subparagraphs 2h(1)-(3).*

(3) The decision must be recorded and then communicated in writing to the investigator and the IRB.

c. **Record Keeping.** Each IRB that uses an expedited review process must adopt a method for keeping all members advised of research proposals that have been approved under this process. The minutes and/or the protocol file must reflect the expedited review eligibility category that the research meets.

d. The IRB approval is effective only after approval by the R&D Committee; therefore work on the research may not commence until R&D Committee approval is obtained. The date of continuing review is based on the date of IRB approval. ***NOTE:*** *Refer to subparagraph 7b for information on commencement of research.*

10. INVESTIGATOR RESPONSIBILITIES

a. The investigator must have the appropriate training and be credentialed to conduct research involving human subjects by a program that meets all VA requirements.

b. The investigator must develop a research plan that is scientifically valid, minimizes risk to the subjects, and contains a description of the data and safety monitoring plan that includes the reporting mechanism of AEs to the IRB, and when required to ORO, ORD, and other Federal agencies or sponsors. The plan may vary depending on the potential risks, complexity, and nature of the study. A DSMB or DMC needs to be part of the monitoring plan when required by NIH or FDA. The use of a DSMB or DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are particularly high-risk, or vulnerable populations are included.

c. Investigators involving human beings as subjects in research must obtain

(1) Legally effective informed consent of the subject or the subject's legally authorized representative; and

(2) Legally effective authorization for the use and disclosure of the subject's PHI.

d. If someone other than the investigator conducts the interview and obtains consent, the investigator should formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity. The most recently IRB approved consent form must be used. ***NOTE:*** *The basic elements of informed consent are described in Appendix C.*

e. The informed consent must be documented in accordance with Appendix C of this Handbook.

f. SAE and/or UAE must be reported to the IRB and other required entities. If a DSMB or DMC is used, all events must be reported to the DSMB or DMC and a summary of the DSMB or DMC findings must be reported to the IRB and other entities as required. Other AEs, as defined by the monitoring plan in the protocol, must be reported in accordance with the monitoring plan approved by the IRB and as defined in FDA regulations, or other applicable Federal regulations.

g. All amendments to, or modification of, the research proposal including the consent form must be approved by the IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject.

h. The investigator is responsible for obtaining initial and continuing IRB review and approval and for submitting to the IRB requests for modifications to the protocol. The investigator is expected to know the date of the continuing review and to be aware that the project is automatically suspended when the continuing review does not occur on schedule.

i. If the investigator leaves the VA facility the original research records must be retained at the institution.

j. 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 in Appendix E and may be used by an investigator to determine what information needs to be provided to the IRB with a request.*

11. RESEARCH INVOLVING HUMAN SUBJECTS WITH SURROGATE CONSENT

a. Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent).

(1) This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity (e.g., a study of treatment options for comatose persons can only be done with incompetent subjects).

(2) Such consent may be obtained from: a health care agent appointed by the person in a DPAHC or similar document; court-appointed guardians of the person, or from next-of-kin in the

following order of priority, unless otherwise specified by applicable state law: spouse, adult child (18 years or older), parent, adult sibling (18 years 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.*

(3) Such consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements in subparagraphs 11a(3)(a-d), or as established by a legal determination. ***NOTE:*** *The consent requirements described in this Handbook are not intended to preempt any applicable Federal, State or local laws that require additional information to be disclosed for the informed consent to be legally effective in accordance with 38 CFR 16.116(e).*

(a) The practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

(b) Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.

(c) Disclosures required by this Handbook to be made to the subject by the investigator must be made to the subject's surrogate.

(d) 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.

b. Before an incompetent person or persons with impaired decision-making capacity may be considered for participation in any VA research, the IRB must find that the proposed research meets all of the conditions contained in Appendix D, paragraph 6.

12. PAYMENT FOR SUBJECTS

a. VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's medical care and when it makes no special demands on the patient beyond those of usual medical care. Payment may be permitted, with IRB approval, in the following circumstances:

(1) **No Direct Subject Benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation.

(2) **Others Being Paid.** In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

(3) **Comparable Situations.** In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate.

(4) **Transportation Expenses.** When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

b. Prospective investigators who wish to pay research subjects must in their proposal:

(1) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;

(2) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and

(3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or influence on the perspective research subjects to volunteer for, or to continue to participate in, the research study; and that the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study.

c. The IRB and R&D Committee must review all proposals for payment of subjects to ensure conformity with VA policies.

d. 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.

13. USE OF VA RECORDS FOR RESEARCH AND DEVELOPMENT

a. 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.

b. 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).

c. 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).

14. INVESTIGATIONAL DRUGS IN RESEARCH WITH HUMAN SUBJECTS

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

a. 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. 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). For purposes of this Handbook, 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. 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 Subcommittee on Human Studies, 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.

d. The PI must inform the Chief, Pharmacy Service, and the R&D Committee when a study involving investigational drugs has been terminated.

e. All applicable requirements in M-2, Part VII, Chapter 6, or superseding policy document must be met.

f. 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)).

g. 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.

h. 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.

i. **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.

15. INVESTIGATIONAL DEVICES IN RESEARCH WITH HUMAN SUBJECTS

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.

a. The IRB reviewing investigational medical device protocols must have written procedures for: conducting the reviews, determining if the device represents a "significant risk," and reporting findings to the investigator.

b. 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 must determine and document if the device represents SR or NSR. ***NOTE:*** *See FDA Information Sheets, 1998, for lists of SR and NSR devices or the FDA web site (www.FDA.gov).*

c. SR device studies must be conducted in accordance with the full IDE requirements (21 CFR Part 812). Pursuant to these regulations, 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.

NOTE: *The IRB needs to verify the existence of the IDE when applicable.*

d. 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)).

NOTE: *NSR devices may represent greater than minimal risk depending upon the research study.*

e. Unless otherwise notified by the FDA, a NSR study is considered to have an approved IDE if all abbreviated requirements are fulfilled.

f. 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).

g. NSR device studies may commence immediately following IRB and R&D Committee approval, if no changes are required by either committee.

h. The VA facility must have procedures for receipt, control, custody, and dispensing of the investigational devices.

i. The PI is responsible for compliance with all applicable FDA regulations.

j. Emergency use of unapproved devices must follow FDA guidance.

16. PARTICIPATION OF NON-VETERANS AS RESEARCH SUBJECTS

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.

CATEGORIES OF EXEMPT RESEARCH

1. Research activities in which the only involvement of human subjects will be in one or more of the following categories may be exempt from review by the Institutional Review Board (IRB) unless otherwise required by the IRB. Guidance on research that may be exempt, but includes vulnerable populations such as children or prisoners may be found in Appendix D. The exempt status must be approved by the IRB Chair or an IRB member designated by the Chair. When research is determined to be exempt the IRB and the Research and Development (R&D) Committee must be notified and the exemption documented in the IRB records.

NOTE: *Research involving prisoners or focused on pregnant women may not be exempt. There are restrictions on the use of exemption for research involving children.*

2. 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. ***NOTE:*** *The Department of Veterans Affairs (VA) also includes 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.

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.*

f. Taste and food quality evaluation and consumer acceptance studies as defined in 38 CFR 16.101(b).

ACTIVITIES APPROPRIATE FOR EXPEDITED REVIEW

Research activities included in paragraph 2 may be reviewed by an expedited review process, unless otherwise required by the Institutional Review Board (IRB). (Authority: Title 45 Code of Federal Regulations (CFR) 46.110, 38 CFR 16.110, and 21 CFR 56.110.) The following is extracted from 63 FR 60364-60367, November 9, 1998, "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure." ***NOTE:*** *An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 38 CFR 16.110.*

1. **Applicability**

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

(1) Research that presents no more than minimal risk to human subjects, and

(2) Research that involves only procedures described in paragraph 2. The research activities should not be considered of minimal risk merely because of their inclusion in paragraph 2. Inclusion on this list of research activities means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

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

c. The expedited review process may not be used for classified research involving human subjects.

d. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply to expedited review.

e. The research categories appropriate for expedited review pertain to both initial and continuing IRB review.

2. Research Categories

a. Clinical studies of drugs and medical devices, only when one of the following conditions is met.

(1) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.

NOTE: *Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.*

(2) Research on medical devices for which an investigational device exemption application (21 CFR Part 812) is not required; or the medical device is cleared and/or approved for marketing and the medical device is being used in accordance with its cleared and/or approved labeling.

b. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(1) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 milliliters (ml) in an 8-week period and collection may not occur more frequently than 2 times per week; or

(2) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than two times per week. ***NOTE:*** *Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" see 45 CFR 46.402(a). Source: 63 Federal Register (FR) 60364-60367, November 9, 1998. VA does not conduct research-involving children as subjects unless a waiver has been obtained from the CRADO (see App. D).*

c. Prospective collection of biological specimens for research purposes by noninvasive means. Examples are as follows:

(1) Hair and nail clippings in a non-disfiguring manner.

(2) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

(3) Permanent teeth if routine patient care indicates a need for extraction.

(4) Excreta and external secretions (including sweat).

(5) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.

(6) Placenta removed at delivery.

(7) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

(8) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(9) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

(10) Sputum collected after saline mist nebulization.

d. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. ***NOTE:*** *For VA approved research, the term x-rays as used in this Appendix means ionizing radiation as defined in paragraph 3 of this Handbook.* Where medical devices are employed, they must be cleared and/or approved for marketing. ***NOTE:*** *Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.* Examples of procedures eligible for expedited review are:

(1) Physical sensors that are applied either to the surface of the body or at a distance, and do not involve input of significant amounts of energy into the subject, or an invasion of the subject's privacy.

(2) Weighing or testing sensory acuity.

(3) Magnetic resonance imaging.

(4) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.

(5) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

e. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). ***NOTE:*** *Some research in this category may be exempt from the VA regulations for the protection of human subjects (38 CFR 16.101(b)(4)). This listing refers only to research that is not exempt.*

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

g. Research on individual or group characteristics or behavior (including, but not limited to, research on: perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior), or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

NOTE: *Some research in this category may be exempt from the VA regulations for the protection of human subject (38 CFR 16.101(b)(2) and (b)(3)). This listing refers only to research that is not exempt.*

h. Continuing review of research previously approved by the convened IRB as follows:

(1) Research in which the enrollment of new subjects is permanently closed; all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or

(2) Research in which no subjects have been enrolled and no additional risks have been identified; or

(3) Research in which the remaining research activities are limited to data analysis.

i. Continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (listed in subpars. 2b through 2h of this App.) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

THE INFORMED CONSENT

1. **General Requirements for Informed Consent.** An investigator may not involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the person or the person's legally authorized representative. If someone other than the investigator conducts the interview and obtains consent from a patient, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

***NOTE**: This policy does not apply to research ruled exempt from Institutional Review Board (IRB) review. See Appendix A.*

a. An investigator must seek such consent only under circumstances that:

(1) Provide the prospective subject or the subject's legally-authorized representative sufficient opportunity to consider whether or not to participate, and

(2) Minimize the possibility of coercion or undue influence.

b. The information that is given to the subject or the subject's representative must be in language understandable to the subject or the subject's representative.

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

d. Department of Veterans Affairs (VA) Form 10-1086, Research Consent Form, or an electronic version of VA Form 10-1086, must be used as the consent form, and all required elements must be completed.

2. **Basic Elements for Informed Consent**

a. In seeking informed consent, the following information must be provided to each subject:

(1) Name of the study.

(2) The name of the Principal Investigator (PI).

(3) A statement that the study involves research.

(4) An explanation of the purposes of the research and the expected duration of the subject's participation.

(5) A description of the procedures to be followed and identification of those being done for research purposes.

(6) Identification of any procedures that are experimental.

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

(8) A description of any benefits to the subject, or to others, which may reasonably be expected from the research.

(9) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(10) 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.

(11) For research involving more than minimal risk an explanation as to whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and if so, what they consist of, or where further information may be obtained.

(a) According to Title 38 Code of Federal Regulations (CFR) 17.85 "Treatment of Research-Related Injuries to Human Subjects," VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Except in limited circumstances, the necessary care must be provided in VA medical facilities. Exceptions include: situations where VA facilities are not capable of furnishing economical care; situations where VA facilities are not capable of furnishing the care or services required; and situations involving a non-veteran research subject. Under these circumstances, Directors may contract for such care. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. The informed consent form needs to include language explaining VA's authority to provide medical treatment to research subjects injured by participation in a VA research project. ***NOTE:*** *VA regulations on research related injuries (see 38 CFR 17.85 apply to minimal-risk research.*

(b) The regulation at 38 CFR 17.85 does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances must be included in the consent form. ***NOTE:*** *It is strongly suggested*

that the investigator make provisions for coverage of such cost in research awards and contracts.

(12) An explanation of whom to contact for answers to questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject. At least one contact's name and phone number must be other than the investigator's or study personnel.

(13) A statement that participation is voluntary, and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(14) A statement that a veteran-subject will not be required to pay for care received as a subject in a VA research project except as follows:

(a) In accordance with Title 38 United states Code (U.S.C.) 1710(f) and 1710(g) certain veterans are required to pay co-payments for medical care and services provided by VA. Veterans receiving medical care and services from VA that are not rendered as part of the VA-approved research study, must pay any applicable co-payment for such care and services.

(b) Suggested wording for the consent form needs to note this requirement. For example: “Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payments requirements will continue to apply medical care and services provided by VA that are not part of this study.”

(c) Investigators need to note, pursuant to 38 CFR 17.102, charges will not be made for medical services, including transportation furnished as part of a VA-approved research study. Section 17.102 requires that if services are furnished to a person who is not eligible for the services as a veteran, the medical care appropriation will be reimbursed from the research appropriation.

b. **Additional Elements of Informed Consent**. One or more of the following elements of information must also be provided to each subject when appropriate:

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

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

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

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

(7) If the investigators believe that the human biologic specimens obtained could be part of, or lead to the development of a commercially valuable product, or if the specimens are to be retained after the end of the study, current VA policy and Veterans Health Administration (VHA) regulations must be followed. ***NOTE:*** *If genetic testing is to be done, VA requirements pertaining to genetic testing must also be met.*

(8) As appropriate, a statement regarding any payment the subject is to receive and how payment will be made.

c. As defined in 38 CFR 16.116(c) an IRB may:

(1) Approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or

(2) Waive the requirements to obtain informed consent, provided the IRB finds and documents 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 or 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.

d. As defined in 38 CFR 16.116(d), an IRB may:

(1) Approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in this appendix; or

(2) Waive the requirements to obtain informed consent, provided the IRB finds and documents that :

(a) The research involves no more than minimal tangible or intangible risk to the subjects;

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

(c) The research could not practicably be carried out without the waiver or alteration; and

(d) Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

e. The informed consent requirements stated 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.

NOTE: *Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.*

3. Documentation of the Informed Consent

a. Except as provided in subparagraph 3d of this appendix, informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by:

(1) The subject or the subject's legally-authorized representative,

(2) A witness whose role is to witness the subject's or the subject's legally-authorized representative's signature, and

(3) The person obtaining the informed consent.

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

(1) The consent form must be the most recent IRB-approved consent form. The approval must be documented by the use of a stamp or preprinted box on each page of the consent form that indicates the date of the most recent IRB approval of the form. The IRB must maintain a copy of the approved form in its records.

(2) The original signed consent form must be filed in the subject's case history.

(3) A copy of the signed informed consent must be provided to the subject or the subject's legal representative.

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

(1) The subject's participation in the study involves:

(a) Only one encounter,

(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.

d. Consent Form. Except as provided in subparagraph 3f herein, the consent form may be either of the following:

(1) **Written Consent Document**. VA Form 10-1086 (either paper or electronic version)," must be used as the consent form and must embody the elements required by this appendix and 38 CFR 16.116. In addition, it must contain any additional elements as required by the IRB. The consent form may be read to the subject or the subject's legally-authorized representative. The investigator must ensure that the subject (or representative) is given adequate opportunity to read the form and ask questions before signing it.

(2) **Written Consent Document (Short Form).** A shortened written consent document stating that the elements of informed consent required by this appendix and 38 CFR 16.116 have been presented orally to the subject or the subject's legally-authorized representative. When this method is used, there must be a witness to the oral presentation. This process includes the following:

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

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

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

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

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

(1) At a minimum, the progress note must include:

(a) The name of the study,

(b) The person obtaining the subject's consent,

(c) A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,

(d) A statement that the study was explained to the subject, and

(e) A statement that the subject was given the opportunity to ask questions.

(2) An entry must also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated. ***NOTE:*** *Consent and entry notes can be combined when both occur at the same visit.*

f. **Waiver of Requirement for a Signed Informed Consent**

(1) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects, if it finds either:

(a) That the only record linking the subject and the research would be the consent document and the principal risk to the subject would be potential harm resulting from a breach of confidentiality. Each subject must be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(b) That 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.

(2) In cases in which the documentation requirement is waived, the IRB must document the reason for the waiver and may require the investigator to provide subjects with a written statement regarding the research.

VULNERABLE POPULATIONS

1. PURPOSE. This appendix provides additional protections to vulnerable populations participating in Department of Veterans Affairs (VA) research and additional guidance to Institutional Review Boards (IRBs) reviewing research involving vulnerable populations as defined in Title 38 Code of Federal Regulations (CFR) 16.111(b). ***NOTE:*** *Although the Veterans Health Administration (VHA) regulations may be more restrictive than the Department of Health and Human Services (DHHS) regulations and guidance, the VHA regulations and policy must be followed; additionally, VHA has not adapted regulations similar to DHHS regulations 45 CFR 46 Subparts B through D into it's regulations at 38 CFR Part 16.*

2. DEFINITIONS

a. **Children** are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

b. **Delivery** means complete separation of the fetus from the woman by expulsion, extraction, or any other means.

c. **Fetus** is the product of conception from the time of implantation until delivery.

(1) **Viable fetus** is now termed a "viable neonate."

(2) Nonviable fetus is a fetus ex utero that, although living, is not able to survive to the point of independently maintaining heart and respiration. ***NOTE:*** *In 45 CFR 46 Subpart B, this definition is used as the definition of a non-viable neonate.*

(3) **Dead fetus** is a fetus which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

d. **In vitro fertilization** is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

e. **Neonate** means newborn.

(1) **Viable neonate** means being able, after delivery, to survive to the point of being independently maintaining heart and respiration (given the benefit of available medical therapy).

(2) **Non-viable neonate** means the same as a non-viable fetus.

f. **Pregnancy** is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

g. **Prisoner** is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

3. VULNERABLE POPULATIONS. Vulnerable populations as listed in the Federal regulations include:

a. Pregnant women and fetuses;

b. Prisoners;

c. Mentally disabled and those with impaired decision-making capacity;

d. Children; and

e. Economically and educationally disadvantaged persons.

4. PREGNANT WOMEN AND FETUSES AS VULNERABLE POPULATIONS

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

b. Research related to in vitro fertilization must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

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

(1) Determine that the proposed research meets the requirements outlined in this appendix;

(2) Determine that adequate provision has been made to monitor the risks to the subject and the fetus.

(3) Determine that adequate consideration has been given to the manner in which potential subjects are going to be selected, and that adequate provision has been made to monitor the actual informed consent process such as:

(a) Overseeing the actual process by which individual consents required by this appendix are secured either by approving enrollment of each individual into the activity, or by verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed, and

(b) Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

NOTE: *These determinations must be documented in the IRB minutes.*

d. **General limitations**

(1) Activities related to pregnant women must not be undertaken unless:

(a) Except if appropriate studies on animals and non-pregnant individuals have been completed, and data for assessing potential risks to pregnant women and fetuses is provided.

(b) The purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal, and, in all cases, is the least possible risk for achieving the objectives of the activity.

(c) Individuals engaged in the activity will have no part in:

1. Any decisions as to the timing, method, and procedures used to terminate the pregnancy; or

2. Determining the viability of the fetus at the termination of the pregnancy.

3. Introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy.

(2) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of research activity

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

(a) The purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or

(b) The risk to the fetus is minimal.

(c) The mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if:

1. The purpose of the activity is to meet the health needs of the mother,

2. His identity or whereabouts cannot reasonably be ascertained,

3. He is not reasonably available, or

4. The pregnancy resulted from rape.

5. PRISONERS AS A VULNERABLE POPULATION IN RESEARCH. Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer**.** If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). ***NOTE:*** *Requirements for requesting a waiver may be obtained by contacting the Office of Research and Development at VA Central Office or by accessing the VA research web site at http://www.va.gov/resdev.*

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

a. Research involving subjects who are mentally ill or subjects with impaired decision-making capacity warrants special attention. Research involving these populations frequently presents greater than minimal risk; may not offer direct medical benefit to the subject; and may include a research design that calls for washout, placebo, or symptom provocation. In addition, these populations are considered to be vulnerable to coercion.

b. **IRB composition**

(1) The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.

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

c. 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.

d. The IRB must make a determination in writing of each of the criteria listed in subparagraph 6c. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives as defined in paragraph 11 of this VHA Handbook.

e. Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

f. 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.

7. CHILDREN AS A VULNERABLE POPULATION IN RESEARCH. VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans. Therefore, research involving children must not be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D 46.401 – 46.409, Additional Protections for Children Involved as Subjects in Research). ***NOTE:*** *For requirements for requesting a waiver contact 202-254-0183.*

ELEMENTS OF DOCUMENTATION REQUIRED FOR WAIVER OF AUTHORIZATION (Title 45 Code of Federal Regulations (CFR) 164.512(i)(2))

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

2. The documentation must include all of the following:

a. Identification of the IRB

b. Date of IRB approval of waiver of authorization

c. Statement that alteration or waiver of authorization satisfies the following criteria:

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

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

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

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

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

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

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

e. 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)).

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