VA Pittsburgh Healthcare System
Institutional Review Board

Standard Operating Procedures

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Glossary of Terms

Adverse Event (AE). 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 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, the research intervention, or the assessment.

a. Serious Adverse Event (SAE). A SAE is defined as:
    i. Death;
    ii. A life threatening experience;
    iii. Hospitalization (for a person not already hospitalized);
    iv. Prolongation of hospitalization (for a patient already hospitalized);
    v. Persistent or significant disability or incapacity;
    vi. Congenital anomaly and/or birth defects; or
    vii. An event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

b. Unanticipated/Unexpected Adverse Event. Any adverse event and/or reaction, the specificity or severity of which is not consistent with the VAPHS IRB approved informed consent, protocol, investigator brochure, or product labeling.

c. Internal Adverse Event. An adverse event experienced by a subject enrolled by the investigator(s) at VAPHS.

d. External Adverse Event. An adverse event experienced by a subject enrolled by investigators at other institutions engaged in the same clinical trial or a different clinical trial using the same investigational agent or intervention.

Assent: An affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Coordinating facility: VAPHS is considered a coordinating facility when a VAPHS investigator is responsible for the overall supervision of more than one participating facility.

Engagement in research: VAPHS is engaged in research if its employees or agents perform activities as described in Section 3 (Definition of Human Subject and Research) of VAPHS IRB SOP.

Exception. A protocol exception is a deviation from the protocol approved in advance by the IRB. A researcher may request an exception to deviate from the protocol for the purposes of maintaining scientific integrity or to avoid additional risks or burden to subjects or to minimize the impact of an unanticipated problem on the study.

Guardian: An individual who is authorized under Commonwealth of Pennsylvania law or the law of another competent jurisdiction to consent on behalf of a child for general medical care.

Imminent Threat of Adverse Event in Research. Any situation in which an adverse event in research has not yet occurred, but is likely to occur, as determined by an IRB, research, or clinical team member, without preventative measures.

IRB Initiated Suspension of Approval. Refers to a determination made by the VAPHS IRB (either by the fully convened board or the IRB chair/designee) to temporarily withdraw IRB approval for some or all activities of a currently approved research study.

IRB Initiated Termination of Approval. Refers to a determination made by the VAPHS IRB (either by the fully convened board or the IRB chair/designee) to permanently withdraw IRB approval for some or all activities of a currently approved research study.

Multi-site human research: research where different aspects of a research study are conducted at different institutions that are not covered by the Federalwide Assurance (FWA) of the VAPHS IRB.

Non-Compliance

a. Non-compliance Refers to failure to follow the federal regulations, VA requirements (including VA directives, handbooks, and guidance), Institutional Review Board (IRB) requirements or determinations, and/or institutional policies and procedures related to the protection of human research participants.

b. Serious Non-Compliance. Refers to willful and neglectful failure to adhere to IRB or HRPP regulations, requirements, or determinations or violations of procedures, policies, regulations or laws that results in increased risks to subjects or in adverse effects on the rights and welfare of research subjects.

c. Continuing Non-Compliance. Refers to a pattern of non-compliance that suggests an inability or unwillingness to maintain compliance with IRB or HRPP regulations, requirements or determinations.

Participating facility: VAPHS is considered a participating facility when it is engaged in a research study and an investigator from another facility is responsible for the overall supervision of the study.

Parent: A child's biological or adoptive parent.

Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research.

Research Misconduct. Fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results.

a. Fabrication is making up data or results and recording or reporting them

b. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

c. Plagiarism is the appropriation of another person's ideas, processes, or results, or words without giving appropriate credit and can occur in proposing, performing, or reviewing research, or in reporting research results.

Sponsor: A sponsor is the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study. Sponsors may enter into agreements with intermediaries that act as agents, such as contract research organizations or coordinating centers. For the purposes of this section, the term "sponsor" refers to the sponsor or its agents. Sponsors enter into arrangements with organizations to conduct research, here referred to as sponsored research. In sponsored research, both the sponsor and VAPHS have obligations to protect research participants

Sponsor-Investigator: An individual who both initiates and actually conducts, alone or with others, a clinical investigation; i.e., under whose immediate direction the investigational drug or device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

Substantive Action**.** An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

Unanticipated Adverse Device Effect. (a) Any serious adverse effect on health or safety or (b) any life- threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or (c) any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Problems Involving Risks to Subjects or Others. Those events that (a) are not expected (in terms of nature, severity or frequency) given the nature of the research procedures and the subject population being studied; (b) related or possibly related to participation in the research; and (c) suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected Death. The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of reporting requirements.

VAPHS Investigator/VAPHS research staff: an individual with an appointment at the VA facility who is authorized to act on its behalf.

Standard Operating Procedures for an Institutional Review Board (IRB)
Operated by the VA Pittsburgh Healthcare System

Introduction

This VA Medical Center Institutional Review Board's (IRB) Standard Operating Procedure (SOP) is a reference for IRB members and investigators. This SOP details the policies and procedures specifying the regulations and policies governing human subjects' research and the requirements for submitting research proposals for review to the IRB (or Human Studies Subcommittee) and the Research and Development (R&D) Committee. It is the expectation of VAPHS that all individuals involved with the HRPP understand and apply their obligation to protect the rights and welfare of research participants.

1. Ethical Principles Governing the IRB.

VA Research must be carried out in an ethical manner (38CFR16.103(b)(1)). The basic ethical principles guiding research involving human subjects are provided in the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. Three basic principles contained in The Belmont Report (Appendix A) are central to the ethics of research involving human research and guide the IRB in assuring that the rights and welfare of subjects are protected:

A. **Respect for persons** is applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.

B. **Beneficence** is applied so that possible benefits are maximized and possible risks are minimized to the persons involved.

C. **Justice** is evidenced in the equitable selection of subjects.

2. The Regulatory Mandate to Protect Human Subjects.

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

A. **Department of Health and Human Services (DHHS) Regulations at 45CFR46**. In January 1991 the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VA at 38 CFR 16, the Common Rule is also codified by the Department of Health and Human Services (DHHS) as Subpart A of the DHHS regulations at 45 CFR 46. DHHS has three additional Subparts in the regulations, as well, that are not in 38 CFR 16.

B. **VA regulations at 38 CFR 16 and the Federal Policy (Common Rule) for the Protection of Human Subjects. In addition, 38 CFR 17.33 provides regulations for patient rights**. 38 CFR 17.85 discusses treatment of research related injuries to human subjects and 38 CFR17.45 addresses medical hospital care in research studies. 38 CFR 17.92 addresses outpatient care for research studies. Codified by the VA at 38 CFR 16, the Common Rule is identical to Subpart A of the DHHS regulations, but does not include the additional DHHS Subparts B, C, and D. 38 CFR 16.103 (a) addresses the institutional assurance and the IRB registration process.

C. **Food and Drug Administration (FDA) Regulations at 21CFR50 (Informed Consent Regulations), 50 Subpart D (Safeguards for Children), 56 (IRB Regulations), 312 (Investigational New Drug Applications-IND), 361 (Radioactive Drugs), 612 (Biological Products), and 812 (Investigational Device Exemptions-IDE).**

3. Definition of Human Subject and Research (38 CFR 16.102; VA Handbook 1200.5, Paragraph 3, Parts g. and v.).

VA regulations at 38 CFR 16.102(d) define **research** as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

VA regulations at 38 CFR 16.102(f) define **human subject** as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information." **Private information** includes information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. Private information must be individually identifiable. **Identifiable** means that the identity of the individual is or may readily be ascertained by the investigator or associated with the information.

VA policy (VA Handbook 1200.5, paragraph 3, part g.) highlights that the definition of human subject includes investigators, technicians, and other assisting investigators when they serve in "subject" roles by being observed, manipulated, or sampled.

FDA regulations at 21 CFR 56.102(c), define **research** as "… any experiment that involves a test article and one or more human subjects…." The FDA regulation further states that "…The terms research, clinical research, clinical study, study, and **clinical investigation** are deemed to be synonymous for purposes of this part." 21 CFR 56.102(e) defines **human subject** as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient." FDA regulations at 21 CFR 812.3(p) define a human subject as "a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease."

An activity is "Human Research" according to FDA regulations if both of the following are true.

1. The activity involves an FDA-regulated test article because one or more of the following are met:
   (a) the activity involves the use of a *drug*, other than the use of a marketed *drug* in the course of medical practice;
   (b) the activity involves the use of a *device* to evaluate safety or effectiveness of that *device*;
   (c) data from the activity will be submitted to, or held for inspection by, the FDA in support of a marketing or research application for an *FDA-regulated product*.

2. The activity involves human participants because one or more of the following is true:
   (a) the test article will be used on one or more humans;

(b) data obtained from controls will be submitted to, or held for inspection by, the FDA in support of a marketing or research application for an *FDA-regulated product*;
(c) data obtained from use of a *device* on tissue specimens will be submitted to, held for inspection by, the FDA in support of a marketing or research application for an *FDA-regulated product*.

FDA regulations apply:

1) To any use of a drug, except for the use of a marketed drug in the course of medical practice
2) To all clinical investigations of devices to determine safety and effectiveness, except as provided in 21 CFR 812.2 (c)
3) To all clinical investigations that are not subject to requirements for prior submission to the FDA under 21 CFR 505(i) or 21 CFR 520(g), but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Therefore, there may be situations in which the FDA regulations apply although the research may not involve an FDA regulated test article or situations in which the research involves an FDA-regulated test article, but is not subject to FDA regulations. For example, electrocardiograms recorders are an FDA-regulated medical device, however, a research protocol in which electrocardiograms are being performed as part of clinical care, or in which the safety or effectiveness of the electrocardiogram recorder is not under study, would not be subject to FDA regulations.

Federal regulations and VAPHS policies require IRB review of research involving human subjects. The VAPHS IRB documents the determination of whether or not a proposed activity is human research under the DHHS, FDA or VA regulations using the Human Subject Research Determination Checklist (Appendix DD). If there is a possibility that any submitted project does not meet the definition of human subjects research, or the project is submitted with a request for a “Not Human Subjects Research” or an “Exempt Status” determination, then review of that project will include an IRB determination as to whether it constitutes human subject research, by use of the Human Subject Research Determination Checklist. This determination may be made by the IRB Chair or designee and included on the IRB agenda as a notification.

VAPHS is **engaged in human** subjects research if its employees or agents intervene or interact with living individuals for research purposes or obtain release or access to individually identifiable private information for the purpose of research. VAPHS is not considered engaged in human subjects research when, for example, a VA investigator from another facility is collecting observational data (e.g., a survey) from subjects at VAPHS and there is no participation from VAPHS staff.

4. Institutional Review Board (IRB) Roles and Authorities.

A. Institutional Authority of the IRB (38 CFR 16.109; VA Handbook 1200.5, Paragraph 5).

The Medical Center Director is responsible for all research activities conducted under medical center auspices. The R&D Committee, which reports to the Director, oversees the IRB. The VAPHS operates one IRB for all divisions.

B. Purpose of the IRB (38 CFR 16.109).

The VAPHS IRB's primary responsibility is to ensure that the rights and welfare of subjects are protected in the VAPHS human subject research program (38 CFR 16.109). In doing so, the IRB ensures that the human subject research is conducted ethically, in a safe manner and in compliance with VA and other Federal regulations, the requirements of applicable state law, the FWA, and the institutional policies and procedures. The IRB accomplishes initial as well as prospective and continuing review of this VA's human subject research. This includes review of the protocol, the informed consent process, procedures used to enroll subjects, data collection tools and methods as well as ongoing assessments of adverse events in order to provide continuing risk/benefit assessment.

C. The Authority of the IRB (38 CFR 16, 17; 21 CFR 50, 56; and 45 CFR 46).

The Authority of the IRB (38 CFR 16, 17; 21 CFR 50, 56; and 45 CFR 46) is granted by VA Pittsburgh Healthcare System Institutional Official.

The IRB, designated by the VAPHS Director and the R&D Committee and named in the Federal Wide Assurance (FWA – see Appendix B), must prospectively review and make a decision concerning all human subject research conducted at VAPHS facilities or by VAPHS employees or agents, or otherwise under the auspices of the VA. Further, the IRB has statutory authority to take any action necessary to protect the rights and welfare of human subjects in the VAPHS facility's research program. The IRB has the authority to approve, require modifications in, or disapprove the facility's human subject research and to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (38 CFR 16.109).

The IRB will abide by all federal and state laws as they apply to human subjects research; in cases where the state law and federal law differ, VAPHS will abide by the more stringent law, e.g. mentally impaired subjects.

Although the IRB is a subcommittee of the R&D Committee, neither the Director nor the R&D Committee can approve research involving human subjects that has not been approved by the IRB of record (38 CFR 116.112). If in the course of its review, the R&D Committee requires changes to the protocol that relate to the determination of the protection of the human subjects, the R&D Committee must refer those changes back to the IRB for its approval before the R&D Committee can give final approval.

The IRB has authority to suspend or terminate the enrollment and/or ongoing involvement of human subjects in the facility's research as it determines necessary for the protection of those subjects (38 CFR 16.113), including research not being conducted in accordance with the IRB's requirements or research that has been associated with unexpected serious harm to participants. The IRB has the authority to observe and/or monitor, or to have a third party observe and/or monitor, the VAPHS's human subject research, including consent process and conduct of the research, to whatever extent the IRB considers necessary to protect human subjects.

The R&D Committee serves as a parent committee to all of its subcommittees, including the IRB, and must review and approve subcommittee actions, minutes, and periodic reports. All study protocols that have been reviewed and approved by the IRB must also be reviewed and approved by the R&D Committee, regardless of funding status and source, prior to study initiation. No research may be undertaken without full review and approval of the R&D Committee and all appropriate subcommittee(s). See further description of the R&D Committee in Section 4.G.

D. Independence of the IRB

The IRB functions as an independent body as described in Section 3.C above. Investigators are not allowed to seek communication with IRB reviewers regarding any submission while it is under review. If initial written or electronic communications between the IRB and an investigator fail to resolve misunderstandings or disagreements, the IRB Chair or Vice-Chairs or designated members may enter into direct communication with an investigator to move the business of the IRB forward. If such efforts do not succeed, the appeal of an IRB determination may be pursued as outlined in section 4.E. of these IRB Standard Operating Procedures.

Any attempt to bring undue influence or coercion, or to intimidate or harass, an IRB member or staff person, or other HRPP staff person in connection with his/her duties for the IRB, either directly or indirectly, is considered serious research impropriety (VA Handbook 1058.2, Research Misconduct). Such an attempt will be addressed by: prevention; reporting of an actual attempt; investigation and assessment of the attempt; and responses made to address this inappropriate behavior.

Prevention includes properly educating and training all investigators, research staff, IRB members and staff, and VA administrative personnel to inform them that any attempt to apply undue influence or coercion upon the IRB, its members, staff, or procedures, is a serious form of research impropriety. Further, these same groups are educated or given regular communications on the need to regard all IRB meeting proceedings, documents, and related electronic communications, as strictly confidential.

Allegations of undue influence, coercion, or harassment may come from different sources, including but not limited to, outside entities, IRB members, and VAPHS staff. The anonymity of the source is preserved whenever possible. Attempts to exert undue influence to IRB members or staff or HRPP staff, are reported to the Research Compliance Officer. The Research Compliance Officer will prepare a written report and forward it to the Chair of the Research Compliance Committee or Deputy ACOS/R&D. The RCC Chair will determine whether any immediate investigation is needed prior to the convened meeting of the RCC.

The report along with any other relevant documents will be placed on the RCC agenda for review.

The RCC has the responsibility and authority to respond to attempts to unduly influence the IRB. The Research Compliance Committee will conduct further investigation as needed, make an assessment of the report, and decide upon actions to address the problem. Any member of the RCC named in a report, will be excused from committee deliberations and from receiving committee minutes on the issue. See further description of the RCC Committee in Section 4.G.

The types of responses to attempts to unduly influence the IRB may include, but are not limited to:

1. Further education or training.
2. Remedial Counseling with ACOS, COS, and/or Facility Director to address the issue.
3. In the case of an investigator whose attempt(s) to influence the IRB constitute serious or continuing noncompliance, reporting to the relevant federal agencies.
4. Disciplinary procedures, as outlined in the VAPHS RCC SOP, Section VII.

A description of actions taken by the RCC will be provided to the originator of the report of undue influence, under conditions of confidentiality, if desired by that person.

E. The Principal Investigator (21 CFR 56.108(b), 312.64, and 312.66; VA Handbook 1200.5, Paragraph 10).

The IRB recognizes one Principal Investigator (PI) for each project. The PI is an individual who actually conducts a clinical 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 PI has ultimate responsibility for his/her research project and all official IRB correspondence is addressed to the PI. A PI must be either compensated by VA, work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970. A co-investigator is an individual under the direction of the 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. Co-investigators communicate with the IRB through the PI. A co-investigator may have varying degrees of VA employment including no VA employment at all.

The Responsibilities of the IRB to the PI:

1. The IRB shall evaluate and render a decision for all complete submissions for initial review or continuing review within 60 days of the receipt of the completed application packet by the research office.
2. The IRB will report its findings and actions to the PI in writing, including:
    a. The decision to approve, disapprove, or require modifications to secure approval.
    b. Any modification to secure approval.
    c. If the IRB disapproves a research activity, a statement of the reasons

for its decision will be provided and the investigator will be provided an opportunity to respond in person or in writing, as described in Section 6.Q.

3. The IRB shall evaluate all protocol modification requests, unanticipated problems (including protocol deviations), and adverse events within 60 days of their receipt by the Research Office.
4. The IRB will forward all approved projects to the R&D Committee immediately after full approval has been granted by the IRB.
5. The IRB shall communicate all approved protocol modifications and all unanticipated problems and adverse events to the R&D committee in writing, in the form of the IRB minutes.
6. In cases of contingently approved protocols, the IRB will allow the investigators six weeks to respond to the IRB with the requested modifications. Submissions after this specified time frame will require updated application packets and supporting information. If a consent form revision is requested by the IRB, following the date of notification, no further patient enrollment can occur until the revised consent form is approved by the IRB.
7. The IRB will review investigators' responses.
8. The IRB will determine whether the medical records have to be flagged to protect the participant's safety by indicating participation in the study and the source of more information on the study. The IRB may not require the medical record to be flagged if participation in the study involves only one encounter, the use of a questionnaire or previously collected biological specimens, or if identification as a participant in a particular study will place the participant at greater than minimal risk.

The Responsibilities of the PI:

1. The PI is responsible for the implementation of research.
2. The PI determines that the resources necessary to protect participants are present before conducting the research study.
3. The PI recruits participants in a fair and equitable manner, weighing the potential benefits of the research to the participants against their vulnerability and the risks to them.
4. The PI bears direct responsibility for ensuring the protection of every research subject. This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits.
5. The PI monitors participants for potential harm and take steps to minimize or mitigate those harms when possible.
6. The PI is responsible for preparing and submitting a data safety and monitoring plan for each study.
7. The PI must ensure that all members of the research team always comply with the findings, determinations, and requirements of the IRB.
8. The PI must ensure the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team are authorized to actually obtain and document consent.
9. In cases where the IRB has authorized waiver or alteration of the informed consent document or process, the PI is responsible for ensuring that the procedures are conducted in accordance with the federal requirements of

such research ([38 CFR 16.116(c and d)] Waiver or Alteration of Informed Consent Requirement).

10. The PI is responsible for ensuring that all human subject research that he/she conducts in the VAPHS has received initial prospective review and approval by the IRB as well as the approval of the R&D Committee.
11. The PI is responsible for ensuring that continuing review and approval of the research has been accomplished within the time frame stipulated by the IRB.
12. The PI must notify the IRB promptly of any unanticipated problems or adverse events that occur during the course of the study according to the VAPHS IRB Unanticipated Problems Reporting Policy (Appendix O) or the VAPHS IRB Adverse Event Reporting Policy (Appendix Q). The PI must also notify the IRB promptly of any newly identified or increased risks to subjects, and any non-compliance with applicable regulatory requirements or determinations of the IRB (21 CFR 56.108(b) and 312.64).
13. The PI must submit proposed changes in research and in consent forms to the IRB for approval.
14. If a Data Safety Monitoring Board (DSMB) is used, the principal investigator is responsible for reporting defined events to the DSMB and a summary of the DSMB findings must be reported to the IRB within five days of receipt.
15. The PI must notify the Education and Compliance Office of all study monitoring visits by employees of monitoring organizations or sponsors. Results of external monitoring visits must be reported to the office within 24 hours; serious non-compliance must be reported immediately. Written reports of monitoring visits must be forwarded to the IRB upon receipt.
16. The PI must have completed training in human subjects protection as well as good clinical practice as specified by the IRB and must renew such certification annually between October 1 and 31 of each year. The PI is also responsible for ensuring that all co-investigators and all study personnel involved with research through interaction with human subjects or human subject data (regardless of whether or not the data contain private identifiers and regardless of the type of interaction with human subjects data) have completed such training and renew such certification in a similar fashion. Information on approved training for human subjects protection and good clinical practice training is listed in Appendix C.
17. The PI is responsible for personally training each study personnel, whose name(s) shall be submitted to the IRB as an authorized representative for obtaining informed consent. The PI is also responsible for ensuring that such personnel have been appropriately credentialed according to the standards required by the Research Office as well as ensuring that their personnel actually follow procedures described to them in the course of their training and practice within the scope of their privileges approved by the Research Office.
18. If the study involves healthcare issues that the PI is not qualified to address based on education or area of expertise, he or she must identify a qualified clinician to be responsible for all study-related healthcare decisions.
19. The PI must ensure that communications to the IRB or R&D committees are carried out in a timely fashion and in writing.

20. The PI is responsible for submitting required IRB documentation for termination or completion of all IRB approved protocols as outlined in the Research Office website (http://www.vaphs.research.med.va.gov).
21. The PI must report the premature completion of a research study to the IRB.
22. If the PI departs from the VAPHS, it is his/her responsibility to notify the IRB at least 30 days prior to his/her departure and to identify a suitable investigator to resume the PI's role in his/her ongoing studies. The prospective PI must agree to take over these duties in writing and must complete a new investigator's certification form. The prospective PI must also present proof of training required in paragraph 12. The Research Office will not give final clearance for the departing PI until these criteria have been satisfactorily met.
23. The Principal Investigator is required to submit a "Listing of Authorized Representatives to Administer Informed Consent" (Appendix X) for IRB approval at initial review, continuing review, and as personnel change, unless the Principal Investigator is the only person administering informed consent. Co-investigators must also be on the Listing of Authorized Representatives to Administer informed consent if the investigator plans to allow them to sign the consent form.

Updated instructions to investigators for initial submissions and continuing review submissions are available on the Research website at http://www.vaphs.research.med.va.gov or can be obtained by contacting the Research Office at 412-954-5381.

The VAPHS Research Website is available to all investigators, staff, employees, and the public (http://www.vaphs.research.med.va.gov/). The VAPHS IRB SOP's and other relevant policies are posted on this website.

No changes in approved research may be initiated without prior IRB approval, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period (VA Policies 38 CFR 16.103(b)(4) and 38 CFR 16.109(e) and FDA Policy 21 CFR 312.66). Instructions to investigator for submitting amendments/modifications to the IRB are available on the VAPHS Research website at http://www.vaphs.research.med.va.gov.

The principal investigator is also responsible for reporting to the IRB off-site adverse events, defined as adverse events occurring in patients enrolled at a site other than VAPHS, into either the same study or another study utilizing the same drug, device or intervention at another site when the PI has received reports of such adverse events from the coordinating site, regulatory agency or sponsor according to the IRB Adverse Event Reporting Policy (Appendix Q).

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

The IRB shall provide the PI with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the PI an opportunity to respond.

The IRB must carefully and fairly evaluate the investigator's response in reaching its final determination. The IRB minutes reflect the process an investigator must follow in order to

respond to IRB actions. The PI must respond to IRB requests for modification within six weeks of the meeting date in the case of full IRB reviews and within six weeks of the decision date in the case of expedited reviews. There is no time frame limitation for responding to requested changes for tabled protocols; however, such protocols may need updated supporting documentation to be determined by the IRB Coordinator or his/her designee.

General concerns about the IRB actions or Human Research Protection Program may be relayed to the HRPP Executive Committee through the VAPHS Research Office website.

G. Other Related Committees within the VAPHS.

The **Institutional Biosafety Committee** reviews all studies that are submitted to the VAPHS IRB. The IRB requires review and approval of proposals by the **VAPHS Radiation Safety Committee** (Chaired by the Chief, Nuclear Medicine) if the proposals involve ionizing radiation, any type of radiation therapy, or nuclear medicine testing. Such review may take place simultaneously with the IRB review or following IRB review but final IRB approval cannot be granted until the approval of the appropriate sub-committee has been obtained.

All proposals reviewed and approved by the IRB will then be forwarded to the **VAPHS R&D Committee** for approval. Research cannot be initiated until the R&D Committee has granted final approval. The R&D Committee prior to IRB approval will review only “just-in-time” proposals involving human subjects. Such proposals may be submitted to the granting agency without IRB approval however; IRB approval must be sought prior to initiating the trial including any research activity to be used for the purposes of generating pilot data.

The **Research Compliance Committee (RCC)** evaluates compliance issues and approves policies related to IRB and human subjects research. The **HRPP Executive Committee** drafts and implements policies related to the protection of human subjects. See policies of the VAPHS RCC, Appendix D.

H. Other Institutions.

The IRB is responsible for the protection of the rights and welfare of human research subjects at this VAMC and for research conducted under VA auspices. The IRB has no authority over or responsibility for research conducted at other institutions. However, for multicenter studies being coordinated by the VAPHS or for studies that require collaboration with another center, the IRB shall ask for proof of IRB approval and evidence of an MPA or FWA of the participating institutions. The IRB may impose additional adverse event reporting requirements from other sites for studies when the VAPHS is the coordinating site. Non-VAPHS centers do not include the University of Pittsburgh and this rule does not apply to studies conducted by the VA Cooperative Studies Program. For additional information regarding IRB oversight of multisite studies in which the VAPHS is involved, please see section 7.J.

VAPHS and the University of Pittsburgh have established a Memorandum of Understanding (Appendix E) specifying the circumstances under which the VAPHS IRB, the University of Pittsburgh IRB, or both IRBs must approve research. Contact the Research Office at 412-954-5381 if there are any questions regarding where to submit a new application.

I. Sponsored Research

Sponsored research may be funded by the VA or non-VA entities. When a written agreement is available and funds are administered through the Veterans Research Foundation of Pittsburgh (VRFP), the Executive Director of the Foundation will review each proposed sponsored research agreement to identify and address human research protection requirements with the sponsor or investigator sponsor. When funds are administered through VAPHS, the AO/ACOS/R&D will conduct a similar review.

The Sponsored Research Agreement Checklist will be used to document that the written agreement contains the following stipulations:

- VAPHS will comply with the protocol and applicable law and will use procedures that protect research participants;
- identification of who will provide medical care and who is responsible to pay for it in the event of research-related injury;
- the sponsor will promptly report to VAPHS any findings that could (a) affect the safety of participants, (b) affect the willingness of participants to continue participation, (c) influence the conduct of the study, and/or (d) alter the IRB's approval to continue the study;
- plans for disseminating findings from the research and the roles that the investigator(s) and sponsor will have in publication or disclosure of results.

The policies of the VAPHS Human Research Protection Program are applied to all sponsored research. If, in the course of the study, the agreement is modified in a manner that affects the above criteria, the review will be repeated and the results forwarded to the R&D Committee. Incentive payments which are designed to accelerate recruitment that are tied to the rate or timing of enrollment will not be accepted at VAPHS.

J. Regulatory Agencies.

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

K. IRB Staff and Resources.

IRB Staff:

The names and contact information of IRB Staff are detailed on the Research Website, http://www.vaphs.research.med.va.gov.

ACOS/R&D: The ACOS/R&D ensures that the Human Research Protection Program (HRPP) Plan is operational. To do so, the ACOS fulfills the following specific responsibilities:

1) Implementation of the institution's HRPP policy.
2) Reviews and evaluates reports and results of compliance assessment and quality improvement activities.
3) Implementation of needed improvements and follow-up on actions, as appropriate.
4) Monitors changes in VA and other Federal regulations and policies that relate to human research protections.

AO/R&D: The Administrative Officer to the Associate Chief of Staff for Research and Development (AO/ACOS/R&D) is responsible to the ACOS/R&D for the administrative functions of the R&D Program. The functions are:

1) Preparing and revising long-range plans for personnel, equipment, space, and construction requirements.
2) Systematically reviewing and reporting on such administrative functions as manpower utilization, personnel, training, space utilization, publications, supply procedures, and reports.
3) Developing and implementing control procedures for fiscal matters, supplies, equipment, and services.
4) Maintaining inventory records of nonexpendable equipment.
5) Assembling, organizing, and presenting information on budget preparation.
6) Assisting such administrative functions as recruitment of staff, personnel actions, preparation of reports by investigators, provision of facilities for the R&D Committees and its subcommittees (e.g. IRB, IACUC, IBC), and preparation of reports by the ACOS/R&D on the facility's program.

IRB Chairperson: The IRB Chair and Vice-Chair(s) perform their duties as described under section 5.A. The Research Office will support the IRB Chair and Vice-Chair(s).

IRB Coordinator: The IRB Coordinator is responsible for:

1) Directing and overseeing all IRB support functions and operations,
2) Training, supervising, and evaluating IRB staff,
3) Maintaining the official roster of IRB members,
4) Scheduling IRB meetings,
5) Coordinating the distribution of pre-meeting materials,
6) Compiling the minutes of the IRB meetings in compliance with regulatory requirements,
7) Promptly reporting changes in IRB membership to the Office for Human Research Protections and to VA Office of Research Oversight,
8) Maintaining all IRB documentation and records in accordance with regulatory requirements,
9) Assisting new IRB members in completing orientation procedures and meeting required education standards,
10) Ensuring that all IRB records are secured and properly archived,
11) Facilitating communication between investigators and the IRB,
12) Tracking the progress of each research protocol submitted to the IRB,

13) Maintaining two computerized databases (MIRB and PROMISE) for tracking purposes,
14) Serving as a resource for investigators on general regulatory information, and providing guidance about forms and submission procedures,
15) Training research investigators and staff,
16) Maintaining training documentation and reference materials related to human subject protection requirements,
17) Maintaining and updating the IRB forms,
18) Drafting reports and correspondence to research investigators on behalf of the IRB(s) or IRB Chairperson(s) regarding the status of the research, including conditions for approval of research and cases of adverse events or unanticipated problems,
19) Drafting reports and correspondence directed to research facility officials, federal officials, and others on behalf of the IRB(s) or IRB Chairperson(s),
20) Maintaining quality control of IRB support functions,
21) Assisting in evaluation, audit, and monitoring of human subject research as directed by the IRB, the R&D Committee, or the ACOS/R&D,
22) Keeping manuals and Standard Operating Procedures up to date,
23) Assisting with Accreditation Visits,
24) Coordinating and assisting during regulatory inspections and site visits.
25) Validation of the IND or IDE number.

Resources:

Each year, R&D Committee members and IRB members are provided a survey (Appendix F) to complete. This survey requests feedback on: member workload, meeting conduct, education, and training needs. The members are also given the opportunity to provide comments for improvement in the program. The results from this survey are used to budget resources for that year. Also, each year, the HRPP Executive Committee evaluates the number of proposals that have undergone initial and continuing review during the prior year and makes a projection for the volume of research to be reviewed during the current year. The funds for the HRPP are provided by the Veterans Research Foundation of Pittsburgh, the nonprofit research foundation.

The VAPHS Research Office will provide clerical support to the IRB Chairs for official IRB correspondence through the IRB Office. All appropriate computer systems, software requirements, communication devices, filing systems, and other supplies deemed necessary to run the IRB Office will be provided by the Research Office.

In order to supplement the Research Office operating budget as sent by VACO, certain protocols would be assessed fees by the Research Office or by the IRB. These funds will be used to support the educational expenses of the IRB, training of IRB staff, honoraria of IRB members, and other IRB costs. All pharmaceutical company supported studies will be assessed a 10% Human Research Protection Program administration fee. There is also a fee for initial and continuing review of industry-sponsored projects by the IRB payable to the non-profit foundation. The fee will be automatically deducted from the account of the PI for the relevant study. Exemptions will be considered by application to the ACOS R&D. The review of this project will continue whether or not a fee has been received. Neither the IRB Chair, Vice-Chair(s), nor the members will be informed as to whether a fee has or has not been received to review a study.

5. The Membership of the IRB (38 CFR 16.107; VA Handbook 1200.5, Paragraph 6)

The IRB will have a minimum of five members. The membership is selected to assure appropriate diversity, including representation by multiple professions, multiple ethnic backgrounds, both genders, knowledge of institutional commitments, knowledge and experience with vulnerable subjects, inclusion of both scientific and non-scientific members and one member who has no other affiliation with this VAMC (Appendix G: IRB Membership). The IRB is responsible for ascertaining the acceptability of proposed research in terms of medical center commitments and policies, applicable law, scientific merit, sensitivity to community standard and attitudes, as well as standards of professional conduct and practice. Therefore, the following principles shall be observed in the composition of the IRB**.**

A. Appointment of Chairperson and Vice Chairperson, Length of Service and Duties

The Chairperson of the Institutional Review Board shall be a voting member of the Board who has a significant physical presence at the VAPHS and is involved with the research program.

Appointment: The IRB Chairperson and Vice Chairperson shall be appointed by the Medical Center Director based on the recommendations of the R&D Committee for a term of one year and may be re-appointed without any lapse in time. The Chairpersons shall have the right to resign from the position of Chairperson upon notifying both the Institutional Administration and the Board with three months advance notice whenever possible to allow for an orderly transition.

The IRB Chairperson, as well as the Vice Chairperson, will serve as voting members of the VAPHS HRPP Executive Committee and the RCC. The IRB Chairperson is also automatically nominated as a voting member of the R&D Committee and the IRB Vice Chairperson is automatically nominated as an alternate member of the R&D Committee in order to facilitate improved communication between the two committees. The IRB Chairperson/Vice-Chairperson shall not simultaneously serve as chair of the R&D Committee.

Qualifications: The IRB Chairperson and IRB Vice-Chairperson will have earned the M.D., Ph.D. or equivalent degree and will be nominated to the R&D Committee by the ACOS/R&D for appointment. The IRB Chairperson and Vice Chairperson must have at least one year of IRB membership experience and must have completed specific IRB member training as defined in Section 5.F. prior to appointment as Chairperson.

Authority: The IRB Chairperson and Vice Chairperson have the authority to approve the agendas of the IRB meetings as presented by the Research Office. The IRB Chairs will represent, or appoint other members to represent, the IRB to the institutional administration, and the research staff. The IRB Chairperson or Vice Chairperson also has the authority to call an ad-hoc meeting of the IRB as necessary.

Duties:

1. To convene, conduct and ensure the documentation of all the meetings and official business of the IRB as well as to assure timely distribution of the monthly meeting agenda.
2. To assign reviewers for initial and continuing reviews consistent with protocol content and reviewer expertise.
3. To evaluate each protocol to determine if additional expertise is required from a consultant.
4. To evaluate and, if appropriate, approve all requests for exemption from IRB review as well as requests for expedited review.
5. To evaluate and, if appropriate, approve all requests for minor modifications.
6. To review all reported adverse events and unanticipated problems and determine appropriate course of action.
7. To determine immediate actions to be taken in cases of serious or continuing non-compliance of ongoing research, as well as to meet the reporting requirements of federal agencies.
8. To assure all IRB members meet minimum training requirements for human subjects protection in research.
9. To assure all IRB members and consultants provide a financial conflict of interest statement.

The IRB Chairperson or the Vice Chairperson may designate any one of the voting members of the IRB to carry out any of these duties provided that the IRB designee completes the required documentation on behalf of the Chairperson. The IRB designee shall be an experienced member. A member is considered “experienced” once he/she has completed all required IRB member training, and has served on the IRB for a minimum of six months. Assignments will also be made based on the expertise and type of member appropriate for the item to be reviewed.

The IRB Chairperson may also choose to send any requests for expedited review, request for exempt review, adverse event reports, unanticipated problem reports, and minor modifications to the full IRB. The Chairperson cannot disapprove any proposals by expedited or exempt review mechanisms and must forward requests that may potentially be disapproved, to the full IRB. The Chairperson must seek the opinion of the Vice Chairperson or another IRB member or forward the matter to the full board when he/she is a PI or co-investigator or a consultant for any proposal being considered for approval by expedited review or exempt review, or in cases of evaluation of adverse event reports, unanticipated problems, and/or recruitment materials.

All actions of the IRB Chairperson and Vice-Chairperson(s) shall be documented in writing on the Chairperson Review Form/Coversheet (Appendix H). The IRB Chairperson and Vice-Chairperson(s) are also expected to maintain continuing education in human subjects protection training by attending at least one national training seminar in this area each year.

Evaluation: The IRB Chairperson and Vice-Chairperson(s) will be evaluated annually by the chairperson of the R&D Committee and ACOS. The evaluation will be based on qualifications, fulfillment of education and training requirements, and attendance at required meetings.

B. Appointment of IRB Members, Length of Service and Duties (VA Handbook 1200.5, Paragraphs 6 and 7)

Appointment: IRB members are nominated by the R&D Committee and their names are forwarded to the VAPHS Director. The Medical Center Director shall officially notify members in writing of their appointment to the IRB for a period not to exceed three years. Members may be reappointed without any lapse in time. The IRB member appointments shall be staggered so that approximately 1/3 of the IRB members' terms shall be up for renewal each year. All IRB members must have at least a without compensation (WOC) appointment at the VAPHS in order to serve on the board.

Qualifications of Members/ Composition of Boards: In the appointment of IRB members, equal consideration shall be given to qualified persons of both genders. No appointment to the IRB shall be made solely on the basis of gender. Every effort will be made to ensure that the IRB membership does not consist entirely of men or entirely of women. Whenever possible, members of cultural and ethnic minorities will be included as members in order to represent the population of subjects cared for by the VAPHS. The IRB members will not consist entirely of members of one profession. The IRB members shall be sufficiently qualified to review the research through their experience, expertise and diversity, including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes. Each IRB shall include:

(1) at least one member whose primary expertise is in scientific areas;
(2) at least one member whose primary expertise is in nonscientific areas. These members shall be selected primarily to reflect the values of the research community and the community from which the research subjects are drawn with respect to the rights and welfare of human research subjects. (It is recommended that members of the community such as clergy persons, attorneys, and veterans or representatives of legally recognized veterans organizations be considered for appointments to the IRB);
(3) at least one member who is not otherwise affiliated with the VA medical center and who is not part of the immediate family of a person who is affiliated with the medical center. This role cannot be filled by a veteran who volunteers at the medical center in any capacity including that of a research subject.
(4) In addition to the above requirements, if vulnerable subjects are to be enrolled into clinical studies, the IRB must include a member who protects the rights, welfare and interests of the vulnerable population. An ad-hoc member may need to be added to the IRB membership for this purpose if there is no such expertise among the other IRB members. The addition of the ad-hoc member to the IRB must be indicated on the FWA and reported to ORO. Ad hoc members are further explained below.

Duties: Each IRB member is expected to attend monthly meetings of the IRB. Members are also expected to provide a complete, detailed and written review of assigned protocols as primary or secondary reviewers when they are assigned a review. Each assigned reviewer is also expected to complete appropriate reviewer checklist(s) (Appendices I and J) and to provide the written review and completed checklist(s) to the IRB coordinator prior to the meeting. Reviewers who are assigned a review but who are not able to participate in a

meeting shall forward a complete written review along with a completed checklist to the IRB coordinator no less than 24 hours prior to the meeting time.

The IRB Chairperson has the authority to declare the position of any IRB member vacant if the IRB member misses more than two consecutive IRB meetings or more than five meetings during the course of a 12 month period or fails to consistently provide written reviews when requested. In this case a nomination for a replacement will be requested from the R&D Committee for consideration by the Director of the VAPHS.

Evaluation: IRB members will be evaluated annually by the IRB chairperson and the vice chair. The evaluation will be based on qualifications, fulfillment of education and training requirements, and attendance at required meetings.

Adequate Scientific Expertise, Ad Hoc Members, and Consultants: If there is not one person on the IRB with the expertise to conduct an in depth review and answer specific questions which may arise during review of a protocol, the IRB will: (1) defer consideration of the protocol to another meeting; or, (2) invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. (21CFR56.107f) Such individuals may not vote with the IRB, or contribute to its quorum.

For example, a study involving children would require a health care professional with pediatric expertise to ensure that adequate protections are in place for this vulnerable population.

Ex-Officio Members: Representatives of the Research Office or the Institutional Administration may be appointed to the IRB as consultants and advisors on administrative matters. They take part in deliberations but do not vote, and they provide administrative support for the IRB.

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

C. Alternate IRB Members.

Alternate members may substitute for regular members and are formally appointed as alternate members by the director of the VAPHS. Alternate members may be nominated by the R&D Committee and appointed by the Director. These alternates replace regular IRB members who are, on occasion, unable to attend convened meetings of the IRB. At any given time, at least one non-affiliated representative, one patient advocate and one physician/scientist member shall have an appointed alternate member. The IRB roster identifies the primary member for whom each alternate member may substitute. The alternate member's qualifications shall be comparable to those of the primary member to be replaced. When an alternate member replaces the primary member, the alternate member shall have received and reviewed the same material that the primary member would have received. In addition, the IRB minutes shall document when an alternate member replaces a primary member.

D. Use of Consultants (38 CFR 16.107(f)).

The IRB is authorized to obtain services of outside reviewers when the IRB Chair determines that appropriate scientific or scholarly expertise is required. The board will invite experts to assist in the review of issues that may require expertise unavailable on the board. Invited experts do not have a vote but are requested to provide a written, in-depth review of the material presented. The IRB Chairperson can request the services of a consultant through the ACOS. The IRB presents a specific set of questions to the consultant in order to allow the members to complete their review adequately. The IRB may elect to seek a complete review. Consultants will be asked to document their response to specific set of questions or complete the applicable IRB reviewer checklist. The Consultant does not replace the reviewer system but supplements it with added expertise to aid the reviewers.

E. Conflict of Interest (38 CFR 16.107(e).

No IRB member, ad hoc members, or consultants may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (See Section 16). Any members or consultants who have conflicts of interest are required to recuse themselves from deliberations and are not counted toward the quorum for that specific protocol. Members with a conflict of interest shall have this documented in the IRB minutes. Each IRB agenda will include a definition of a conflict of interest for the individual or individual's immediate family and will list all of the sponsors for agenda items to be discussed at that meeting.

F. Training and Development of IRB Chair and Members (ORD May 8, 2000, and March 14, 2001, Memoranda).

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

Before taking their place as voting members of the IRB, each new member will receive 1) human subjects education training, and 2) the policies and procedures of the IRB. New members will also be provided all pertinent ethics documents. In addition, members must annually take the VA-sponsored online course in human subjects protection and good clinical practices. Certification status for each member will be entered into MIRB.

G. Compensation for IRB Service.

IRB members are generally not compensated for serving on the IRB. The ACOS/R&D shall, on an annual basis, provide each IRB member and Chairperson with a formal letter, to be included in the individual's personnel file, describing the critical importance and extremely time-consuming nature of their IRB service. IRB members who are paid employees of the VA are not otherwise compensated for serving on the IRB. IRB members who are not otherwise affiliated with the VAPHS or its collaborating institutions may be compensated for their service at a rate determined by the ACOS/R&D. Non-VA members of the IRB are given a Without Compensation appointment (WOC) and an Honorarium on a per meeting attended basis.

H. Liability Coverage for IRB Members.

The Department of Veterans Affairs is a self-insured entity. For IRB members who are employees of the Department of Veterans Affairs (with or without compensation), the Federal Tort Claims Act (FTCA, 28 United States Code Sections 1346(b) and 2671-2680) would apply to and provide coverage for claims by a third party against VA employees acting within the scope of their employment in connection with their IRB duties. The FTCA provides an exclusive remedy against the United States for personal injury or death, arising or resulting from the negligent or wrongful act or omission of any employee of the government while acting within the scope of his/her duties. The Department of Justice makes the final decision about whether and individual is covered under the provisions of FTCA. If an IRB member is served with documents naming them in a lawsuit or claim, the IRB member shall notify the Pittsburgh Office of the Regional Counsel, ACOS/R&D, and IRB Chairperson immediately for assistance and advice.

6. IRB Record Keeping and Required Documentation (38CFR115).

A. Record Retention (38 CFR 16.115(b)).

The IRB shall keep records related to a research study for at least six (6) years after a study is completed. If a protocol is cancelled without participant enrollment, IRB records will be maintained for at least six (6) years after cancellation. The IRB shall keep records not relating to a research study will be retained for at lease six (6) years. All active records are maintained by the IRB staff and are located in the research office in locked cabinets. All non-active records are maintained by the Records Control Officer and are secured in the research record archives. All records will be retained in accordance with VHA's Records Control Schedule.

The following records are maintained in the IRB Office:

1) Copies of all proposals, critiques, consent forms, progress reports, (including final reports), reports of injuries to participants, statements of significant new findings provided to participants, emergency use reports, and adverse event reports;

2) Copies of all budgets, accounting, and auditing records;

3) Complete minutes of IRB meetings, which include attendance, absentees, designated alternates, those on extended leave of absence, actions, a summary of discussions of controverted issues and their resolutions, a record of the number of members voting for, against, and abstaining, and the reasons for requiring changes in the protocol or for disapproving a protocol;

4) Records of continuing review activities and of reports of the monitors;

5) Correspondence between the investigators and the IRB;

6) Correspondence between the IRB, the investigator, the monitors, or the research office concerning IRB business;

7) A list of IRB members indicating name, earned degrees, representative capacity, board certifications and license, employment or other relationship to VAPHS, and the terms of the appointment to the IRB;

8) A copy of the written standard operating procedures (this document);and

9) Copies of all correspondence between human subjects and the IRB (including the monitors).

10) Correspondence between the IRB and R&D Committee.

A database (MIRB) containing the investigators name, approval period, project title, and status is also kept (See Section 6.I.).

B. Access to IRB Records.

Access to IRB records is limited to the ACOS/R&D, AO, IRB Chairperson, IRB members, IRB Coordinator, IRB staff, authorized VA representatives, and officials of Federal and State regulatory agencies, including ORO, OHRP, and the FDA. Research investigators will be provided reasonable access to files related to their research. All other access to IRB records is limited to those who have legitimate need for them, as determined by the Medical Center Director, the R&D Committee, and VACO.

Specific records are made available to only authorized personnel, i.e. those with human subject protection functions and to the subjects or their legal representatives. A recorded log containing the signature of any person(s) accessing these files will be maintained by the research office.

C. IRB Records.

IRB Records include files organized into the following categories:

1) Written Standard Operating Procedures
2) IRB membership rosters
3) Training records
4) IRB correspondence
5) IRB research application (protocol) files
6) MIRB Database (Research protocol tracking system)
7) Documentation of exemptions and exceptions
8) Documentation of expedited reviews
9) Documentation of scientific evaluations
10) Minutes of convened IRB meetings
11) Documentation of review by another institution's IRB when appropriate
12) Documentation of MOU with the University of Pittsburgh.
13) Federal Wide Assurance
14) Serious Adverse Event Reports and Unanticipated Problem Reports
15) PROMISE Database

D. Current IRB Registration and Membership Roster.

The current IRB membership rosters are maintained in the IRB Office (Appendix G). The IRB staff is responsible for maintaining the roster and submitting to ORO and OHRP as indicated by the FWA. Along with the roster a copy of each member's CV or resume is maintained in the IRB Office.

The IRB Membership Roster shall include the following information required by OHRP:

1) Names of IRB Members
2) Names of alternate members and the corresponding regular member(s) for who each alternate may serve
3) Earned degrees of each member and alternate, where applicable
4) Specific scientific qualifications (such as board certifications and licenses) or other

relevant experience sufficient to describe each member's chief anticipated contribution to IRB deliberations

5) The representative capacity of each member or alternate
6) Any employment or other relationship with the VAPHS or with the VAPHS's collaborating institutions (e.g., full or part-time employment, stockholder, member of governing board paid or unpaid consultant)

E. Education and Training Records.

The IRB shall maintain accurate records listing research investigators, IRB members, and IRB staff who have fulfilled the facility's HRPP training requirements.

The following individuals must complete an educational course or complete a web-based course on both the protection of human research subjects and Good Clinical Practice (GCP):

1) All investigators (principal investigators and co-investigators);
2) All research coordinators or managers;
3) All research assistants involved in human studies research;
4) All staff members of the Research Office;
5) All members of the R&D Committee, and;
6) All members and staff of the VA Institutional Review Board (IRB), exclusive of secretarial support.

All individuals subject to this policy will be required to update their training annually, thereafter, between January 1st and September 30th of each year. The list of approved educational courses can be found in Appendix C.

IRB Staff will verify that the requirements listed above are met by receipt of a certificate of completion from the respective program. Receipt of education certificates will be tracked using the MIRB database. All individuals appearing on the Research Staff Form for initial or continuing review submissions will be cross-referenced with education records in the MIRB database. A submission will not be reviewed by the IRB if one or more members of the research team fail to meet these training requirements.

In addition, all investigators and research coordinators must attend HRPP educational sessions, which will be conducted and tracked as described in the Education and Compliance Policies, Appendix K.

The FWA requires that signatory officials complete the Training Module for Assurances (Module 1). Local Signatory Officials include the Medical Center Director and the Network Director. The ACOS/R&D, IRB Chairperson(s), Vice-Chairperson(s), and IRB staff must complete the Training Modules for Assurances (Modules 1 through 3) available on the OHRP website. IRB members will meet the minimum human subjects education requirement as described above. The IRB Office will also maintain these records.

F. Written Standard Operating Procedures and Guidelines (38 CFR 16.103(a-b) and 108, 115(a)(6)).

The IRB SOPs are available to investigators on the Research Website. While the Research Compliance Committee reviews and approves specific policies, the HRPP Executive

Committee is responsible for the compilation of IRB policies and procedures into the IRB SOPs which are made available to the IRB members. The HRPP Executive Committee reviews the SOPs no less frequently than every 3 years.

G. IRB Correspondence (38 CFR 16.115(a)(4)).

Accurate records are maintained of all communications to and from the IRB. Copies are filed in the IRB's investigator project file. A hard copy of all correspondence between the IRB and the investigator is maintained in the investigator's protocol file. Hard copies of approvals and stamped consent forms are sent to the investigator. E-mail and facsimile correspondence is also used for other communication. E-mail correspondence will be printed and stored in the project folder.

H. IRB Research Application Files.

The IRB shall maintain a separate file for each research application. Protocols are numbered sequentially in the order in which they are received.

Each IRB research application (protocol) file will contain the following materials:

1) The Request to Review Form, Part I;
2) The IRB-approved informed consent document (DHHS consent form if applicable), (VA Form 10-1086), with the approval stamp;.
3) Scientific evaluations of the proposed research, if any. For drugs, the Investigator's Brochure; for devices, the FDA Investigational Device Exemption (IDE) approval letter;
4) Applications for Federal support, if any;
5) A complete copy of the protocol (DHHS protocol if applicable), or research plan, or investigational plan;
6) Advertising or recruitment materials, if any;
7) Applications for protocol amendments or modifications;
8) Continuing review progress reports and related information;
9) Reports of unanticipated problems involving risks to subjects or others;
10) Reports of adverse events occurring within the VAPHS (or involving employees or agents of the VAPHS) and reported to any regulatory agency;
11) Reports of external adverse events received from sponsors or cooperative groups;
12) Data and Safety Monitoring Board (DSMB) reports, if any;
13) Results of any internal quality control and monitoring activities;
14) Results of any external monitoring activities, including reviews provided to the investigator by sponsors, cooperative groups, or Federal agencies;
15) All IRB correspondence to or from research investigators;
16) All other IRB correspondence related to the research;
17) Documentation of all IRB review and approval actions, including initial and continuing convened (full) IRB review;
18) Documentation of type of IRB review; and,
19) Documentation of project closeout.

I. Research Tracking System.

The IRB uses a computerized tracking system, MIRB, to track protocols. Upon receipt, all

proposals are entered into the database and assigned a unique identification number.

MIRB includes the following information:

1) Title of the Research (Protocol)
2) Names of the PI and co-investigators where appropriate
3) Funding source (if any)
4) Date of initial approval
5) Date of most recent continuing approval
6) End of current approval period
7) Type of review (expedited, convened review or exempt)
8) Current status (under review, approved, suspended, closed)

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

FDA regulations at 21 CFR 50.23 permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) where the clinical investigator and a physician not otherwise involved in the research certify in writing that (1) the subject is confronted with an immediately life threatening emergency; (2) informed consent cannot be obtained because of an inability to communicate; (3) time is not sufficient to obtain consent from the subject's legally authorized representative; and (4) there is no alternative approved or generally recognized therapy that provides equal or greater likelihood of saving the subject. If time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and within five working days after the use of the article, have the determination reviewed and evaluated in writing by an independent physician.

This written certification must be submitted to the IRB within five working days of the use of the test article. The IRB Coordinator is responsible for maintaining this documentation in IRB records. The Chief of Staff is expected to verify that conditions for the use have been met on VA Form 10-1221, in accordance with M-2, Part 1, Chapter 3.05, Consent for Use of Investigational Drug for Either Diagnostic or Treatment Purposes by or Under the Direction of the Veterans Administration. Any subsequent use of the test article must be as part of an IRB approved protocol.

Emergency use of investigational drugs requires that the patient become a participant in a research protocol ((21 CFR 50.3(g) and VA Handbook 1200.5, Paragraph 14, Parts f-h.). If the patient is treated outside a research protocol, then the Under Secretary for Health must approve.

K. Documentation of Exemptions from IRB Review Requirements for Emergency Use of a Test Article (21 CFR 56.104c)

FDA regulations at 21 CFR 56.104(c) permit the emergency use of a test article without IRB review. Emergency use is defined as use of a test article on a human subject in a life threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). If the patient is treated

outside a research protocol, then the Chief of Staff must approve. Written documentation of the emergency use must be submitted to the IRB within five working days. Any subsequent use of the test article requires IRB review. The IRB Coordinator is responsible for maintaining this documentation in IRB records.

L. Documentation of Expedited Reviews (38 CFR 16.110(b); FR 60364-60367 & 60353-60356, November 9, 1998).

Eligible categories.

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

(2) Research that involves only categories described in below. The research activities should not be considered of minimal risk merely because of their inclusion in the categories below. 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.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply to expedited review.

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

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) below are met.

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

b. Research on medical devices for which;

1. An investigational device exemption application (21 CFR Part 812) is not required and the device is categorized as non-significant risk; or

2. The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

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

b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than two times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples are as follow:

a. Hair and nail clippings in a non-disfiguring manner;

b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

c. Permanent teeth if routine patient care indicates a need for extraction;

d. Excreta and external secretions (including sweat);

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

f. Placenta removed at delivery;

g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

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

i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

j. Sputum collected after saline mist nebulization.

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

- 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;

- Weighing or testing sensory acuity;
- Magnetic resonance imaging;
- Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
- Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

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

(7) Continuing review of research of research previously approved by the convened IRB. (See item (2) below).

Approval of minor changes. Minor changes are defined as any change that would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study. If approved, the continuing review date does NOT change, but remains the same as determined at the most recent review.

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

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

(2) If a proposal has been initially approved through the non-expedited review procedure, the continuing review may not be done by the expedited review procedure. Exceptions are:

a) 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
b) Research in which no subjects have been enrolled and no additional risks have been identified; or
c) Research in which the remaining research activities are limited to data analysis.
d) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories 3.b. through 3.h. 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.

At the time of initial filing, the IRB Chairperson or Designee will evaluate each proposal to determine if it fits criteria for expedited review. The Chairperson or his/her Designee can also handle minor changes in previously approved studies that are made during the approval period. The Chairperson may approve (expedite) research studies as defined above but consent must still be obtained unless criteria for waiver of informed consent are met. The reviewer's actions are reported at the next IRB meeting. Disapproval of projects by expedited review procedures is prohibited.

The IRB initial approval is effective only after approval of the R&D Committee***.*** The date for continuing review is based on the date of IRB review and approval. Work on the protocol may not commence until R&D Committee approval is obtained.

Record Keeping. The IRB will keep all members advised of research proposals that have been approved under this process. The minutes and the protocol file will reflect the expedited review eligibility category that the research meets.

M. Documentation of Convened IRB Meetings – Minutes (38 CFR 16.115(a)(2)).

A member of the IRB staff completes the minutes of the convened IRB meetings.

Minutes of IRB meeting proceedings shall be written within three weeks of the meeting date. Once approved by the members at the subsequent IRB meeting, the minutes shall not be altered by anyone including a higher authority. Minutes of IRB meetings shall contain sufficient detail to show:

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

(2) Attendance at the meetings including those members who are participating through video or teleconference;

(3) Alternate members attending the meeting and members participating by video or teleconference have received all pertinent material before the meeting and reviewed all required information and were able to actively and equally participate in all discussions;

(4) Actions taken by the IRB; including separate deliberations for each action;

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

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

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

(8) A written summary of the discussion of refuted issues and their resolution;

(9) Review of additional safeguards to protect vulnerable populations if entered as study subjects; and

(10) For protocols involving the use of placebos or that involve symptom provocation, a written summary of the discussion regarding the need for these and the safeguards that are in place, plus the resolution of the discussion of these issues.

(11) The frequency of continuing review of each proposal as determined by the IRB. The IRB shall assure that continuing review will be conducted within the once a year requirement of 38 CFR 16.109(e) and VA Handbook 1200.5, Paragraph 7, Part g., according to the degree of risk. Studies involving minimal risk as determined by the IRB will be reviewed every 12 months while studies involving greater than minimal risk will be reviewed every 3, 6 or 12 months. The continuing review interval is determined by the IRB Level of Scrutiny. A moderate/intermediate level of IRB scrutiny constitutes a six-month continuing review interval. A high level of IRB scrutiny constitutes a three-month continuing review interval.

(12) Records of continuing review activities.

(13) The rationale for significant risk/non-significant risk determination.

The Sample Minute Format can be found in Appendix M.

After approval by the IRB Chairperson, the minutes will be forwarded to the ACOS/R&D, Chief of Staff and Director for signature and approval. The IRB minutes serve as notification of IRB determinations to these organizational officials. IRB staff will forward a copy of the IRB meeting minutes to the R&D Committee for local review. The VA Office of Research Oversight will randomly request copies of the minutes.

N. Attendance at IRB Meetings.

The IRB minutes shall list attendance as follows:

(1) Names of members present
(2) Names of absent members
(3) Names of alternates attending in lieu of specified (named) absent members. Alternates may substitute for specific absent members only as designated on the official IRB membership roster
(4) Names of consultants present
(5) Names of investigators present
(6) Names of guests present

O. Quorum Requirements and Voting at IRB Meetings (VA Handbook 1200.5, Paragraph 7, Part f.).

The minutes shall include a statement of quorum requirements to transact business. A quorum equals more than half of voting members. If a quorum is lost during a meeting, the IRB will not vote until it is restored.

A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in non-scientific areas, must be present to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.

A licensed physician that is a voting member must be present when the IRB reviews research involving FDA-regulated articles.

Members may be present in person or via audio (telephone) or audio-visual teleconference. Members present via teleconference shall be noted as such in the meeting minutes, which shall also indicate that the members received all pertinent information prior to the meeting and were able to actively and equally participate.

IRB minutes shall include documentation of a quorum and votes for each IRB action and determination by recording votes as follows: number voting for, number voting against, number recused, number excused. The names of IRB members who left the meeting because of a conflicting interest along with the fact that a conflicting interest was the reason for the absence will be documented in the minutes.

Members absenting themselves due to conflicts of interest may not be counted toward quorum requirements or be counted as among the majority of members necessary to constitute a quorum.

An individual who is not listed on the official IRB membership roster may not vote with the IRB.

Any ex-officio member of the IRB may not vote with the IRB.

When a member and his/her alternate both attend the meeting, only one can vote.

P. Actions Taken by the Convened IRB (38 CFR 16.109; 115).

IRB minutes shall include all actions taken by the convened IRB and the votes underlying those actions. These actions shall also be provided in writing (VA form 10-1223 Report of Subcommittee on Human Studies) to investigators after formal approval from the R&D Committee is received. IRB actions for initial or continuing review of research include the following:

(1) Approved with no changes (or no additional changes). The research may proceed.

(2) Approvable with minor modifications to be reviewed by the IRB chair or designee. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol approved by the designated reviewer.

(3) Approvable with modifications to be reviewed by the fully convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.

(4) Tabled pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.

(5) Disapproved. The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility.

Q. Basis for Requiring Changes or Disapproving Research (38 CFR 16.109(d)).

The minutes of IRB meetings shall include the basis for requiring changes in or disapproving research. This information shall also be provided in writing to the investigator, who shall be given an opportunity to respond in person or in writing.

R. Summary of Controverted Issues at Convened Meetings (38 CFR 16.115(a)(4)).

The minutes of IRB meetings shall include a written summary of discussion of all controverted issues <u>and</u> their resolution. In such cases the Chairperson will complete the resolution to such discussions during the course of verifying the accuracies of the IRB minutes.

S. Documentation of Review by Another Entity's IRB.

Refer to Section 7.J. VAPHS Involvement in Multi-Site Studies

7. Types of IRB Review Determinations.

All human subject research conducted at this VAMC or by VAPHS employees or agents or otherwise under VA auspices must be prospectively reviewed and approved by the IRB and the R&D Committees. No research may be initiated or continued at the facility or by employees or agents without prospective approval of a designated IRB. Regardless of the type of review (exempt, expedited or full board), the investigator is notified in writing of the IRB's determinations.

A. Review by the Convened IRB (38 CFR 16.108(b)).

The IRB is required to conduct initial and continuing reviews of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more categories appropriate for expedited review.

For research to be approved, it must receive the approval of a majority of those members present at the meeting where a quorum is present.

The IRB holds a regularly scheduled monthly meeting. The R&D Committee meets bi-monthly. Each committee meets at least 11 times per year. A schedule of these events is available in Appendix N and on the Research Website http://www.vaphs.research.med.va.gov/.

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

Prior to the convened meeting, all members of the IRB shall be provided with detailed initial review materials that thoroughly describe the research so that they may discuss the protocol adequately and determine the appropriate action during the convened meeting.

The materials received and provided to all members in the IRB agenda packet include all relevant items listed in Appendix U. The agenda packet is provided at least eight days prior to the meeting:

Prior to being placed on the IRB meeting agenda and distributed to IRB members, each initial review protocol is reviewed for completeness by the Research Office staff, including the IRB Coordinator. Unless a determination of expedited review or exemption from IRB review is made by the IRB Chair or Vice Chair or Designee, the items listed above are distributed to all members. All members have access to reviewer checklists for initial review. The reviewer's checklists are designed to assure compliance of protocols with federal requirements and include risk assessment as defined in VA Handbook 1200.5, Paragraph 7, Part a. Risk assessment and level of scrutiny assignment are described in section 8.A. Each assigned reviewer is expected to complete the appropriate initial review checklist(s).

During the convened meeting, the primary and secondary reviewers provide a verbal presentation of the project overview as well as concerns regarding items identified on the checklists. The proposal is then opened to deliberations. After deliberations are completed, any member can choose to make a motion for further actions as described in the actions of

the IRB (See section 6.P.). A vote is then taken as described in section 6.O.

The IRB decision is then reported to the PI as described in section 6.P. Following final IRB approval, the notice of approval and the proposal packet is forwarded to the R&D Committee for review and final approval.

C. Continuing Review by the Convened IRB (38 CFR 16.103 and 109(b)(4)).

The IRB is required to conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The approval period for research is based upon the date the IRB approved the protocol or approved the protocol with modifications. This approval can occur either at a convened IRB meeting or by means of expedited continuing review by a qualified, designated IRB member.

Continuing review must occur even if:

1) The research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions.
2) The remaining research activities include collection or analysis of private identifiable information.

Investigators are notified at least 60 days in advance by the IRB Office, prior to protocol expiration date, to submit materials for continuing review. At this time the investigator is notified that failure to submit continuing review materials by the specified date will result in expiration of IRB approval. They are also notified at the same time that "The continuation of research after expiration of IRB approval is a violation of the regulations [21 CRF 56.103(a)]. If the IRB has not reviewed and approved a research project by the project's expiration date, the research activities should cease. No new subjects may be enrolled in the study." The expiration date is the last date that the protocol is considered approved by the IRB, for example, if the approval is April 1, 2008 to April 1, 2009, the study expires March 31, 2009. Thus, the IRB approval period for research may extend no more than 365 days after the convened IRB meeting at which the research was last approved, or the date of the expedited review process if expedited review was performed. (See Section 7.N.)

VAPHS IRB conducts a comprehensive and thorough continuing review for all protocols for which it is responsible. All members scheduled to attend the IRB meeting are provided with all relevant items listed in Appendix U. The entire IRB file is available for any member's review prior to and during the convened meeting. The continuing review application includes the number of participants accrued, a summary of adverse events, unanticipated problems, participant withdrawals (including reason for withdrawal), complaints about the research, modifications made to the research, any recent literature relevant to the research, interim findings, any DSMB reports if applicable, investigator's risk assessment, gender and minority status, number of participants considered as members of vulnerable populations, and a statement that all serious or unexpected adverse events have been reported as required.

At the time of continuing review, IRB reviewers complete the Continuing Review checklist (Appendix J) which is presented to the committee at the meeting. If the IRB has a safety concern or other concern, the IRB may request verification or additional information from

sources other than the investigator. The IRB must also determine that the current consent form is still accurate and complete. The IRB does not require consent form changes if enrollment is closed. The IRB must also assure that any significant new findings that arise from their review process and that may relate to subjects' willingness to continue participation will be provided to participants by the investigator.

The IRB assesses risk at the time of continuing review, similar to the assessment done at the initial review process (Section 8.A). The IRB also re-assesses the current assigned risk level when reviewing reported adverse events during the approval period as well as new developments in the field that may have an impact on the previously assigned risk level and scrutiny level. The scrutiny level may also be influenced by any compliance problems or subject complaints observed during the prior approval period. The IRB Reviewer checklists (initial and continuing review, Appendices I and J) provide documentation of these risk assessments. The IRB minutes clearly describe the level of risk as well as the level of IRB scrutiny and continuing review interval. If risk level and or scrutiny level are changed at the time of continuing review, the basis of the changes shall be documented in the IRB minutes. The MIRB database tracks this information.

Multi-site continuing review submissions are handled in accordance with Section 7.J. VAPHS Involvement in Multi-Site Studies

D. Review of Modifications/Amendments by the Convened IRB

Investigators must report and the IRB will review any proposed changes in previously approved research, including proposed changes in research staff and investigators, research proposal, informed consent documents, recruitment materials, etc. No changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects. These changes must be:

(1) Promptly reported to the IRB
(2) Reviewed by the IRB to determine whether the change was consistent with ensuring the participant's continued welfare.

Modifications to an approved proposal are categorized as either major or minor.

Major modifications to an IRB-approved research protocol or informed consent document must undergo full board review and approval at a convened IRB meeting. A major modification is defined as any change that could increase the risks or decrease the benefits of the study or substantially changes the specific aims or design of the study. Examples of changes that might be considered major modifications include:

(1) Broadening the range of inclusion criteria.
(2) Narrowing the range of exclusion criteria.
(3) Alterations in the dosage or route of administration of an administered drug.
(4) Extending substantially the duration of exposure to the test material or intervention.
(5) The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations.
(6) The addition of serious adverse events or other significant risks.

(7) Changes which, in the opinion of the IRB chairperson or his/her designee, do not meet the criteria or intent of a minor modification.

All members, scheduled to attend the IRB meeting, are provided with and review the modification request form and all modified documents. Proposed modifications involving only staff do not require a modification request form; however, they must include a memo outlining the staff changes.

If the proposed amendment will alter the risk associated with biosafety or radiation safety processes, appropriate committee approvals must approval.

IRB reviewers utilize the Modification Review Checklist (Appendix FF). The IRB will determine if there are any significant new findings might relate to participants' willingness to continue participation are provided to participants.

E. Types of IRB Review Systems.

The Primary and Secondary reviewer system is used at the VAPHS. The IRB Chairperson or Vice-Chairperson assigns a primary and a secondary reviewer to each new submission and a primary reviewer to each continuing review submission consistent with protocol content and reviewer expertise. Both reviewers are required to submit written reviews summarizing the protocol and outlining basis for recommending changes and examples of changes to be made, as well as a completed IRB Reviewer Checklists (See sections 7.B. and 7.C.).

The primary and secondary reviewers are considered the lead reviewers on the IRB for submissions assigned to them. They are responsible for (1) being thoroughly versed in all details of the research; (2) conducting an in-depth review of the research using the IRB reviewer checklists; and (3) leading the discussion of the research at the convened meeting.

This primary and secondary reviewer system notwithstanding, all IRB members shall be provided with the required materials described in sections 7.B. and 7.C. (Appendix U) of this document to ensure thorough initial and continuing review of each research proposal. The entire IRB file shall be available to all IRB members prior to and during the convened meeting, and all IRB members shall be afforded full opportunity to discuss each research proposal during the convened meeting.

F. Expedited Review of Research (38 CFR 16.110).

Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in research staff and investigators, research proposal, informed consent documents, recruitment materials, etc No changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects.

VA regulations at 38 CFR 16.110, the Common Rule, and FDA regulations permit the IRB Chair or his/her designee(s) to review research through an expedited procedure if:

(1) The research constitutes a minor change in previously approved research during the period for which approval is authorized; or

(2) The research is not greater than minimal risk and falls within the categories listed in section 6.L.of this document.

Modifications to an IRB-approved research protocol or informed consent document that are not eligible for expedited review by the above criteria, must undergo full board review.

Qualifications of an appropriate designee are described in Section 5.A.

Under an expedited review procedure, the IRB Chairperson, Vice-Chairperson or designee may review and approve the research on behalf of the IRB. The IRB Chairperson, Vice-Chairperson, or designee will follow expedited procedures for the initial or continuing review of research that is no greater than minimal risk *and* falls within the categories published in the November 9, 1998 Federal Register 63 FR 60364-60367; 63 FR 60353-60356 DHHS-FDA list of research eligible for expedited IRB review (See Section 7.H). The expedited reviewer is prohibited from disapproving research. If the reviewer feels disapproval is appropriate, he/she then forwards the proposal to the fully convened IRB with the recommendation to disapprove. Investigators are required to submit the same materials for expedited review as would be submitted for full board review. The assigned reviewer will receive the complete submission packet, according to the type of submission, as described in Appendix U. The criteria for approval using the expedited review procedure are the same as those for review by the convened IRB.

All IRB members shall be advised of research that has been approved under expedited procedures (38 CFR 16.110(c)). This is done by listing the research, including the type of review, date of review, and designated reviewer, in the agenda of the next IRB meeting under the notifications section. The convened IRB will then review and vote on approving all of the notifications presented to them.

If the fully convened IRB disapproves an expedited review notification, the IRB will be presented the entire proposal at the next fully convened meeting. In such a case, the review will be handled in accordance with the initial review procedures. During such a proceeding, the person completing the initial expedited review will not serve as the primary reviewer.

Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

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

Modifications to an approved proposal are categorized as either major or minor changes.

A minor change is one that (a) does not introduce new risks that exceed those ordinarily encountered by the subjects in daily life or in the performance of routine physical or psychological examinations and (b) does not decrease the benefits of the study; and (c) does not substantially change the specific aims or design of the study. Examples may include but are not limited to:

1. changes in funding, project title, study staff,

2. narrowing the range of inclusion criteria,
3. broadening the range of exclusion criteria.
4. changes which improve subject protections or serve only to reduce risks to subjects.
5. small changes in experimental procedures, design, or analysis which improve benefits.

If the change in protocol is relatively minor (e.g., change in investigator, change in a sequence protocol activities) it may not be necessary to have subjects sign new consent forms.

Non-Minor Changes.
A change that is not minor introduces risks to subjects exceeding those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations. Examples of changes that are not minor include:

1. the addition of an intervention of greater than minimal risk not addressed in the original consent form,
2. disclosure of a previously unidentified risk.
3. alterations in the dosage or route of administration of an administered drug.
4. extending substantially the duration of exposure to the test material or intervention.
5. the deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations.
6. the changes which, in the opinion of the IRB chairperson or his/her designee, do not meet the criteria or intent of a minor modification.

In these instances, the investigator may be required to have all new subjects sign a revised consent form and all currently enrolled subjects who may be affected by the change sign an addendum to the consent form.

H. Expedited Initial and Continuing Review: Permitted Categories.

IRBs may utilize expedited procedures for the initial or continuing review of research that is no greater than minimal risk ***and*** falls within the categories published in the November 9, 1998, Federal Register 63 FR 60364-60367; 63 FR 60353-60356 DHHS-FDA list of research eligible for expedited IRB review as follows:

<u>Initial Review</u>:

(1) Clinical studies of drugs and medical devices only when condition (1) or (2) is met:

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

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

involving significant risk devices do not qualify for expedited review at initial review.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

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

(b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than two times per week.

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

Examples:

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

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

(c) Permanent teeth if routine patient care indicates a need for extraction;

(d) Excreta and external secretions (including sweat);

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

(f) Placenta removed at delivery;

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

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

(i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(j) Sputum collected after saline mist nebulization.

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

Examples:

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

(b) Weighing or testing sensory acuity;

(c) Magnetic resonance imaging;

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

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

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). Collection of data from voice, video, digital, or image recordings made for research purposes.

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

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

Continuing Review:

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

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related

interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) Where no subjects have been enrolled and no additional risks have been identified; or

(c) Where the remaining research activities are limited to data analysis.

(d) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two through eight of the categories published in the November 9, 1998 Federal Register (FR 60364-60367; FR 60353-60356 DHHS-FDA list of research eligible for expedited IRB review) 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.

I. Use of Subcommittees to Support IRB Activities.

The IRB Chairperson may appoint subcommittees on an ad hoc basis to perform non-review functions as needed, such as monitoring compliance with IRB regulations. Actions of the subcommittees are brought to the full committee for review and concurrence.

J. VAPHS Involvement in Multi-Site Studies

This section describes the responsibilities of both the VAPHS investigator and the VAPHS IRB for communicating with other IRBs when research involving human subjects is performed at multiple sites (e.g. multi-site clinical trials, VA Cooperative Studies, and studies performed in conjunction with the University of Pittsburgh/University of Pittsburgh Medical Center). The VAPHS IRB must ensure that all facilities participating in research have adequate review and oversight regarding the study in order to protect the safety and interests of study participants. Each institution/site is responsible for ensuring the protection of human subjects participating in approved research and communication among participating sites. Furthermore, each IRB-of-record is responsible for education and credentialing verification for participating investigators and staff.

Before a study can begin at VAPHS, it must be approved by the IRB of record of the coordinating facility, the VAPHS IRB and the VAPHS Research and Development Committee (R&D). VAPHS can only serve as the IRB of record for institutions covered by its Federalwide Assurance (FWA). The VAPHS FWA can not be modified to include non-VA institutions.

<u>VAPHS as a participating facility</u>

The VAPHS participating investigator has overall responsibility for the conduct of the study at VAPHS including submission of the protocol and informed consent form to both the IRB and R&D committees. The VAPHS participating investigator is responsible for providing the VAPHS IRB with the following (documented on the form “VAPHS as a Participating Site in a Research Study Conducted at Multiple Sites”- Appendix GG):

1) The name of the Coordinating Center and Sponsor.
2) The communication plan between the investigator and the Coordinating Center or Sponsor relevant to the protection of research subjects (for example, the mechanism in place for reporting of unexpected problems, adverse events, or interim results).
3) Copies of all external Data Safety Monitoring Board/Committee Reports and any other information relevant to the risks of research (SOP Section 6) are to be submitted at the time of each continuing review.
4) Any applicable contracts.

The IRB is responsible for reviewing the study protocol and informed consent for VAPHS. After the VAPHS IRB approves the study protocol and informed consent, the study must be approved by the R&D Committee before the study can be initiated.

<u>VAPHS as a coordinating facility</u>

For the purpose of this section, the VAPHS coordinating investigator is the person responsible for the following:

- coordinating the multi-site study from VAPHS;
- serving as the single liaison with outside regulatory agencies, with other participating facilities;
- ensuring that all aspects of internal review and oversight procedures are complete;
- obtaining VAPHS IRB review and approval;
- ensuring that all participating facilities obtain review and approval from their respective IRB of record; and
- ensuring that all protocol modifications are approved in a timely fashion.

When VAPHS serves as a coordinating center for a multi-site study, the VAPHS coordinating investigator indicates on the application form of the IRB submission that VAPHS is the coordinating facility for the multi-site study (Part 1, Request to Conduct Research). The VAPHS coordinating investigator must also:

- indicate whether research activities at participating institutions are defined as being engaged in research (See Section 3);
- provide VAPHS IRB with the name of each participating facility, each participating facility's FWA number, the contact name and information for the investigator at each participating facility and the contact name and information for the IRB of record at each participating facility;
- define the communication plan to assure that information relevant to the participant protection (e.g. unanticipated problems, serious adverse events, interim results) is shared with all participating investigators and their respective IRBs of record (as documented on the form "Application for VAPHS to be the Coordinating Site for a Research Study Conducted at Multiple Sites"- Appendix HH);
- submit any subsequent modifications to the initial application to the IRB (as documented on the form "Modifications to Application for VAPHS as Coordinating Site for a Research Study Conducted at Multiple Sites- See Appendix II)
- define the method for ensuring that all participating facilities have the most current protocol version;
- describe the method for confirming that all amendments and protocol modifications have been communicated to participating sites;

- submit copies of any case report forms to be used at the participating sites;
- ensure that the research study is reviewed and approved by the IRB and any other appropriate committees at the participating multi-site facilities;
- submit approval letters from all the IRBs of record and any other appropriate committees to VAPHS IRB;
- report any lapse in approval or suspension at any of the other sites;
- maintain documentation of all correspondence between participating facilities and their respective IRBs, including copies of the approved consent forms.
- if applicable, describe how and when tissue or blood samples will be collected, where the analysis of such samples will be performed, and how samples will be submitted to laboratories. Additional information should also be included to address:
    - who is responsible for shipping any biological sample collection kits to the participating sites.
    - Information regarding how the samples should be labeled to protect the confidentiality of subjects
    - A description of how and when lab reports will be sent to the participating site investigators
    - A description of how abnormal lab results will be addressed at screening, throughout the study and during follow-up.
- If applicable, describe how drugs or devices will be delivered to the participating sites and how dispensing or distribution of the drugs/devices will be monitored. A copy of any proposed inventory/accountability form should also be submitted to the IRB.

The VAPHS IRB is responsible for reviewing the study protocol, applicable contracts, and confirming documentation of FWA status from each participating facility. The VAPHS IRB is responsible for reviewing the participating multi-site facility's IRB review and approval.
Sites may be added to the study only after approval by VAPHS IRB upon confirmation of the above items.

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

Data and Safety Monitoring Boards are formal committees chartered to review study data and determine the safety of continuing study interventions. DSMBs generate reports of their findings which are communicated to all site investigators. Investigators are required to forward DSMB reports to the IRB within five working days of receipt. The review of DSMB reports is handled in the same manner as internal reports of unanticipated problems or adverse events. In addition, all formal DSMB reports generated for a study must be attached to the IRB continuing review application, even if previously submitted. Minutes or reports generated from local data and safety monitoring plans need not be submitted unless requested by the IRB.

When DSMBs are used, the IRB conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others

and any other information needed to ensure that its continuing review is substantive and meaningful.

L. Review of External Monitoring Reports.

Investigators participating in multi-site studies are required to forward reports of external monitoring visits by employees of pharmaceutical companies, Contract Research Organizations (CROs), or the VA Cooperative Studies Program (CSP). Reports should be submitted to the IRB upon receipt.

The IRB will handle these reports in the same manner as other notifications. The IRB may forward monitoring reports to the RCC as necessary. Communication between the IRB and other applicable entities will be handled in accordance with Section 7.J., VAPHS Involvement in Multi-Site Studies

M. Outcomes of IRB Review (38 CFR 16.109 and 115).

The IRB shall notify investigators and the R&D Committee (through the IRB Coordinator where applicable) in writing of its determinations. IRB actions are listed in Section 6. P.

N. Expiration of Approval Period (38 CFR 16.109(e)).

VA regulations at 38 CFR 16.109(e), the Common Rule, and FDA regulations require that the IRB conduct substantive and meaningful continuing review of research not less than once per year. Thus, the IRB approval period for research may extend no more than 365 days after the convened IRB meeting at which the research was last approved, or the date of the expedited review process if expedited review was performed. (See Continuing Review.) The regulations permit no grace period to this 1-year requirement, therefore, research that continues after the approval period expires is considered research conducted without IRB approval.

If the continuing review submission is received by the IRB before the actual expiration date but not in time for the IRB to grant continuing approval prior to expiration, then study approval will expire and no new subjects may be enrolled until continuing review and approval occurs. If the study expiration date passes and no continuing review materials are received by the IRB, the study is considered to have an expired approval and must be re-reviewed and approved by the IRB as an initial submission prior to reinstatement of the study.

Previously enrolled subjects may continue their involvement in research in which IRB approval has expired only where the IRB determines that continued involvement is in the best interest of the subjects.

The IRB office is responsible for promptly notifying the PI and the study sponsor of the expired approval and the determination that enrollment of new subjects may not occur until continuing review has been approved. Once notified of the expiration, the PI must immediately submit to the IRB Chairperson a list of all enrolled research subjects to date. Intervention and interactions on current subjects may continue only when the fully convened IRB, or the IRB Chair, in consultation with the Chief of Staff (COS), determines it to be appropriate (e.g., there is an over-riding safety concern or ethical issue involved such that

discontinuing participant would cause harm). Note: If the study is FDA-regulated, the COS and IRB Chair must follow FDA requirements in 21CFR 56.1086(b)(3) in making their decision.

Expirations of IRB approval are not considered reportable to institutional officials, OHRP and ORO, but may be reportable to other regulatory agencies (See VAPHS Research and Development Report Policy). If the investigator fails to respond to the IRB office requests for submission of the continuing review materials, the RCC can make a determination of continuing non-compliance, which is reportable to institutional officials and all applicable regulatory agencies.

O. Administrative Hold of a Protocol

Administrative Hold is a voluntary action by an investigator to temporarily stop some or all research activities in a currently approved protocol. An Investigator may voluntarily hold a protocol if the investigator or the sponsor have identified a previously unknown or unanticipated problem. Administrative Hold requests should be reported regardless of whether they occur during the study, after the study is completed, or after a subject or subjects have withdrawn/been withdrawn or completed the study.

Administrative Hold of an IRB-approved research protocol by the principal investigator and/or sponsor of the research study should follow the IRB submission and reporting guidelines as set forth in Section 9 described within Unanticipated Problems. The Unanticipated Problem form will be utilized in the event that an Administrative Hold is requested and should be reported no later than 5 business days after discovery or notification of the problem.

P. Determination of Quality Assurance or Quality Improvement (QA/QI) versus Research.

As a part of hospital operations, service lines are expected to complete quality assurance projects. These quality assurance projects frequently use research methodology, blurring the line between research and quality assurance. The VAPHS Research Office acknowledges that requiring submission of all quality assurance projects to the IRB would unnecessarily burden both non-researchers and the IRB. However, when quality assurance projects meet the definition of human subjects research (Section 3), they must be submitted to the IRB for review. Staff members are urged to compare their written project plan to the QA/QI worksheet to determine if they should submit their project to the IRB. If any question exists as to the status of the project, it should be submitted to the IRB for a formal determination. The IRB may deem the effort as QA/QI or as human subjects research. See Appendix S for the full QA/QI policy and Appendix T for the QA/QI Worksheet.

Q. Determination of Exemptions (45 CFR 46.101(b), 38 CFR 16.101; VA Handbook 1200.5, Paragraph 8 and Appendix A, 21. CFR 56.104 and 21 CFR 56.105).

At the time of initial filing the Chairperson or his/her Designee will evaluate each proposal to determine if it fits criteria for exempt review. The Chairperson may approve the exemption as is, request modifications, or disapprove the exemption and forward the protocol to the IRB for review. If exemption is found to be appropriate, the Chairperson will complete the review and

approval and notify the full IRB of the exemption at the next scheduled meeting (see IRB Chairperson's Exempt Review Form, Appendix L). The notification will be documented in the agenda of the IRB meeting. The approval of the exemption will be forwarded to the R&D committee. The R&D Committee will monitor these studies.

All exemptions claimed for research conducted in this facility or by employees or agents of this facility must be evaluated and approved by the IRB Chairperson or IRB Designee and receive concurrence from the VA Pittsburgh Healthcare System (VAPHS) Research and Development (R&D) Committee (VA Handbook 1200.5, Appendix A). The reviewer will complete an IRB Exempt Review Form (Appendix L). Investigators will be notified of the IRB determination in writing.

The following criteria are used to determine that participants are protected in exempt research:

a. The research involves no more than minimal risk to participants
b. Selection of participants is equitable
c. There are adequate provisions to maintain the confidentiality of the data and privacy interest of participants
d. If there are interactions with participants, there will be a consent process that will disclose such information as:
    i. That the activity involves research
    ii. A description of the procedures
    iii. That participation is voluntary
    iv. Name and contact information for the investigator

Additionally, in determining whether to approve an exemption, the IRB considers issues related to the organization's ethical standards such as the following:

- Is the study ethical?
- Does the study have sound research design?
- Does it involve vulnerable populations?
- Are additional protections needed?
- If applicable, are there procedures for handling participant problems or complaints?

In accordance with Federal Regulations research activities in which the only human subjects involvement will be in one or more of the minimal risk categories listed below may be deemed exempt from IRB review requirements. Exempt status cannot be applied to research involving prisoners, research focused on pregnant women, and with the exception of a category 6 exemption, FDA regulated research (unless the sponsor or sponsor-investigator receives a written waiver of IRB requirement from the FDA).

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices such as:

    a. Research on regular and special education instructional strategies, or

    b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior unless:

a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

b. 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. The Department of Veterans Affairs (VA) also includes loss of insurability in this category.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph 2, if:

a. The subjects are elected or appointed public officials or candidates for public office, or

b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the course of research and thereafter.

(4) 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.

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

*[***NOTE:*** *In accordance with VA policy, 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 the Office of Research and Development, the Office of Research Oversight, the Office of General Counsel, and the other experts, as appropriate.*

(6) Taste and food quality evaluation and consumer acceptance studies if:

a. Wholesome foods without additives are consumed, or

b. A food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration, or approved by the Environmental Protection Agency, or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

The VAPHS IRB also recognizes that in accordance with FDA regulations (21 CFR 56.104 and 21 CFR 56.105), exemptions from IRB requirement may be granted in the following instances:

(a): Any investigation which commenced before 7/27/81, and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before 7/27/81.

(b) Any investigation that commenced before 7/27/81 and was not otherwise subject to requirements for IRB review under FDA regulations before that date.

(c): Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Please refer to Section 17 for additional procedures related to emergency use of a test article and IRB notification.

If a modification is made to a protocol that has been previously determined to be exempt from IRB review, the modified protocol must be reviewed by the IRB again to ensure that the criteria for exemption have not been altered.

8. IRB Review and Approval Considerations.

The IRB will review only completed applications. IRB submission requirements are listed in Appendix U and the new submission checklist is in Appendix V.

A scientific review takes place for all submissions. For studies being submitted for peer-reviewed funding, a scientific review is conducted by a body of the investigator's peers. For investigators affiliated with a center of excellence, the review is conducted by that center's scientific review body and the recommendations are forwarded to the SRS. For investigators not affiliated with a center of excellence, the initial scientific review is conducted by the SRS. Final recommendations of the SRS are then forwarded to the R&D Committee. For studies that do not seek peer review funding, and/or are privately funded the scientific review process occurs at the section chief and service line VP level. The approval of the application by the section chief and VP is considered to indicate sound scientific design and is scrutinized by the IRB and R&D committees.

The IRB will determine that all of the following requirements are satisfied before approving proposed research:

A. Levels of Risk (38 CFR 16.102(l) and 110).

The IRB continues to evaluate research proposal risk including consideration of the study design, scientific rationale, procedures to minimize risk, process for monitoring and reporting adverse events, presence of a DSMB, scientific training and qualifications of investigators and research staff, and human subjects protection training of investigators and research staff

The risk assessment is made considering Social; Physical; Psychological; and Economic risk. Legal risk must be considered when assessing social and economic impact of participating in the study. When additional questions involving legal risk arise, the Office of Regional Counsel will be consulted. The IRB determines if the application is of minimal risk or greater than minimal risk. **Minimal risk** means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.

All research studies that have been assigned a Greater than Minimal level of risk are prohibited from enrolling subjects who are currently participating in another Greater than Minimal Risk research study unless a waiver of multiple enrollment has been granted by the IRB (See Appendix JJ- Multiple Enrollment Policy) The IRB Chairperson, or his/her designee will review all requests for waivers of multiple enrollment and make a determination as to whether multiple enrollment poses any increased risk to the prospective research subject. The Chairperson, or his/her designee, has the authority to grant the waiver, deny the waiver, or defer the request to the fully convened IRB. The fully convened IRB may grant the waiver request, grant the waiver request with stipulations, or deny the request. The investigator will be notified of the IRB's decision in writing.

In addition, the IRB determines a level of scrutiny. The IRB levels of scrutiny are as follows: *Low*, *Moderate*, and *High*. A *Low* level of scrutiny indicates a continuing review interval of 12

months. A *Moderate* level of scrutiny indicates a study continuing review interval of six months. A *High* level of scrutiny indicates a continuing review interval of three months. The IRB also re-assesses the current assigned risk level when reviewing serious adverse events.

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

To approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures that are already being performed on the subjects for diagnostic or treatment purposes.

The IRB examines the research plan, including research design and methodology, to determine that there are no obvious flaws that would place subjects at unnecessary risk. This includes the risk that the research is so poorly designed or is so lacking in statistical power that meaningful results cannot be obtained. The IRB does not hesitate to consult experts when aspects of research design seem to pose a significant problem.

The IRB also considers the professional qualifications and resources of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges. Only investigators with a VA appointment and acceptable human subjects education certification are permitted to submit proposals to the VAPHS IRB.

C. Risks Reasonable Relative to Anticipated Benefits (38 CFR 16.111(a)(2)).
The IRB determines that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result.

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

Both tangible and intangible risks to human subjects are reasonable in relation to any anticipated benefits (risk/benefit ratio) to subjects, and the importance of the knowledge that may reasonably be expected to result. Poorly designed research has no benefits and, therefore, cannot have a positive risk/benefit ratio.

(1) In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapy the subjects would receive even if not participating in the research (38 CFR 16.111(a)(2)). The risks and benefits related to genetic research must be considered. The risks and benefits may be to the individual or to groups representative of the individual subjects. These groups may be, but are not limited to, racial, ethnic, occupational, (member of one) gender or genetic group.

(2) 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.

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

To approve research, the IRB determines that the selection of subjects is equitable. The IRB evaluates the purposes of the research, the research setting, the inclusion/exclusion criteria and recruitment procedures.

In assessing whether selection of subjects is equitable, the IRB should take into account the purposes of the research and the research setting. The IRB considers the scientific and ethical reasons for including vulnerable populations such as:

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

The IRB is aware of the importance of including members of minority groups in research, particularly when the research holds out the prospect of benefit to individual subjects or the groups to which they belong. Non-English speaking participants should not be systematically excluded because of inconvenience in translating informed consent documents. The IRB ensures that subjects are not taken from one group of people because it is convenient.

The IRB considers the scientific and ethical reasons for excluding classes of persons who might benefit from research. The IRB is mindful of the desirability of including both women and men as research subjects and should not arbitrarily exclude the participation of persons of reproductive ages. Exclusion of such persons must be fully justified and based on sound scientific rationale.

Non-Veterans may be entered into VA-approved research studies only when there are insufficient Veterans available to complete the study in accordance with 38 CFR 17.45 and 38 CFR 17.92. All 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 VAPHS research.

E. Review of Informed Consent Requirements (38 CFR 16.111(a)(4) and 116).

The IRB is responsible for the review and approval of the informed consent form prepared by the investigator. The informed consent form must contain all of the required elements and each page shall be numbered. IRB approval of the consent form will be documented through the use of a stamp or preprinted box on each page of the consent form which indicates the date of the most recent IRB approval of the document, the date the approval expires (maximum of 365 days from the date of approval) and the initials of the IRB Chairperson or designee. VA Form 10-1086 shall be used as the consent form and the most recent version of the standard last pages will be incorporated (see the VAPHS Informed Consent Template, Appendix W).

The IRB will assure that:

(1) Informed consent information must be presented in a language that is understandable to the subject.
(2) No informed consent process may include any exculpatory language (a) through which the subject is made to waive, or appear to waive, any of the subject's legal rights; or (b) through which the investigator, the sponsor, the VA, or VA's employees or agents are released from liability for negligence, or appeared to be so released.
(3) Informed consent must be obtained prior to initiation of any procedures, including screening, that are performed solely for research purposes.

F. Documentation of Informed Consent (38 CFR 16.117).

It is the responsibility of the investigator to assure that the informed consent process as performed by the investigator and investigator's staff has been appropriately documented. (For detailed information regarding documentation requirements, refer to Section 11.) Documentation of the informed consent process includes filing the original executed informed consent form in the subject's case history located in the investigator's files.

(1) A copy of the signed and dated informed consent shall be provided to the subject or the subject's legal representative.

(2) The IRB will determine where other copies of the signed informed consent should be maintained, for example in the patient's medical record. The original informed consent document will be maintained in the investigator files.

(3) To protect the subject's safety, the patient record (electronic or paper) may be flagged to indicate the subject's participation in the study, and the source of more information on the study. The IRB may waive this requirement if:

a. The subject's participation in the study involves only one encounter, involves only the use of a questionnaire or the use of previously collected biological specimens.
b. 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.

(4) For studies involving greater than minimal risk, the requirements to flag the chart will not be waived.

(5) A progress note shall be made in subject's medical record that includes the date the subject was entered into the study, the title of the study, the name of the PI, and the name of the person obtaining the informed consent. If the requirement for a written informed consent has been waived by the IRB, the note must so state.

(6) A progress note shall also be placed in the subject's medical record when the subject begins study participation.

Investigators are required to maintain case histories (e.g. subject files, research records, study files) on each research subject. The level of detail required in these case histories varies with the complexity of each study; however, for all studies the case history must document that informed consent was obtained prior to participation in the study. (VA Handbook 1200.5, Paragraph 10 and FDA Policy 21 CFR 312.62b)

The Principal Investigator on a particular research study is ultimately responsible for ensuring that informed consent is obtained from each research subject before that subject participates in the research study. The Principal Investigator is not required to personally conduct the consent interview and is permitted to delegate the task of obtaining informed consent to another individual trained and knowledgeable about the particular research study and the risks and benefits of the study. The VA Research Consent Form reflects that someone other than the Principal Investigator may obtain the consent. The Principal Investigator is required to submit a "Listing of Authorized Representatives to Administer Informed Consent" (Appendix X) for IRB approval at initial review, continuing review, and as personnel change, unless the Principal Investigator is the only person administering informed consent. Co-investigators must also be on the Listing of Authorized Representatives to Administer Informed Consent if the investigator plans to allow them to sign the consent form. At the end of this list, there is an Investigator's Statement requiring the Investigator to certify that the individual providing the consent has the adequate training and knowledge to explain to the research subject the nature and purpose, the potential benefits, and the possible risks associated with participation in the study.

G. Review of Plans for Data and Safety Monitoring.

The research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects. This includes establishing a Data Safety Monitoring Board (DSMB) as required by DHHS or FDA regulations. As stated in the federal regulations governing human subject protections, 1) the research plan, when appropriate, shall make adequate provisions for monitoring of the collected data to ensure the safety of research subjects; and 2) there shall be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the research data. In addition, for studies that do not have or are not required to have a DSMB a general description of the data and safety monitoring plan must be submitted to the IRB as part of the proposed work. This plan must contain procedures for identification and reporting of adverse events. It must also include:

(1) Who will screen the data.
(2) How and where will the data for this study be stored once it is collected.
(3) Who will have access to data and how access will be regulated, restricted and documented.
(4) If the data is transferred to another site or location, how is this to be done.
(5) How will the group ensure data and safety monitoring.
(6) Provisions to make sure that no one without appropriate human subjects protection training will be allowed to access the data and that all individuals dealing with the data will have appropriate training as required by the IRB.

H. Privacy of Subjects and Confidentiality of Data (38 CFR 17.33(a), (f), .278 and .500-.571).

Adequate provisions must be taken to protect the privacy of subjects and to maintain the confidentiality of identifiable data. The IRB ensures that there are adequate provisions to protect the privacy of subjects and the confidentiality of data. Privacy refers to people and confidentiality refers to data. When thinking about privacy distinct from confidentiality, the IRB considers factors, such as:

a) The time and place where participants give information

b) The nature of the information the participants give

c) The nature of the experience given to the participant (e.g. persons might not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building.)

d) Who receives and can use the information

When research information also includes “protected health information” as defined in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, the VHA policy on release of information for research purposes shall be in accordance with the VHA Handbook 1605.1, “Privacy and Release of Information”. The collection of information about individuals is limited to that which is legally-authorized, relevant, and necessary. All information must be maintained in a manner that precludes unwarranted intrusion upon individual privacy. Information is collected directly from the subject individual to the extent possible. At the time information is collected, the individual must be informed of the authority for collecting the information, whether providing the information is mandatory or voluntary, the purposes for which the information will be used, and the consequences of not providing the information. When the Common Rule and the HIPAA Privacy Rule differ with respect the privacy and confidentiality of data, the one with the stricter rules for protection of confidentiality is to be followed.

In addition, traditionally the IRB has required that each protocol contain a Data and Safety Monitoring Plan (see Section G above).

The IRB evaluates whether or not the protocol outlines specific steps that will be taken (i.e., during study participation, after study participation, and with the publication of study results) to ensure that the subject’s participation in the research study and respective data will be confidential.

The IRB must approve the methods used to obtain information about subjects, about individuals who may be recruited to participate in studies, and about the nature of the information that may be sought. The IRB must approve the use of personally identifiable records and the methods to protect the confidentiality of research data. The IRB must determine whether a Federal Certificate of Confidentiality should be obtained. The consent form must include disclosure to participants about these actions and steps taken to protect confidentiality.

"Cold-calling" is the practice of investigators or research staff, who are unfamiliar to the potential research subject, initiating personal or telephone contact with the subject based on knowledge of confidential information (e.g., medical record information) regarding the subject

and without prior introduction to the subject. Recruitment of patients by the investigator "cold calling" is not permissible. A "cold calling" situation does not apply when the investigator is also involved in the patient's clinical care.

If initial contact with potential subjects is made by mail, the lack of a response cannot be considered to be acceptance to be approached. If subjects are asked to respond by mail, responses should be postage paid.

VAPHS IRB and R&D Committee must approve all human subject research activities conducted at VAPHS. This includes all recruitment of subjects for human research projects. Investigators or study personnel may not obtain consent from patients or distribute flyers or other advertising materials to recruit patients for human research projects unless approved by the VAPHS IRB and VAPHS Research and Development Committee.

Under certain circumstances providers may inform patients that they may qualify for studies at outside institutions. These studies must provide experimental interventions that are not available at VAPHS and all treatments available at VAPHS have been exhausted. The provider should not inform patients of such studies if the provider has a potential conflict of interest, including financial interests in the study in question. If these criteria are met the provider may inform the patient about the study but may not refer the patient to participate in the study. The patient may be given contact information regarding the study, but appointments may not be made for the patient, and the patient may not be given recruitment flyers or other advertisements unless approved by the VAPHS IRB.

VA personnel may obtain and use medical, technical, and administrative records from this or other VA facilities for approved research purposes. Requests for records from other facilities must be approved by the R&D Committee and the Medical Center Director before being submitted to the appropriate Service Director in VA Central Office.

Persons not employed by the VA can only access medical and other VA records within the restrictions of the Federal Privacy Act and other statutes. Access to VA patient records by non-VA entities for research purposes must be approved by the CRADO. Requests for such documents must be submitted to the Chief Officer, Office of Research and Development in VA Central Office at least 60 days before access is desired. Requests for information filed pursuant to the Freedom of Information Act (FOIA) must be handled in accordance with VA FOIA implementing guidelines.

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

I. Additional Safeguards for Vulnerable Subjects (38 CFR 16.111(a)(3) and VA Handbook 1200.5, Appendix D).

The IRB evaluates the study population and determines whether safeguards have been included to protect the rights and welfare of vulnerable subjects. Vulnerable populations are defined by the VAPHS as follows: pregnant women and fetuses; prisoners; mentally ill

persons and those with impaired decision making capacity; children; and economically and educationally disadvantaged persons.

VA policies dictate that research involving a fetus, in-utero or ex-utero (including fetal tissue) or in-vitro fertilization **shall not** be conducted by VAPHS investigators while on official duty at VA facilities or approved off-site facilities.

VA policies dictate that research in which pregnancy is the focus **shall not** be conducted by VAPHS investigators while on official duty at VA facilities or approved off-site facilities.

VA policies dictate that research involving prisoners **shall not** be conducted by VAPHS investigators while on official duty at VA facilities or approved off-site facilities.

Mentally ill persons or those persons with impaired decision making capacity are a vulnerable population in research. 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.

(1) IRB requirements:

(a) The IRB membership shall include at least two members who are familiar with the population to be recruited. One member shall be an expert in the area of the research and consideration may be given to adding a member of the population or a family member of such a person or a representative of an advocacy group for that population but this is not an absolute requirement.

(b) The IRB shall utilize ad hoc members as necessary to assure appropriate expertise. Such ad hoc members may not vote with the IRB or contribute to the quorum.

(2) Criteria for IRB approval:

(a) Incompetent persons or persons with impaired decision making capacity are the only suitable 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.

(b) Favorable risk/benefit ratio. The proposed research entails no significant risks, tangible or intangible or, if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision making capacity will not 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.

(c) Voluntary participation. In situations where the potential research subject is incompetent to provide informed consent, the investigator should still attempt to obtain assent from the potential subject. Some persons may resist participating in a research protocol that has been approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.
The IRB will evaluate whether assent of the participants is a requirement, and if so, request a plan for assent from the investigator. The IRB will then evaluate the plan to determine if it is adequate.

(d) Well-informed representatives. Procedures have been devised to assure 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) 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.

(3) IRB Procedures**.** The IRB shall make a determination in writing of each of the criteria listed above. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision making capacity in research projects on the basis of informed consent from authorized representatives or next-of-kin.

(a) Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. The IRB may consider several options to further protect these subjects

(b) 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.

(c) 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.

(d) Disclosures required by IRB to be made to the subject by the investigator must be made to the subject's surrogate.

(e) If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

(f) The VAPHS Ethics Committee may be requested to review this type of research as needed.

Surrogate consent may be used only when the prospective subject is incompetent as determined by the investigator in consultation with the COS and by a psychiatrist or licensed psychologist (if diagnosis is based on mental illness), after appropriate medical evaluation, and there is little or no likelihood that the subject will regain competence within a reasonable period of time or as established by legal judgment.

For potential research subjects who lack decision-making capacity and are incapable of making an autonomous decision, the following individuals are permitted, consistent with VA Regulations and Pennsylvania State Law, to provide consent to research procedures, in the following order of priority:

(1) Agent previously appointed pursuant to a Durable Power of Attorney, properly executed while the research subject possessed capacity to make decisions. If the Durable Power of Attorney grants the Agent powers to authorize medical and surgical procedures, the Agent may consent to medical research involving medical and surgical procedures, unless specifically excluded by the Principal in Durable Power of Attorney document.

(2) Guardian of the Person appointed under State Law. In Pennsylvania, a Guardian does not automatically have the power to consent to medical research. The Guardian must petition the court to obtain specific permission to engage in any experimental medical procedures.

(3) Next of kin, in the following order of priority:

Spouse
Adult Child(ren)
Parent(s)
Sibling(s)

Research involving children. The VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans and is not authorized to care for the offspring of Veterans. Therefore, research involving children shall not be conducted by VAPHS investigators while on official duty or at VA or approved off-site facilities. If an investigator wishes to perform research involving children, a waiver from the CRADO must be obtained prior to initiating the research. The only type of research involving children permissible at the VAPHS would be that involving genetic studies, these would be considered by the IRB on a case-by-case basis. VHA Directive 2000-043, “Banking of Human Research Subjects’ Specimens”, would be followed for this type of research.

J. Criteria for Requiring Review More Often than Annually (38 CFR 16.103(b)(4)(ii)).

The assigned level of scrutiny determines length of continuing review. Levels of scrutiny are described in Section 8.A.

The IRB must recognize that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. For example, when a new intervention is being tested, the risks may not be completely known. The IRB shall monitor the research project closely, and require more frequent review.

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

(1) Probability and magnitude of anticipated risks to subjects.

(2) Likely medical condition of the proposed subjects.

(3) Overall qualifications of the PI and other members of the research team.

(4) Specific experience of the PI and other members of the research team in conducting similar research.

(5) Nature and frequency of adverse events observed in similar research at this and other facilities.

(6) Vulnerability of the population being studied.

(7) Other factors that the IRB deems relevant.

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

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

VA designated IRBs shall consider the following factors in determining which studies require such independent verification:

(1) Probability and magnitude of anticipated risks to subjects.

(2) Likely medical condition of the proposed subjects.

(3) Probable nature and frequency of changes that may ordinarily be expected in type of research proposed.

(4) Prior experience with the PI and research team.

(5) Other factors that the IRB deems relevant.

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

L. Auditing and Consent Monitoring

Routine audits are selected by the Education and Compliance Office (see Appendix K) and reviewed by the Research Compliance Committee (see Appendix D). However, the IRB has the authority to request an audit of any study “for-cause” based on submissions to or findings of the IRB. Results of these audits will be forwarded to the full IRB for review and appropriate

action. The IRB also has the authority to review the results of audits managed by the Research Compliance Committee.

In considering the adequacy of informed consent procedures, the IRB may require special monitoring of the consent process by an impartial observer (consent monitor) to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

The IRB may also require that investigators include a “waiting period” within the consent process or use devices such as audio-visual aids or tests of comprehension.

M. Advertisements and Recruitment Incentives.

The IRB shall review advertisements and recruitment incentives associated with the research that they oversee. The final copy of any printed, audio-taped, or videotaped advertisements must be submitted to the IRB for approval. Advertisements, incentives, and payments are directly related to the informed consent process and must be consistent with VA and FDA guidelines. Payments that may be coercive and/or exert undue influence are prohibited. (VHA Handbook 1200.5, Section 12, “Payments for Subjects). Advertisements may not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. IRB Reviewer Checklists will be used to evaluate advertisements.

For FDA-regulated research, advertisements may not: (a) make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with FDA labeling; (b) use terms, such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational; nor (c) allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

(1) The name and address of the clinical investigator and/or research facility.

(2) The condition under study and/or the purpose of the research.

(3) In summary form, the criteria that will be used to determine eligibility for the study.

(4) The time or other commitment required of the subjects.

(5) The location of the research and the person or office to contact for further information.

(6) A clear statement that this is research and not treatment.

(7) A brief list of participation benefits, if appropriate.

Advertisements may state that subjects will be paid for participation (i.e., for lost time, travel expense) and the amount to be paid, but this information should not be emphasized (i.e., by such means as large or bold type). This should be placed in a non-prominent location.

No advertisement may contain exculpatory language through which the subject is made to waive, or appear to waive, any of the subject's legal rights. Nor can such language appear to release the investigator, the sponsor, the VA, or the VA's employees or agents from liability for negligence.

Recruitment procedures should be designed to assure that informed consent is given freely and to avoid coercion or undue influence. To evaluate this, the IRB should know from what population the subjects will be drawn, what incentives are being offered, and the conditions under which the offer will be made. Unless the advertisement is associated with a more than minor change to the protocol, it can be approved by expedited mechanism. Advertisements that are to be displayed at the VA Pittsburgh Healthcare System must also be approved by Director/Public Relations Officer after IRB approval is obtained. The IRB must approve any and all recruitment incentives to investigators, physicians, and other health care providers for identifying and/or enrolling subjects for studies. Recruitment incentives to the investigator from a sponsor may not create undue influence to recruit patients for a study and must be reasonable in relation to the work being performed. Payments which are designed to accelerate recruitment that are tied to the rate or timing of enrollment or which are designed to compensate professionals in exchange for referrals of potential subjects are prohibited at VAPHS.

N. Obtaining Informed Consent from Non-English Speakers (38 CFR 16.116)

VA regulations at 38 CFR 16.116, the Common Rule, and FDA regulations require that informed consent be obtained in language that is understandable to the subject (or the subject's legally authorized representative).

In accordance with these regulations, IRBs may require that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent. Witness requirements apply to non-English speaking subjects as well. In addition, for participants who do not speak English, the witness must be conversant in both English and the language of the participant.

When a full-length form embodying all required elements is required by the IRB to document consent, that form must be written in a language understandable to the subject. IRBs shall require that appropriately translated consent documents be submitted to the IRB for review and approval prior to their use in enrolling subjects. The IRB may utilize expedited review procedures in approving such documents if the English language consent document has already been approved, and the investigator attests in writing to the accuracy of the translation.

VAPHS IRB does not permit the use of a short form consent document in lieu of translation of the entire consent document.

O. Payment to Research Subjects (VA Handbook 1200.5, Paragraph 12).

The IRB shall review any proposed payments to research subjects associated with the research that they oversee. VA policy (VA Handbook 1200.5, Paragraph 12, Part a.) prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care. All information concerning payment, including the amount and schedule of payments, is set forth in the consent document. Payments to research subjects may not be of such an amount as to result in coercion or undue influence on the subject's decision to participate. Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation. For example, payment may not be withheld as a condition of the subject completing the research. If the subject withdraws early, payment must be prorated to reflect the time and inconvenience of the subjects participation up to that point.

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

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

(2) Others being paid. In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

(3) Comparable situations. In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.

(4) When the participant will incur transportation expenses that would not be incurred in the normal course of receiving treatment and are not reimbursed by another mechanism.

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

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

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

(3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

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

P. Compensation for Injury (38 CFR 17.85).

The IRB shall ensure that subjects are provided with accurate information about the availability of compensation and/or treatment for injury occurring in the research reviewed. However, this requirement does not apply to:

(1) Treatment for injuries due to non-compliance by a subject with study procedures; or
(2) Research conducted for the VA under a contract with an individual or non-VA institution.

Q. Certificates of Confidentiality.

Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. This is rare in the VA; however, in such situations the designated IRBs may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA. The CoC was developed to protect against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

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

R. Compliance with All Applicable State and Local Laws

All human subject research conducted at the VAPHS or by VAPHS employees or agents or otherwise under the auspices of the VA must comply with applicable state and local laws. The IRB shall familiarize itself with the requirements of all applicable state and local laws pertinent to the conduct of human subject research and shall ensure that the research it approves complies fully with all such requirements.

Content of consent form must be compliant with State law. If a potential subject has a Guardian appointed under Pennsylvania state law (20 Pennsylvania Consolidated Statute Section 5501, et. seq.), the Guardian must petition the court to engage in medical experiments (interpreted by VA Regional Counsel to be the same as medical research). If there is no specific Pennsylvania State court order allowing the Guardian to consent to medical experiments, then the potential subject's guardian cannot be requested to consent to

medical research on behalf of his/her ward. If the potential subject has a Guardian appointed under state law outside Pennsylvania, the potential subject's Guardian cannot consent to medical research until the IRB obtains an opinion from the Regional Counsel's office concluding that the Guardianship powers and duties from a particular state allow for such consent on behalf of the ward for medical research.

If a potential subject has a Durable Power of Attorney executed pursuant to Pennsylvania law (20 Pennsylvania Consolidated Statutes Section 5602), and the Durable Power of Attorney contains the following language, authorizing the agent "To authorize medical and surgical procedures," the agent may consent to medical research on behalf of the principal if the principal lacks capacity to consent to the medical research independently.

There are other state laws, which may come into play regarding certain types of research. The IRB will be educated about the following state laws by the Office of Regional Counsel at least once annually.

28 Pa. Code Section 201.29(o), Resident Rights (Nursing Homes)
29 Pa. Code Section 1001.161, Research in Prehospital Care
35 Pa. Consolidated Statutes Sections 5641 & 5642, Informed Consent for Treatment of Breast Disease
35 Pa. Consolidated Statues Section 10025, Prohibition of Tissue Sales

The IRB will refer to the Office of Regional Counsel any issues regarding interpretation of the state law.

S. Waiver or Alteration of Informed Consent Requirements (38 CFR 16.116(d), 21 CFR 50.20 and .23).

VA regulations at 38 CFR 16.116(d) and the Common Rule permit an IRB to approve a consent procedure which does not include or which alters some or all of the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. To approve such a waiver or alteration, the IRB must find and document that:

(1) The research involves no more than minimal risk to the subjects.

(2) The waiver or alteration shall not adversely affect the rights and welfare of the subjects.

(3) The research could not practicably be carried out without the waiver or alteration.

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

In the case of full board review, these findings and their justifications shall be clearly documented in IRB minutes when the IRB exercises this waiver provision. In the case of expedited reviews, these findings and their justifications is documented on the reviewer checklist which is maintained in the protocol file. This waiver provision is not applicable to

research governed by FDA regulations, and the VAPHS IRB cannot approve such alterations or waivers for FDA-regulated research (21 CFR 50.20).

Under FDA regulations (21 CFR 50.23), if consent is not deemed feasible and thus, is not obtained, the investigator and another physician not otherwise participating in the clinical investigation must certify, in writing, the following:

(1) The subject is in a life-threatening situation necessitating the use of the article.

(2) Informed consent cannot be obtained because of an inability to communicate with or obtain legally effective informed consent from the subject.

(3) There is not time to obtain consent from the subject's legal representative.

(4) There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the subject's life.

If the Investigator feels the test article needs to be used immediately to preserve the subject's life, and there is not time to make the independent determinations above, then those determinations may be delayed until after the test article is used. Within five working days after the use of the article, however, it must be reviewed and evaluated in writing as noted above. The written determinations required above must be submitted to the IRB within five working days after the use of the test article. The expedited mechanism of review can be used for requests for waiver of informed consent if other criteria for expedited review are met as specified in Section 6.L.

VAPHS IRB does not permit the use of a short form consent document in lieu of translation of the entire consent document.

T. Waiver of Documentation of Consent (38 CFR 16.117c).

VA regulations at 38 CFR 16.117(c) and the Common Rule permit an IRB to waive the requirement to obtain written documentation of informed consent. *(Note: This provision can be used only for the waiver of documentation of consent, not for waiver or alteration of consent itself.)* To approve such a waiver, the IRB must find and document **either** of the following conditions:

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

OR

(2) The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally

required outside of the research context. This provision is also applicable to FDA-regulated research.

In cases in which the documentation requirement is waived, the IRB requires that a script for verbal interaction be submitted, reviewed and approved by the IRB. Additionally, the IRB may require the PI to provide subjects with a written statement regarding the research. In the case of full board review, IRB minutes shall clearly reflect this waiver provision and the justification for its use. The expedited mechanism of review can be used for requests for waiver of documentation of informed consent if other criteria for expedited review are met as specified in Section 6.L.

In the case of expedited reviews, this waiver provision and the justification for its use will be documented on the reviewer checklist which is maintained in the protocol file.

9. Evaluation of Problems and Adverse Events

This section describes: (1) the types of events/problems that require reporting to the VAPHS IRB, (2) the procedures for submitting such events/problems, (3) the review process taken by the IRB (including possible actions taken by the IRB) and, (4) the procedures for conveying information related to these actions to the Principal Investigator and other appropriate VAPHS committees or staff members.

A. Adverse Events (21 CFR 312.66)

1. **IRB Reporting Guidelines**
   a. **Internal Adverse Events:**
   Reporting Levels:
   At the time of review all VAPHS protocols are assigned an Adverse Event Reporting Level which corresponds to the types of internal adverse events which must be reported to the IRB as described below:
   - Adverse Event Reporting Level 1 (AE1): Studies designated AE1 are required to report all serious adverse events and all unanticipated adverse events, regardless of the relatedness to the research. Typically, studies designated AE1 will be interventional studies. All studies involving the use of an investigational drug or device will be designated AE1
   - Adverse Event Reporting Level 2 (AE2): Studies designated AE2 are required to report only serious adverse events possibly or probably related to the study procedures and unanticipated adverse events that are possibly or probably related to the study procedures. Typically, studies designated AE2 will be observational, registry, or tissue banking studies.

   Investigators involved in the conduct of IRB-approved research studies shall report internal adverse events to the IRB Office within the following timeframes:

   - All fatal adverse events, whether expected or unexpected must be reported to the IRB within <u>1 business day</u> of the investigator becoming aware of the event. For studies designated AE1, fatal adverse events must be reported regardless of the relatedness to the research. For AE2 studies, only those fatal events that are possibly or probably related to the research need to be reported. (*Note: It is recognized that the information available during this 24 hour period may not be sufficient to permit accurate completion of the required adverse event reporting forms. However, the IRB should, at a minimum, be notified of the fatal adverse event during this time frame, with subsequent follow-up submission of a more detailed written report.*)

   - All serious, but not fatal events, whether expected or unexpected, shall be reported to the IRB within <u>3 business days</u> of the investigator becoming aware of the reaction. This will include all serious, but not fatal, events regardless of relatedness to the research for AE1 studies and only those serious, but not fatal events that are, at a minimum, possibly related to the research for AE2 studies.

- All unexpected, but not serious adverse events shall be reported to the IRB within 5 business days of the investigator becoming aware of the reaction. This will include all unexpected, but not serious adverse events, regardless of relatedness to the research for AE1 studies, and all unexpected, but not serious adverse events that are, at a minimum, possibly related to the research for AE2 studies.

b. External Adverse Events:

When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether the report identifies the adverse event as being:

1) Unanticipated/Unexpected
2) Related or possibly related to participation in the research; and
3) Serious or otherwise one that suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the investigator determines that all three of the above criteria have been met, the event must be reported to the IRB within 5 business days of the investigator's notification of the event.

If the event does not meet all three of the above criteria, the event must be reported to the IRB at the time of continuing review (as described in Section 9.A.2.b below)

2. Submission Procedures:

a. Adverse Events meeting the IRB Reporting Guidelines (as described in Sections 9.A.1.a and 9.A.1.b) will be submitted to the IRB Office on the VAPHS Adverse Event Reporting Form (See VAPHS Adverse Event Reporting Form- Appendix R).
The PI completes the Adverse Event Reporting Form, provides a brief written summary of the event and submits the form and summary to the IRB office. (Note: When the study is part of a multi-site trial or is a pharmaceutical industry sponsored trial, a standard AE reporting form may already be in use to provide details of the event to the sponsor. These reports can be attached to the VAPHS AE Reporting Form in lieu of a written summary. If the PI recognizes that the Adverse Event involves risk to subjects or others and a modification to the IRB consent and/or protocol is required, he/she may also submit revised copies of the consent and/or protocol, as well as a Modification Request Form. The IRB Office will provide the investigator with a written receipt of the submission.
b. In addition, all external adverse events (regardless of whether they meet the reporting guidelines described in 9.A.1.b) will be summarized and reported to the IRB on the VAPHS External Adverse Event Log (See VAPHS External Adverse Event Log- Appendix KK) at the time of continuing review.

3. **Review Procedures:**

   a. The IRB Office Staff forward the report to the IRB Chairperson, Vice-Chairperson or a qualified member of the IRB designated by the Chairperson to review the report. The reviewer will use the AE Evaluation Form to determine if the event raises new concerns about risks to subjects or others.
   b. If the event does not raise new concerns (if, for example, the likelihood, severity and specificity are adequately described in the protocol, investigator's brochure, and informed consent document), the reviewer should document this determination in writing. The report along with documentation of the reviewer's determination (as indicated on the AE Evaluation Form) is placed in the IRB Research Application (Protocol) file and listed on the agenda of the next IRB meeting.
   c. If the event is determined by the IRB reviewer to raise new concerns about risks to subjects or others, the reviewer will forward the report, with the reviewer's recommendations (as indicated on the AE Evaluation Form), for review at the next convened meeting of the full board;
   d. During the meeting of the convened IRB, the committee determines whether the event meets the definition of an unanticipated problem and whether further action is required. IRB actions may include:
      - Request for further clarification from the investigator
      - Modifications to the protocol (e.g., additional tests or visit to detect similar events),
      - Modifications to the consent form
      - A requirement to inform already enrolled subjects about the risk
      - A change to the continuing review period
      - Additional monitoring by the IRB
      - Further inquiry into other protocols utilizing the particular drug/device/procedure in question
      - Suspension or termination of the research
      - Reporting the event to institutional officials and/or regulatory agencies
      - No action

      The board's decision will be documented in the meeting minutes.

   e. In instances where the reviewer has immediate concerns about the safety and welfare of research subjects that cannot wait until the next scheduled meeting of the fully convened IRB, he/she has the authority to take immediate action(s) (e.g., call for an emergency meeting of the convened board, suspend study procedures, etc.) as appropriate, as long as the justification for such actions is documented. The convened IRB will review the report, with the reviewer's recommendations at the next meeting and make a determination as in d. above.

4. **Notification(s):**
   It is the responsibility of the IRB Chair or designee to provide prompt written notification of the review of all adverse events and the subsequent actions taken. A copy of the notification will be maintained in the IRB file.

5. **Reporting**
   Adverse events will be reported to VAPHS Officials and the appropriate regulatory agencies as described in Section 9.F.

B. Unanticipated Problems Involving Risks to Subjects or Others [45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]

This policy applies to all human subjects' research conducted in the VA, as well as to all investigators, IRB members and staff, R&D members and staff, and institutional officials. Others who may report possible unanticipated problems include subjects, subjects' family members, the VA patient relations offices, sponsors and other auditors, and others not involved with the research project but having information about a possible unanticipated problem.

1. **IRB Reporting Guidelines:**
   Possible unanticipated problems should be reported regardless of whether they occur during the study, after the study is completed, or after a subject or subjects have withdrawn/been withdrawn or completed the study. Although unanticipated problems are often definitely or possible related to study procedures, they are not necessarily be caused by those procedures

   Examples of event that should be reported to the IRB for review and subsequent determination may include (but are not limited to): (1) unresolved complaints or violent or illegal behavior, (2) loss of research data, (3) breach of privacy or confidentiality, (4) reports of injury or death involving subject or others, (5) a research subject becomes unexpectedly pregnant or is incarcerated, (6) pharmacy or lab errors, (7) scientific reports, (8) interim data analyses, (9) DSMB findings, (10) inability to conduct specified safety assessments, (11) loss or disclosure of individually identifiable protected health information, (12) findings of scientific or ethical misconduct, (13) sponsor monitor reports, (14) protocol deviations, exceptions or violations, (15) compliance reports, (16) events that require prompt reporting to sponsor, institutional or oversight officials, (17) IRB Continuing Reviews and (18) adverse events.

   Reports of events may come from any person, office, committee or organization having information about a possible unanticipated problem and should be reported as soon as possible. Principal investigators, however, must report the following events to the IRB as soon as possible, but <u>no later than 5 business days</u> after notification of the event:

- All injuries, side effects, breaches of confidentiality, deaths, or other problems (with the exception of Adverse Events which fall under the policy described in Section 9.A) that occur any time during or after the research study (either internal or external), which in the opinion of the principal investigator: (a) Involve harm to one or more subjects or others, or placed one or more subjects or others at increased risk of harm; (b) are unanticipated/unexpected; and (c) are related or at least possibly related to participation in the research (In accordance with OHRP

guidance, and event is considered possibly related if there is a reasonable possibility that the event may have been caused by the procedures involved in the research).

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.

- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research subject.

- Incarceration of a subject or unexpected pregnancy of a subject.

- Event that requires prompt reporting to the sponsor

- Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team

- Any unauthorized use, loss, or disclosure of individually identifiable patient information or violation of VAPHS information security requirements (Note: These incidents require reporting as described in VAPHS Policy on Reporting Loss or Theft of VA Research Data)

- Any protocol deviation (meaning an accidental or unintentional change to the IRB approved protocol).

- A protocol exception should be a one-time event and the IRB approval for its implementation does not change the approved protocol. If the exception being requested will apply to other subjects, a modification request of the protocol and informed consent (if applicable) should be submitted to the IRB.

  Examples include (a) enrollment of a subject who fails to meet current IRB approved inclusion or exclusion criteria or (b) deviations from scheduled visits or procedures

  To request a protocol exception, investigators must submit a Protocol Exception Request form to the IRB. Requests will be reviewed by the IRB Chair or Designee. The investigator will be notified, in writing, of the decision.

- Unanticipated adverse device effect.

2. Submission Procedures:

a. Events reported by the PI:

The PI completes the VAPHS Unanticipated Problems Reporting Form (See

VAPHS Unanticipated Problems Reporting Form -Appendix P), attaches any supporting documentation (de-identified) and submits the information to the IRB office. If the PI recognizes that the event/problem involves risk to subjects or others and a modification to the IRB consent and/or protocol is required, he/she may also submit revised copies of the consent and/or protocol, as well as a Modification Request Form.

b. Events reported by other persons, committees, organizations, etc:
Any such events must be reported to the ACOS/R&D (either in writing or via verbal communication). If the Unanticipated Problem is deemed a compliance issue, the ACOS/R&D will prepare a written summary of the event and forward a copy of the summary to the Research Compliance Office to include on the agenda for the next meeting of the Research Compliance Committee (RCC). (See RCC Policies- Appendix D). If the ACOS/R&D determines that the event is not a compliance issue it will be forwarded to the IRB office for review.

3. Review Procedures:

a. The IRB Chairperson, Vice-Chairperson or a qualified member of the IRB designated by the Chairperson reviews all such reports. The reviewer must make a determination whether a reported event meets the definition of an unanticipated problem involving risks to subjects or others. (See Appendix P)

b. If it is determined that the event does not meet the definition of an unanticipated problem, no action is required, and the reviewer should document this determination in writing. The report along with the reviewer's determination is placed in the IRB Research Application (Protocol) file and listed on the agenda of the next IRB meeting.

c. If the event does meet the definition of an Unanticipated Problems report, along with the reviewer's recommendations (as documented on the Unanticipated Problem Evaluation Form, is forwarded to all IRB members for review at the next convened meeting. The IRB Reviewer has access to the protocol file in the IRB office, if review of additional materials is found to be necessary to properly adjudicate the unanticipated problem report. Should the fully convened IRB require the protocol file in its entirely at the time of the meeting, the file will be provided to the committee during its deliberations.

d. During the convened meeting review, the IRB may request one or more of the following actions:
    - Modification of the protocol
    - Modification of the information disclosed during the consent process
    - Providing additional information to current subjects (This must be done whenever the information may relate to the subject's willingness to continue participation) and identifying who should provide that information
    - Providing additional information to past subjects and determining who should provide that information
    - Requiring current subjects to re-consent to participation
    - Requesting a for-cause internal audit
    - Coordinating corrective action with other services in the medical center (lab, pharmacy, nursing service, medical service, surgical service etc.) to resolve the problem.

- Referring the problem to other organizational entities (e.g., legal counsel, risk management, institutional official, RCC, etc)
- Alteration of the frequency of continuing review
- Observation of the research or the consent process
- Requiring additional training of the investigator and/or the research staff
- Notification of investigators at other sites
- Reporting the event to institutional officials and/or regulatory agencies
- Suspension or termination of the research according to IRB SOP (See Section 9.E)
- Obtaining additional information
- Revise policies and procedures
- Taking no action

The board's decision will be documented in the meeting minutes.

e. If the reviewer has immediate concerns about the safety and welfare of research subjects that cannot wait until the next fully convened IRB meeting, the reviewer has the authority to take immediate actions (e.g., call for an emergency meeting of the convened board, suspend study procedures, etc.) as appropriate, as long as the justification for such actions is documented on the Unanticipated Problems Evaluation Form. The convened IRB will review the report, with the reviewer's recommendations at the next meeting and make a determination as in d. above.

4. Notification:

a. Notification to the Investigator:

It is the responsibility of the IRB Chair or designee to provide prompt written notification of review of all unanticipated problems involving risk to subjects or others and the subsequent actions taken. A copy of the notification will be maintained in the IRB file.

b. Notification to Appropriate VAPHS Staff

It is the responsibility of the IRB Chair or designee to provide prompt written notification of any unanticipated problem involving unauthorized use, loss, or disclosure of individually identifiable patient information or violation of VAPHS information security requirements to the VAPHS Privacy Officer and/or Information Security Officer.

5. Reporting:

Unanticipated Problems will be reported to VAPHS Officials and the appropriate regulatory agencies as described in Section 9.F.

C. Non-compliance

Allegations of research non-compliance are initially reviewed by the Research Compliance Committee (RCC) – (Appendix D). At the conclusion of RCC review, any non-compliance determined to be serious or continuing and/or any non-compliance that

potentially impacts human subject safety will be forwarded to the IRB office to be included on the next IRB agenda for full board review. A copy of all relevant items reviewed by the RCC, and any correspondence between the RCC and the investigator, along with the RCC's recommendations will be forwarded to the IRB Office by the Research Education and Compliance Office. Copies of these items will be provided to all members of the IRB as part of their agenda packet. Additionally, a primary reviewer will be assigned by the IRB Chair or Designee to evaluate the non-compliance. The IRB has full authority and shall take appropriate action to prevent harm to subjects to protect subject rights and to ensure the continuing safety of research subjects. IRB analysis of the problem, assessment of harm to subjects and use of corrective actions described below will apply. Investigations of research non-compliance involving human research activities will be conducted under due process and the rights of all individuals involved will be respected.

1. **Examples of Materials Provided to and Reviewed by the IRB**
   - A copy of written allegations or a summary of verbal allegations.
   - A copy of an accused individual's response to allegations or a summary of his/her verbal response.
   - A copy of relevant internal or external audits or reports.
   - A summary, if any, of relevant previous findings of serious or continuing non-compliance.
   - As warranted, any relevant IRB documents.
   - As warranted, parties involved may be requested to attend an IRB meeting to address allegations or findings of non-compliance.
   - As warranted, any other information felt to be relevant to the review of the allegation by any of the parties involved.

2. **IRB Considerations when Evaluating Serious or Continuing Non-compliance**
   - Did it or could it result in serious harm to subjects?
   - Did it or could it significantly impact subject safety?
   - Did it or could it significantly impact the research record or data integrity?
   - Was it an isolated event, first occurrence or part of a pattern?
   - Was it reported by the investigator or by a third party?
   - Was it intentional?
   - Was it reckless?
   - Were laws, regulations or policies violated?
   - What caused the problem?
   - What needs to be done to prevent recurrence?
   - What type of corrective action plan is needed?
   - Should the project be suspended or terminated?

3. **IRB Action Considerations for Non-Compliance Determined to be Serious or Continuing**
   - Require a corrective action plan. If a problem persists (i.e. there has not been compliance with the corrective action) after the HRPP has identified it as a problem, complete an analysis and provided written notification of corrective action, then the non-compliance will be considered to be continuing non-

compliance and will be reported to institutional officials, regulatory agencies and sponsors if applicable.

- Suspend or terminate the study in question (or other studies, if applicable) and notify institutional, regulatory and sponsor officials.
- Place restrictions on this or other studies. (e.g., stop enrollment, not allow initiation of new studies.
- Request a for-cause internal audit.
- Determine if modification of the research and/or re-training of study staff are a condition of re-approval. Determine if the research data can be used.
- If the IRB determines that additional training will not resolve the problem privileges to conduct research will be restricted or terminated.
- Determine if subjects (current and past if warranted) should be notified, when subjects should be notified, how subjects should be notified, what information should be provided to the subjects, and who should provide subjects with such information. The IRB makes these determinations based upon what it judges to be in the subject's best interest and understands that the information and the manner in which it is conveyed to subjects could influence a subject's decision to continue participation in the research.
- Determine if a new investigator needs to assume responsibility for the study and determine if other research staff changes are necessary.
- Determine if the consent form needs revision, if subjects should be re-consented or if the consent process should be changed.
- Assign an outside monitor to supervise the continuation and/or withdrawal process.
- Determine an appropriate Continuing Review timetable.
- As warranted, coordinate actions with other services in the medical center (lab, pharmacy, nursing service, medical service, surgical service etc.).
- Concur with the recommendation made by the RCC.
- Determine that non-compliance is not serious or continuing.
- Any other action the IRB deems appropriate.

The board's decision will be documented in the meeting minutes.

4. Notification:

a. Notification to the Investigator:

It is the responsibility of the IRB Chair or his/her designee to provide prompt written notification to the Principal Investigator of any IRB determination of non-compliance that impacts subject safety and/or welfare, and any subsequent actions required. A copy of the notification will also be provided to the PI's supervisor. A copy of the notification will be maintained in the IRB file.

b. Notification to Research Compliance Committee:

It is the responsibility of the IRB Chair or his/her designee to provide prompt written notification to the Research Compliance Committee of any IRB determination of non-compliance and any subsequent actions. A copy of the notification will be maintained in the IRB file.

5. Reporting:

Serious or continuing non-compliance will be reported to VAPHS Officials and the appropriate regulatory agencies as described in Section 9.F.

D. Research Misconduct

Allegations of research misconduct are handled in accordance with *VHA Handbook 1058.2, Research Misconduct* and are overseen by the RCC and ACOS/R&D).
ACOS/R&D will inform the IRB if the alleged scientific misconduct potentially impacts human subject safety. The IRB has full authority and shall take appropriate action to prevent harm to subjects to protect subject rights and to ensure the continuing safety of research subjects. IRB analysis of the problem, assessment of harm to subjects and use of corrective actions described above will apply. Investigations of research misconduct involving human research activities will be conducted under due process and the rights of all individuals involved will be respected.

E. Suspension or Termination of IRB Approval of Research (38 CFR 16.113).

1. Review Procedures:

The IRB has the authority to terminate or suspend its approval of a research protocol that is not being conducted in accordance with regulatory or IRB requirements or that is associated with or has the potential to cause serious harm to human research subjects. If the IRB Chairperson (or his/her designee) has immediate concerns about the safety and welfare of research subjects that cannot wait until the next fully convened IRB meeting, he or she may suspend or terminate study approval as long as the justification for such actions is documented and included in the meeting agenda for the next meeting of the fully convened IRB. The IRB may also vote in a convened meeting to suspend or terminate approval. In this instance, the IRB will document its decision in the meeting minutes.

The IRB will not review a new submission from an investigator who has a for-cause suspended study. For-Cause indicates that a compliance issue has been identified and action has been taken by the RCC or IRB due to non-compliance. Exceptions to this policy can be granted on a case-by-case basis by the RCC or RCC Chairman.

2. Subject Safety Considerations:

Once notified of the suspension, the PI must immediately submit to the IRB Chairperson a list of all enrolled research subjects to date. The PI must also specify those subjects for whom suspension of the research would cause harm. The IRB Chairperson, with appropriate consultation with the Chief of Staff (COS) will determine if those subjects may continue in the research. Note: If the study is FDA-regulated, the COS and IRB Chair must follow FDA requirements in 21CFR 56.108(b)(3) in making their decision.

If study approval is terminated the IRB (either the fully convened board, or the Chair/designee, in more urgent situations) must determine if enrolled subjects should be notified. When follow-up of the subjects for safety or effectiveness reasons is

permitted or required by the IRB, the subjects should be so informed and any adverse events or other outcomes identified during follow-up should be reported to the IRB.

3. Conditions for Re-Approval:
In the case of suspended studies, the conditions set forth at the time of suspension must be met and IRB review and re-approval must occur prior to re-initiation of the research. The PI must submit a continuing review application and the IRB will conduct continuing review as set forth in Section 7.c. Once the study has been re-approved, the IRB Chair/designee will be responsible for notifying the investigational pharmacist (if applicable).

4. Notification:

a. Notification to the Investigator:
The IRB chair or designee will notify the PI of its decision in writing within 14 days of the determination. The notification will include a written statement of the reasons for the IRB's actions. In cases of suspension, explicit terms and conditions under which the suspension will be lifted will also be included in the notification. The investigator shall be provided with an opportunity to respond in person, at a fully convened meeting, or in writing. A copy of the notification will also be provided to the PI's supervisor.

b. Notification to the Investigational Pharmacist:
It is the responsibility of the IRB Chair or his/her designee to provide prompt written notification to the Investigational Pharmacist of any IRB initiated suspensions or terminations of research projects that include use of an investigational drug.

c. Notification to Research Compliance Committee:
It is the responsibility of the IRB Chair or his/her designee to provide prompt written notification to the Research Compliance Committee of any IRB initiated suspensions and terminations of IRB approved research projects This does not include expirations of IRB approval.

d. Notification to the R&D Committee:
It is the responsibility of the IRB Chair or his/her designee to provide prompt written notification to the R&D Committee of any IRB initiated suspensions and terminations of IRB approved research projects.

F. Reporting to VAPHS Officials and Regulatory Agencies

Please refer to the VAPHS R&D Reporting Policy for guidelines and procedures for reporting to institutional officials and regulatory agencies.

10. Subject and Community Interactions with the IRB

A. The research consent form template includes a mandatory section for study contact information (names, titles, addresses, and telephone numbers for all contacts) in three specific areas:

- General questions about the research are referred to the principal investigator and/or other members of the research team.
- Questions about subjects' rights are referred to the Associate Chief of Staff/R&D, VA IRB.
- Questions about possible research-related injuries or side effects are referred to the research team or other qualified clinician, depending upon the nature of the research. Greater-than-minimal-risk studies are required to provide information for a clinician-investigator who is knowledgeable about the study and qualified to address the medical problem be available 24 hours a day to take subjects' calls.

The internet web site for the Office of Research includes the list of names, titles/positions, telephone numbers, addresses, and e-mail addresses for the Associate Chief of Staff/R&D and all research staff members

Once a concern or complaint is received by the VAPHS Office of Research and Development, the recipient documents the complaint in writing and forwards to the Associate Chief of Staff/R&D. The ACOS/R&D, in consultation with the Research Compliance Office and senior level administration, if necessary, determines if any immediate investigation or action is required and whether or not the complaint meets the definition of an unanticipated problem involving risks to subjects or others. See the RCC SOPs section V.4.c for additional information regarding the review of complaints.

The VAPHS Office of Research maintains an internet web site which lists relevant contact information (i.e., names, titles/positions, addresses, telephone numbers, e-mail addresses). Additional outreach efforts to the general public include an annual research week, where the focus is on disseminating information about the Office of Research and research studies being conducted at VAPHS in forums that are open to veterans utilizing services at the VAPHS as well as for Veterans' Service Organizations. Participant directed outreach activities during Research Week may include, but are not limited to participant satisfaction and opinion surveys, town hall meetings, roundtable discussions, structured interviews of past and current participants. In addition, a quarterly newsletter published by the Office of Research and distributed to all divisions for display and is also made available to the public on the VAPHS Research and Development web site.

B. Community Outreach Activities

The VA sponsors "Research Week" annually in May. The VAPHS uses Research Week as an opportunity to conduct and evaluate community outreach activities. Veterans involved in research are surveyed about their experiences and their satisfaction with the VAPHS Research Program. The Veterans' responses are evaluated by the VAPHS Research

Education and Compliance Office and compiled into a report which is reviewed by the HRPP Executive Committee, who will initiate a plan of action for changes or provide guidance to the research community, if needed.

11. Required Elements of Informed Consent (VA Handbook 1200.5, Appendix C).

A major requirement of research involving human subjects is that investigators must obtain the informed consent of prospective subjects before they can be included in research. Informed consent presumes two simultaneous concepts: informed decision-making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits to reach an informed decision as to whether they will voluntarily participate. Prospective subjects or their legally authorized representative must be given sufficient opportunity to consider whether or not to participate. Subjects must give consent without coercion or undue influence.

The informed consent template(s) included in the Appendix provides guidance on the wording and order. Some sections, indicated in the template, must be included in all informed consent documents without modification or deletion. The VA Form 10-1086, VA Research Consent Form, must be used, approved by the IRB and signed and dated by the subject or the subject's legally authorized representative (Appendix W). A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document. An individual listed on the research staff form may not serve as a witness to the participant or the legally authorized representative signature.

In some cases the IRB or the sponsor may require a witness to monitor the consent process. In these situations, if the witness to the participant's signature is the same person and needs to serve both capacities, a note to that effect is placed under the witness's signature line. The IRB recommends that the informed consent document be written in no more than 8th grade-level English.

The informed consent process begins when the research study is first described to the potential subject and continues throughout the duration of the research study. Some studies are granted a waiver of **documented** informed consent for all or part of the study. In these cases the informed consent script replaces the informed consent document, but the required content of the informed consent process remains the same.

A. Eight Required Elements of Informed Consent. All informed consent documents and informed consent scripts must include the eight required elements of informed consent.

1. **Research Statement.** The research statement must include the following:

   (a) A statement that the study involves research.

   (b) An explanation of the purposes of the research.

   (c) An explanation of the expected duration of subjects' participation.

   (d) A description of what procedures will be followed.

(e) Identification of any procedures that are experimental.

If the treating physician is also the research investigator, some subjects may not realize they are participating in research, but believe they are just being treated for their condition. By specifying the purpose of the research and describing experimental procedures, it is intended that subjects will be able to recognize the difference between research and treatment.

2. Reasonably Foreseeable Risks or Discomforts. Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. When applicable, the frequency of expected risks should be included.

3. Reasonably Expected Benefits to Subjects or Others. Informed consent information must describe any benefits to subjects or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on subjects. It should be noted that most studies will not directly benefit the subject and this should be stated as such. Payment for subject's participation in a research project is not to be considered as a benefit of the research.

4. Appropriate Alternatives. Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject. Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives. It is not sufficient simply to state, "the doctor will discuss alternatives to participating." In studies that do not involve treatment the only alternative may be to decline participation.

5. Extent of Confidentiality. Even in cases where protected health information is not accessed or collected (e.g. survey studies of providers), informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained (or not maintained). Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' private records. In some research, loss of privacy may be the greatest risk of participation.

According to the Privacy Rule of the Health Information Portability and Accountability Act (HIPAA), use and disclosure of protected health information (PHI) is subject to patient authorization. Unless the IRB waives the requirement for authorization to use PHI, informed consent must include the required elements for authorization. The authorization must include:

(a) Specific health information to be used.
(b) People/organizations who may use or disclose the information.
(c) People/organizations who will receive the information (if applicable).

(d) Purpose of the use or disclosure.
(e) Expiration date or event.
(f) Right to refuse to sign the authorization.
(g) Right to revoke the authorization.

6. Compensation or Treatment for Injury. Informed consent information for research involving more than minimal risk must include explanations regarding:

(a) Whether any compensation is available if injury occurs.

(b) A statement that medical care and treatment for injuries suffered as a result of participating in a VA research program is available if injury occurs.

(c) A description of any such compensation or treatments or where more information about them is available.

(d) A description of any applicable state law.

7. Contact Information. Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:

(a) For answers to questions about the research. The PI and other members of the research team are appropriate contacts for this information.

(b) For answers to questions about subjects' rights. The ACOS/R&D is the designated contact for this information. Those studies for which the ACOS/R&D is also the Principal Investigator, the contact person for questions regarding subject's rights' is the Administrative Officer for Research & Development.

(c) In the event of a research-related injury occurs. Depending upon the nature of the research, the research team or other qualified clinician may be designated as this contact.

See the VAPHS Emergency Contact Information Policy and Guidance, Appendix Y, for more information.

8. Voluntary Participation Statement. It is particularly important in the VA context for subjects and prospective subjects to understand and have complete confidence that failure to participate will not jeopardize their VA-provided care. Informed consent information must contain clear statements of the following:

(a) Participation in the research is voluntary.

(b) Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.

(c) The subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

B. Additional Elements Where Appropriate.

Where appropriate, the regulations require that one or more of the following six additional elements are included in the informed consent information:

1. Unforeseeable Risks to Subjects, Embryos, or Fetuses. Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that some risks are currently not known or not foreseeable.

2. Investigator-Initiated Termination of Participation. There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research). The informed consent information must specify these circumstances.

3. Additional Costs. If subjects must bear any additional costs (transportation, time away from work, health costs, etc.), these must be disclosed in the informed consent information. Any such costs must be consistent with Federal laws concerning veterans' eligibility for medical care and treatment.

4. Early Withdrawal/Procedures for Termination. Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.

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

6. Approximate Number of Subjects. When applicable, the informed consent information should disclose the approximate number of subjects to be enrolled.

C. Additional VA-Specific Information. (VA Handbook 1200.5, Appendix C).

VA policy stipulates that informed consent information include the following elements where appropriate:

1. Payment for Treatment. Informed consent information must include a statement that veteran-subjects shall not be required to pay for treatment received as a subject in a VA research program. Investigators should note, however, that veterans in the "discretionary work load" category are subject to co-payments, if so indicated by a means test.

2. Authorization for Use of Bodily Fluids, Substances, or Tissues. If the investigator believes that bodily fluids, substances, or tissues could be part of or lead to the development of a commercially viable product, the informed consent information should include the following statement:

> You authorize the use of your bodily fluids, substances or tissues in this research. It is possible that commercially profitable products may someday be developed from these bodily fluids, substances, or tissues. There are no plans to share any profits from such products with the subjects who were the source of these bodily fluids, substances, or tissues.

3. Consent for Picture and/or Voice. VA Form 10-3203 is required to be completed and submitted with the initial IRB application when appropriate. The PI must obtain consent using VA form 10-3203 from a subject prior to capturing images or voice of the subject, or other persons including VA employees.

4. Payment for participation. The informed consent information should include a clear statement describing any payment the subject is to receive for participation, the required conditions for payment, and the payment schedule. Since VA regulations at 38 CFR 16.116(a)(8), the Common Rule, and FDA regulations all state that subjects may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. For this reason there should be a description of how payment will be prorated and calculated for subjects who withdraw early. See section 8.O. for information regarding whether payment to subjects is appropriate.

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

D. Non-English Speaking Subjects.

The consent document must be in language understandable to the subject. When the prospective subject is fluent in English, and the consent interview is conducted in English, the consent document should be in English. However, when the study subject population includes non-English speaking people so that the clinical investigator or the IRB anticipates that the consent interviews are likely to be conducted in a language other than English, the IRB should assure that a translated consent form is prepared and that the translation is accurate.

A consultant may be utilized to assure that the translation is correct. A copy of the translated consent document must be given to each appropriate subject. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may not be substituted for a written translation.

12. Behavioral and Social Science Research.

Behavioral and Social Sciences research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This section includes discussion of when exemption and expedited review are appropriate for this type of research.

A. Social and Psychological Harms

When evaluating behavioral and social science research, IRBs should carefully examine the research to determine the probability of risk of harm to subjects.

(1) The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.

(2) The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.

(3) If information is being collected on living individuals other than the primary "target" subjects the IRB should consider the risk of harm to those "non-target" individuals, as well.

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

B. Privacy and Confidentiality Concerns.

The use of confidential information is an essential element of much social and behavioral research.

(1) It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements. These have been discussed previously in [other sections], and will also be discussed briefly below.

(2) It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a

breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

C. Safeguarding Confidentiality.

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

(1) When reviewing survey and interview research the IRB members need to be particularly aware of the regulatory provision at 38 CFR 16.117(c)(1) for waiving documentation of consent when a signed consent form constitutes the only link between the research and the subjects and would itself be a risk to the subjects (Section 8.S.).

(2) Among the available methods for ensuring confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

(3) Department of Veterans Affairs (VA) regulations at 38 CFR 16.116(a)(5), Food and Drug Administration (FDA) regulations, and the Common Rule require that subjects be informed of the extent to which confidentiality of research records will be maintained.

(4) IRBs should be aware that Federal officials have the right to inspect and copy research records, including consent forms and individual medical records, to ensure compliance with the rules and standards of their programs. FDA requires that information regarding this authority be included on the consent information for all research that it regulates. Identifiable information obtained by Federal officials during such inspections is protected by the provisions of the Privacy Act of 1974.

(5) IRBs may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. (See Section 8.Q.)

D. Expedited Review of Behavioral and Social Science Research

Research that presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998, Federal Register FR 60364-60367 and FR 60353-60356 might be reviewed by the IRB utilizing expedited procedures.

The categories discussed below are particularly applicable to social and behavioral research. Expedited Categories 1 through 4, 8, and 9 do not apply to behavioral and social science research and are described in Section 7.H.

(1) **Expedited Review of Research Involving Existing Data and Documents (Expedited Category #5)*.*** Minimal risk research involving materials, (including data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes, may be reviewed using expedited procedures.

(a) Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.

(b) Non-exempt research involving materials that will be collected in the future for a non-research purpose.

(2) **Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes (Expedited Category #6).** The IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes.

(3) **Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies (Expedited Category #7).** The IRB may utilize expedited procedures to review the following:

(a) Research on individual or group characteristics or behavior, or

(b) Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

(c) This category covers a wide range of non-exempt social and behavioral research activities when they present no greater than minimal risk to subjects. Examples include, but are not limited to, research on perception, cognition, motivation, identification, language, communication, cultural beliefs or practices.

E. Research Involving Deception or Withholding of Information.

When reviewing research involving incomplete disclosure or outright deception, the IRB must apply both common sense and sensitivity to the review.

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

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in VA regulations and the

Common Rule and 38 CFR 16.116(d). Specifically, the IRB must find and document that all four of the following criteria have been satisfied (see Section 8.S.):

(1) The research presents no more than minimal risk to subjects.

(2) The waiver or alteration shall not adversely affect the rights and welfare of the subjects.

(3) The research could not practicably be carried out without the waiver or alteration.

(4) Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB will consider each criterion in turn, and document specifically (in the minutes of its meeting and/or in the IRB protocol file) how the proposed research satisfies that criterion. Deception in research is not allowed in greater than minimal risk studies.

13. IRB Review of Research Using Data and Specimens.

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. They often use or create tissue, specimen, or data repositories (banks).

A. Prospective Use of Existing Materials.

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

(1) Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under VA regulations at 38 CFR 16.101(b)(4) and the Common Rule because the materials in these studies are not in existence at the time the study is proposed and initiated. (Note: The regulations at 38 CFR 16.101(b)(2) do allow for the exemption of certain types of prospective data collection. See Section 6.K.)

(2) However, the IRB may utilize **expedited procedures** (under expedited category #5, see Sections 6 and 7) to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

B. Retrospective Use of Existing Materials.

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

(1) Such research may be exempt under Department of Veterans Affairs (VA) regulations at 38 CFR 16.101(b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects.

(2) If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.

(3) However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited review had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

C. Research Utilizing Large Existing Data Sets.

Biosocial and bio-behavioral research often involves the use of large, existing data sets.

When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information (see Section 13.B.2 above). Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of large, existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

(1) In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

(2) If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 38 CFR 16.116(d). Many times, a waiver of consent will be appropriate.

(3) In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities. Anonymized data cannot contain any of the 18 HIPAA identifiers and must be anonymized under Common Rule Standards.

(4) An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP) and VA (see d. below).

D. Research Using Data or Tissue Banks (also called Repositories).

Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

VA policy ("Banking of Human Research Subjects' Specimens" VA Directive 2000-043) specifies that human biological specimens, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, must be maintained at VA-approved tissue banks, whether the research is funded or unfunded, and regardless of the funding source. Instructions for requesting an off-site waiver for tissue banking are available on the Research website.

Tissue Bank activities involve three components: (a) the **collectors** of data or tissue samples; (b) the **bank/repository** storage and data management center; and (c) the

recipient investigators. Under a repository arrangement, an IRB formally oversees all elements of repository activity; setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters involve formal, written agreements stipulating conditions as follows:

(1) The repository shall not release any identifiers to the investigator.

(2) The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.

(3) The investigator shall use the data only for the purposes and research specified.

(4) The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

The following guidance is applicable to all VA-approved research protocols that collect, use, or store human biological specimens.

a. Human biological specimens collected under a VA-approved protocol are not considered to be "banked" (stored) specimens if the specimens are used for only the specific purposes defined in the protocol and are destroyed either when the specific testing/use is completed or at the end of the protocol. If the specimens are sent to a non-VA institution for testing/use as defined in the protocol, once the specific analyses are performed, the remainder of the specimens must be destroyed or returned to the VA for destruction. If the specimens are destroyed at another institution, that institution must certify the destruction of the specimens in writing.

b. Specimens collected and stored for future research purposes are considered "banked" specimens. These specimens must be banked in a VA-sponsored or VA-approved tissue bank. Reuse of the specimens must be consistent with the consent under which they were collected, and the reuse must only occur through a VA-approved protocol.

If the protocol requires that the specimens be analyzed/used at a non-VA institution, a written understanding between the VA investigator and the non-VA institution must specify the analysis/use as defined in the protocol. The agreement must also specify that any remaining quantities of the specimens shall be either destroyed or returned to the VA. If the remaining quantity is destroyed, that institution must certify the destruction of the specimens in writing. The remaining quantity may <u>not</u> be retained and/or stored by the non-VA institution.

The investigator storing the banked specimens must maintain a copy of the

original consent under which each specimen was collected, a record of the use of the specimens, and the protocols under which they are used.

c. Linking of the data generated by the specimens and the clinical data should occur within the VA and by VA investigators whenever possible. When this is not possible, the minimal amount of clinical data necessary should be shared with those doing the statistical analysis. The clinical information that is shared should not contain any unique identifiers.

d. The informed consent under which the specimens are collected must meet all the requirements in the VA Handbook 1200.5, Appendix A. In addition, it must clearly state:

    1. Whether the specimen will be used for future research and allow the subject the choice of how the specimen will be used (any research, research by the PI or other researchers, genetic analysis, research related to a specific area, etc.);

    2. Whether research results of reuse of the specimen will be conveyed to the subject;

    3. Whether the subject will be re-contacted after the original study is completed; and

    4. That if the subject so requests, the specimen and all links to the clinical data will be destroyed.

14. IRB Considerations about Ethical Study Design.

A. Epidemiological Research.

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

Epidemiological studies often present significant problems regarding both **privacy** and **confidentiality**.

(1) The IRB must first consider privacy issues, and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

(2) Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

(3) Because epidemiological research typically requires large numbers of subjects, investigators almost always request that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met (38 CFR 16.116(d); specifically that (a) the research presents no more than minimal risk to subjects; (b) the waiver will not adversely affect the rights and welfare of the subjects; (c) the research could not practicably be carried out without the waiver, and (d) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

B. Issues in Genetic Research.

Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB should expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained (See Section 8.G.).

C. Family History Research.

Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member (called a proband) about other family members (third parties). The proband in turn provides sensitive information about other members of the family, each of which is identified only by a code number as the family member's data (e.g., occurrence of a specific illness) is recorded. Thus, an exemption may be granted for the portion of the study gathering data on family members. The proband may further be encouraged by the investigator to separately ask the other family members for permission to be contacted by the research staff or to contact the research staff, so that they may be invited to participate or interviewed in more detail, if desired. A waiver of documentation of consent may also be usefully sought for telephone interviewing or screening which collects and retains sensitive private information from persons who live far from the research site, provided all conditions for such a waiver have been met.

(1) It is important to recognize that the VA regulations at 38 CFR 16.102 (f)(2) and the Common Rule include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information."

(2) Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them.

(3) The IRB must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived (See Section 8.S.) under the conditions specified at 38 CFR 16.116(d). Confidentiality is a major concern in determining if minimal risk is involved. The IRB will consider if informed consent from third parties can be waived in accordance with Section.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

D. Research Involving Potentially Addictive Substances.

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

(1) When this type of research is proposed, the IRB must consider the subjects' capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.

(2) If such research involves subjects that are institutionalized, the subjects' ability to exercise autonomy could be impaired.

(3) The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.

(4) The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.

(5) It is critical that the IRB focus on the considerations of risk and benefit of such research.

15. Potentially Vulnerable Subject Groups

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, VAPHS employs additional safeguards to protect the rights and welfare of these subjects based on 38 CFR18 and 45 CFR 46.111b.

When considering the inclusion of vulnerable subjects in a protocol, the VAPHS IRB will document the category of vulnerability of the proposed study population, and will identify the additional safeguards planned to protect the rights and welfare of the potentially vulnerable subjects.

A. Pregnant Women, Fetuses, and Human in Vitro Fertilization (45 CFR 46, Subpart B).

The VAPHS does not engage in research in which pregnancy is the focus of the research. VAPHS IRB does not permit the exclusion of non-pregnant women of reproductive potential from research unless an appropriate justification has been provided. However, no pregnant woman may be involved as a subject unless the risk to the fetus is minimal. VAPHS takes special precautions to evaluate research that has the potential to involve pregnant women.

For all studies, the VAPHS IRB evaluates carefully whether there is scientific or safety justification to exclude women of child bearing potential, pregnant women, or lactating women. The VAPHS IRB protocol and consent form templates include sections that specifically address pregnancy risks. The VAPHS IRB will review and oversee research involving pregnant women according to DHHS regulations at 45 CFR Part 46, Subpart B. If there is just reason to exclude these populations, the protocol must specify the exclusion criteria and how they will be met (e.g. serum laboratory test). It is the responsibility of the investigator to promptly notify the IRB if an enrolled subject becomes pregnant and to cease research interactions until it can be determined that the potential risk or harm to the fetus has been minimized (45 CFR 46Subpart B).

The VAPHS does not engage in research in which the subject is a fetus, in-utero or ex-utero, or in human in-vitro fertilization research. Neither does the VAPHS engage in human fetal tissue transplantation research (Public Law 103-43). The VAPHS IRB rarely reviews research involving pregnant women; however, will seek services of a consultant, who is knowledgeable on the clinical, ethical, and psychosocial issues of pregnancy and the puerperium, if needed.

B. Research Involving Prisoners (45 CFR 46, Subpart C).

VAPHS considers any individual involuntarily confined or detained in a penal institution as a prisoner. VAPHS does not participate in research involving prisoners unless a waiver has been granted by the Chief Research and Development Officer (CRADO), VA Headquarters. VAPHS recognizes that study participants may become prisoners during research. It is the responsibility of the investigator to promptly notify the IRB if an enrolled subject becomes incarcerated.

When it becomes known that a previously enrolled research subject becomes a prisoner and the relevant research protocol was not reviewed and approved by the institutional review board (IRB) in accordance with the requirements of HHS regulations at 45 CFR Part 46, subpart C, the principal investigator should stop all research interactions and interventions with, and efforts to obtaining identifiable private information about, the now-incarcerated prisoner-subject until the requirements of subpart C have been satisfied with respect to the relevant protocol. However, in special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied. This will then be reviewed by the full IRB and if approved sent to the CRADO for a waiver.

C. Research Involving Children (45 CFR 46, Subpart D and VHA Directive 2001-028, April 27, 2001.)

VAPHS considers any person under the age of 18 years as a child. Effective October 1, 2002, the VAPHS will not conduct research involving children with the exception of minimal risk genetic studies, which may enroll family members less than 18 years of age. A child, about whom data is provided by someone else, is not considered to be a research subject if the data on that child is not private or does not readily identify the child. A Certificate of Confidentiality should be considered for genetic studies in an effort to minimize the risk of breach of confidentiality.

Research involving children approved by the IRB prior to October 1, 2002 will be allowed to continue until the study has been completed. If children are deemed to be participants in a VAPHS genetic research study, approval is required from the Chief Research and Development Officer in addition to review and oversight by the VAPHS IRB, in accordance with DHHS regulations 45 CFR 46, Subpart D.

(1) Inclusion of Children in Research

When children are included in research the plan must also include a description of a) the expertise of the investigative team for dealing with children at the ages included, b) the appropriateness of the available facilities to accommodate the children, and c) the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. The investigators should address their plans for the inclusion of children (including the respective considerations listed above). The IRB considers the appropriateness of the population studied in terms of the aims of the research and ethical standards. IRBs have the responsibility to examine ethical issues, including equitable selection of research participants in accordance with Federal Regulations (45 CFR 46). The participation of children in research is important to assure that they receive a share of the benefits of the research.

(2) Permitted Categories of Research Involving Children

The IRB has special review requirements (45 CFR 46, Subpart D, Sections 401- 409) to protect the well-being of children who participate in research. The IRB may approve research involving children only if the following specific criterion is met:

The research presents no greater than minimal risk to the involved subjects. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves then those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(3) Child Assent and Consent Requirements

(a) The assent of children, ages 6-13 years old, must be obtained prior to their participation in a research study.

(b) Children, ages 14-17 years old, shall read and sign the standard informed consent document prior to their participation in a research study.

Exceptions to the above requirements are limited to a prospective determination by the IRB that:

1) The capability of the children included in the study is so limited that they cannot reasonably be consulted, or

2) That the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research study.

(4) Documentation of Assent

To document obtaining the child's assent to participate in the research study, the following Verification of Explanation statement must appear on the informed consent document (i.e., below the signature line of the parent(s) or guardian) and be signed and dated by the PI or listed co-investigator.

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to (name of child) in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

_____ _____

Principal/Co-Investigator Signature Date

In addition to the requirement for the child’s assent/consent, the child’s parent(s) or guardian must sign the informed consent document as an indication of their permission to have the child participate in the study.

(5) Permission by Parent(s) or Guardian for Children Involved in Research

The permission of the child's parent(s) or guardian must be obtained prior to participation of the child in a research study. An exception to the above requirement is a prospective determination by the IRB that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g. neglected or abused children). Under this circumstance, an appropriate mechanism for protecting the children who will participate as

subjects in the research must be substituted (e.g., see section (7) Wards below). The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the involved children, and their age, maturity, status and condition.

The permission of both of the child's parents is required unless:

a) The research falls under specific criteria 1) or 2) of section 3, paragraph 2 (see above);
b) One parent is deceased, unknown, incompetent, or not reasonably available; or
c) Only one parent has legal responsibility for the care and custody of the child.

(6) Documentation of Permission by Parent(s) or Guardian

The VAPHS IRB does not waive parental consent. The permission of the child's parent(s) or guardian must be documented by the inclusion of signature(s) on the consent form using the following statement:

PARENTAL CERTIFICATION

I understand the information supplied to me concerning the nature of the study and have had the opportunity to ask questions. Therefore, I agree to the participation of my child.

_____

Parent Signature Date

(7) Child Abuse Statement

The following statement shall appear under the Confidentiality section of all informed consent documents involving research studies conducted on children: “If the researchers learn that you or someone with whom you are involved is in serious danger or harm the will need to inform the appropriate agencies as required by Pennsylvania law.” Alternate language for this statement may be used, however, the IRB must review and approve any deviations from standard language.

(8) Limitations on Research Involving Wards

Children who are wards of the Commonwealth of Pennsylvania or any other agency, institution, or entity can be included based on permitted categories in paragraph (3) above, only if such research is:

(a) Related to their status as wards, or
(b) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards

Research involving wards meeting the limitations defined above and approved by the IRB requires the appointment of an adult advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as a guardian or in loco parentis.

1) One individual may serve as an advocate for more than one child.
2) The advocate shall be an adult who has the background and experience to act in, and agrees to act in, the best interests of the ward for the duration of the child's participation in the research and who is not associated in any way with the research, the investigator(s), or the guardian organization.

(9) Pediatric Health Care Expertise

The Human Studies Subcommittee shall have as an ad hoc member or consultant an individual with expertise in pediatric health care and research. This member shall attend all meetings considering research with children, but is not required to have voting status.

(10) Off-Site Locations

In the event that the research with children takes place in an off-site location at another institution:

(a) The IRB responsible for research in that institution must inform the VAPHS IRB of any adverse events or need to deviate from the approved research protocol;

(b) The institution must have federally approved assurance such as a Multiple Project Assurance (MPA) or Federal-Wide Assurance (FWA) in order to gain approval; and

(c) The IRBs of both institutions must arrange to exchange information related to the off-site project including minutes of IRB meetings, scientific reviews, audits, monitoring activities, and other relevant reports.

D. Potentially Decisionally Impaired Subjects.

VAPHS considers a "decisionally impaired" person as one who has either (1) a psychiatric disorder, (2) a neurologic disorder or (3) a developmental disorder that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Other persons, e.g., terminally ill patients or persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interest. Competence may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be reevaluated periodically. "Potential decisional impairment" is a feature of persons with the above major psychiatric disorders, neurologic disorders, or developmental disorders, whose disorder brings a risk of current or future decisional impairment.

In its review of protocols proposing to enter potentially decisionally impaired subjects, the VAPHS IRB will consider (i) whether the selection of such subjects is appropriate, (ii) whether the degree of risk to be born by them is ethical and in accordance with VA policy, (iii) whether confidentiality protections are sufficient, and (iv) whether documentation of capacity to give informed consent is necessary.

(1) Selection of Subjects. Research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Consequently, such individuals should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researcher.

(2) Degree of Risk. The proposed research should entail 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) Confidentiality. Enhanced sensitivity to protect privacy of information is required when such vulnerable subjects will participate.

(4) Documenting capacity to give informed consent. Protocols which will enter potentially decisionally impaired subjects, but which have not been granted IRB approval to enter incompetent subjects, must take steps to assure that subjects are capable of giving informed consent. Accordingly, the following procedure will be followed:

(a) All protocols involving potentially decisionally impaired subjects and determined by the IRB to be of greater than minimal risk, will be required to document capacity to give informed consent for subjects in the vulnerable group.

(b) The instrument for documenting capacity to give informed consent will be a questionnaire of standard format (Appendix Z) designed to assess the subject's comprehension of critical information about the study and about research subjects' rights. This procedure applies only to protocols enrolling competent subjects and serves as an added protection. See Section 8.I. for procedures governing protocols enrolling incompetent subjects.

(c) Investigators will be asked to identify, at the time of submission, whether or not the protocol will seek to enter potentially decisionally impaired subjects. At initial review, IRB members assigned to review the protocol will adapt the standard questions of the questionnaire, if necessary, and specify the responses by a subject that are minimally consistent with capacity to give consent.

(d) If the study is approved, a licensed social worker or registered nurse not associated with the study will be available at the time the subject signs the consent form to enter the study. This health professional will be called to meet in person with the subject, administer the questions on the questionnaire orally, and document the accuracy of the responses. If the subject's responses are at least minimally consistent with capacity, as determined by the IRB, the subject will sign, and the health professional will witness, the consent form. If the subject fails, (s)he may not sign the consent form. It is important that the health professional not offer the correct responses to the subject during the questioning, in case the subject may wish to reattempt the assessment after some further effort to learn the details of participation. The record of the results of the subject's capacity assessment will be placed on file in the principal investigator's files along with the original of the signed consent form.

(5) Other measures to protect decisionally impaired subjects. The IRB will apply other measures as appropriate to offer additional protection to vulnerable subjects, including but not limited to:

(a) Giving the subject a minimum interval of time (e.g., one or more days) in which to consider his/her decision on participation,

(b) Requiring a pre-consent assessment (e.g., when dementia may be present: the Folstein Mini-Mental Status Exam),

(c) Requiring repeat assessments of competency when loss of competency may occur during the course of the study. If evidence of loss of capacity arises at any time, the capacity assessment instrument should be re-administered by a health professional outside the study. If the subject fails to demonstrate capacity, and cannot do so after another informed consent process, this investigator should notify the IRB and the subject should be withdrawn from the research. However, in special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study, the IRB Chairperson may determine that the subject may continue to participate in the research unless there is a risk of harm to the subject in doing so.

(d) Requiring an independent monitor to be present during the recruitment and consenting processes.

E. Subjects Judged Incompetent to Consent: Surrogate Permission

The IRB will use the following criteria to decide whether to approve research proposing to enter incompetent subjects:

(1) Competent persons are not suitable for the research. Incompetent persons must not be subjects in research simply because they are readily available.
(2) The proposed research entails no significant physical, psychological, social, or economic risks, or, if the research does have some probability of harm, there must be at least a greater probability of direct benefit to the participant.
(3) Although incompetent to provide informed consent, subjects may resist participating in a research protocol approved by their representatives. Subjects may not be coerced to participate.
(4) Procedures have been devised to assure that participants' representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision-making capacity. Representatives (health care agents, next-of-kin, or guardians) must be given descriptions of both proposed research studies and their obligations as the subjects' representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

The IRB will document its findings regarding the use of surrogate consent in writing.

The IRB will consult Legal Counsel regarding the identity of legally authorized representatives, based on the DHHS and FDA regulations, who can provide informed consent when the research is conducted within the state of Pennsylvania or outside of Pennsylvania.

F. Employees

VAPHS employees may enroll in research protocols approved by the IRB. The investigator may not enroll an employee under his/her influence or direct supervision unless (a) the identities of employees participating cannot be determined by the investigator or (b) the study is minimal risk. The informed consent document must emphasize the investigator's conflict of interest and voluntary participation of the employee.

G. Students
VAPHS considers individuals undergoing training at VAPHS as students. Employees who are undergoing mandatory training as part of their duties are not students. Students may enroll as subjects in research protocols approved by the IRB. The investigator may not enroll a student under his/her influence or direct supervision unless (a) the identities of students participating cannot be determined by the investigator or (b) the study is minimal risk. Research participation cannot be a course requirement. Recruitment communications and materials must avoid coercive language, and assure there is no penalty for refusal to participate or to withdraw at any time.

H. Educationally disadvantaged and non-English-speaking persons
Individuals who are intellectually unable to understand risk and benefit (e.g. lack of education, illiteracy, language barrier etc.) need additional consideration to protect their rights and welfare. Those not able to understand English require a modified consent process including translation of the consent form (see Sect. 8.n. for more details).

I. Economically disadvantaged
Recruitment materials' and telephone scripts' mention of payments and IRB determination of appropriate payment amounts in relation to risk level must be carefully considered if some or all of the subjects to be enrolled are economically disadvantaged. Payment must not be made for toleration of study procedures entailing increased risk or involving pain; payment for time and travel expenses is appropriate. Payment should be made at intervals as the activities prompting payment (e.g., time spent and travel expenses) occur. Payment incentives for study completion should be small relative to the total amount paid. Payment should be made in accordance with Section 8.O.

J. General steps to be taken by the IRB in reviewing research in which some or all subjects to be enrolled are vulnerable but not otherwise covered by specific policies or procedures.
1. The research should be designed to address the causes or consequences of the vulnerability of the subjects in question.
2. The risk level and benefit-to-risk balance of the study satisfies the criteria set for other vulnerable groups (children or decisionally impaired).
3. Confidentiality protections should receive special consideration as for other vulnerable groups.
4. The informed consent process and conduct of the study must contain measures designed to reverse the effects of the subjects' specific vulnerability as much as possible. Steps may involve special attention to (a) time needed to consider participation, (b) communications with the subjects, (c) payments, (d) reduction of risks affected by vulnerability, and so on.
5. The IRB should have a member or consultant in attendance who is knowledgeable about the group felt to be vulnerable.

If the IRB or investigator determines that a vulnerable population may be used, a plan for additional protections must be submitted to the IRB for review. Instructions to investigator to provide required information to the IRB are incorporated in the Initial Review Submission Form.

The investigator must provide:

(a) A written plan describing additional safeguards to prevent coercion or undue influence,
(b) A written plan describing how a subject's capacity to consent will be assessed,
(c) A written plan describing how a subject or legally authorized representative will be provided with sufficient opportunity to consider whether to participate,
(d) A written plan describing how subjects will be able to give consent without coercion or undue influence, and
(e) A written assertion that all investigator-participant communication will be in a language that is understandable to the subject or representative.

Some effective techniques to minimize coercion and undue influence may be

(1) to include family members in the informed consent process and
(2) to allow a waiting period (e.g. 24 hours) between the presentation of the informed consent document and the beginning of study screening procedures.
(3) to be sure the recruitment and informed consent process does not involve any of the person's own clinical care providers.
(4) to control coercive language in recruitment scripts and materials
(5) to ensure appropriate, non-coercive payments for time, travel, etc.

The IRB may:

(1) observe the consent process
(2) monitor the progress of research involving vulnerable subjects more closely than other research, e.g. Continuing Reviews more often than 12 months,
(3) require a QA audit,
(4) require the availability of an ombudsperson or research subject advocate, and
(5) any other measure deemed necessary to protect such subjects.

K. Human Fetal Tissue Transplantation Research (Public Law 103-43).

This VA does not engage in human fetal tissue transplantation research.

L. Statement on Restricted Research within the VAPHS

The VA policies dictate that research involving the following groups **shall not** be conducted by VAPHS investigators while on official duty at VA facilities or approved off-site facilities.

Planned Emergency Research -Research that involves subjects who, because of their condition are in a life-threatening situation that makes treatment necessary, are unable to provide informed consent, and to be effective, the treatment must be conducted prior to informed consent from the subject's legally authorized representative is possible.

Children- *Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. [45 CFR 46.401(a)].

If an investigator wishes to perform research involving children, a waiver from the CRADO must be obtained prior to initiating the research. The only type of research involving children permissible at the VAPHS would be that involving genetic studies, these would be considered by the IRB on a case-by-case basis. VHA Directive 2000-043, “Banking of Human Research Subjects’ Specimens”, would be followed for this type of research.

Research where pregnancy is the focus- Pregnancy is defined as the period of time from confirmation of a fertilized egg within the uterus until the fetus has entirely left the uterus (has been delivered). Pregnancy is confirmed through a presumptive sign such as missed menses or a positive pregnancy test [45 CFR 46.203(b)].

Involving a fetus, in-utero or ex-utero (including fetal tissue) or in-vitro fertilization - The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)]. The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development.

Embryo: Early stages of a developing organism, used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (i.e., from conception to the eighth week of pregnancy).

Prisoners- Prisoner means 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. [45 CFR 46.303(c)].

16. Managing Conflicts of Interest.

Introduction:

A. Investigator conflicts

A conflict of interest exists when the financial interest has the potential to significantly affect the design, review, conduct or reporting of the research results. The Public Health Service regulations (42 CFR Part 50 Subpart F), and FDA guidance (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860) define a significant financial conflict of interest as anything of monetary value, including but not limited to:

(1) Salary or other payments for services (e.g., consulting fees or honoraria);

(2) Compensation to the investigator if the amount of the compensation could be affected by study outcome;

(3) Equity interests (e.g., stocks, stock options or other ownership interests); and

(4) Intellectual property rights (e.g., patents, copyrights and royalties from such rights).

Further definitions regarding conflict of interest are found in the VHA Handbook 1200.13.

Each PI, co-investigator, consultant and collaborator who plan to devote five or more percent effort to the project will submit a Department of Veterans Affairs Research and Development Conflicts of Interest Survey for all projects reviewed by the IRB. Use of the information on the survey is for the review and approval of this proposed research project only.

The IRB is responsible for identifying, reviewing, and requiring appropriate changes in protocols affected by conflict of interest for research involving human subjects. The IRB may also determine that conflict may not be resolved and that the research protocol should not be conducted. In making their determination, the IRB may consider the actions and recommendations of the Conflict of Interest (COI) working group and the investigator's Conflict of Interest Statement. Conflicts of interest related to VA administrative duties that involve research project or contract management responsibilities must only be reviewed by the IRB if the conflict has been identified by the COI working group as a real conflict (i.e. would change behavior and require a management strategy), not merely a positive response on the conflict of interest form. Voting members who have conflicts of interest are required to recuse themselves from deliberations and are not counted toward the quorum for that specific protocol. Conflicts of interest that have been identified by the COI working group as not requiring IRB review will be listed as a notification in the IRB minutes.

The IRB will be informed of the source of funding and funding arrangements for each protocol. The IRB must determine if the protocol addresses any conflict of interest and the management of the conflict of interest. The IRB may determine that the investigator must disclose to the research subject financial arrangements with the research sponsor including

any incentives to recruit subjects. This disclosure may take the form of a discussion in the consent regarding the source of funding, the payment arrangements for investigators, the nature of the conflict of interest, how the conflict is being managed, and the additional protections that have been put in place. These additional protections may include special measures to modify the consent process, having a non-biased third party obtain the consent, and recruit subjects, or having the investigator recuse him or herself from decision making that may influence the outcome or reporting of the research results.

B. IRB member conflicts

No IRB member, ad hoc member, or consultant can participate in the review of any project in which the member has a conflict of interest (financial or otherwise), except to provide information requested by the IRB prior to IRB deliberations. Conflicts of interest include participation in the project under deliberation as a principal investigator, co-investigator, consultant or collaborator. IRB members, including ad hoc members, are required to file annual conflict of interest disclosures, which are reviewed by the chair and ACOS/R&D. Consultants are required to file a conflict of interest disclosure at the time of consultation. These disclosures will be maintained in the IRB Membership Binder in the IRB Office. Any IRB member who has a financial interest in the project must also be excused from deliberation and voting. Any IRB member who is the mentor or mentee of an investigator or co-investigator of a study must be recused. The minutes of the meetings indicate which members are recused from the meeting due to conflicts of interest.

17. Investigational Drugs, Devices and Biologics.

A. Investigational Drugs and Biologics

The Food and Drug Administration (FDA) regulates clinical investigations (research) conducted with drugs, biologics, devices, diagnostics, infant formulas and, in some cases, dietary supplements and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor. Applicable VA requirements must also be met when FDA regulated test articles are used in human research.

Although FDA regulations allow for planned use of a test article in an emergency setting, commonly referred to as "planned emergency research" (21 CFR 50.24), such studies are not allowed and will not be conducted at VAPHS.

(1) Determination of the Need to Obtain an IND

Biomedical research often involves testing the safety and efficacy of new drugs, devices and biologics that are not yet FDA approved and marketed. New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations. IND refers to an investigational new drug application and is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." ***Investigational new drug*** means a new drug or biological drug used in a clinical investigation. An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met.

The FDA definition of research in the IND regulations is as follows: "Clinical investigation" means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice (21 CFR 312.3(a)). Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.

Not all drugs used in a FDA clinical investigation require an IND. To be exempt from the requirements of the IND regulations, all of the following conditions must apply (that includes the requirement of IRB review and informed consent):

Exemption 1 (21 CFR 312(b)(1):

- The drug is lawfully marketed in the United States
- The investigation is not intended to support a new indication for use nor any other significant change in the labeling for the drug
- The investigation is not intended to support a significant change in the advertising for the product

• The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
• The investigation is conducted in compliance with the requirement for institutional review board review and informed consent, and
• The investigation is conducted in compliance with the FDA regulations on promoting and charging for investigational drugs (21CFR 312.7).

Exemption 2 (21 CFR 312(2)(i):

- A clinical investigation involving one of the following three in vitro diagnostic biological products (blood grouping serum, reagent red blood cells, or anti-human globulin) is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure, and
- It is shipped in compliance with 312.160

Exemption 3 (21 CFR 312(2)(ii):

- A clinical investigation involving an in vitro diagnostic biologic product is one of the following:
  - Blood grouping serum;
  - Reagent red blood cells; or
  - Anti-human globulin.

Exemption 4 (21 CFR 312(3):

- The drug is intended solely for tests in vitro or in laboratory research animals and
- It is shipped in accordance with 312.160.

Exemption 5 (21 CFR 312(5):

- The clinical investigation involves use of a placebo (if an IND is not required for any other part of the clinical investigation).

(2) IND Validation

The IRB will not approve a study using an investigational drug until the IND has been validated, IND exemption has been determined, or an IND has been approved by FDA. It is the investigator's responsibility to supply documentation to the IRB of either (a) source documentation of the IND number for IND validation by the IRB Coordinator, or (b) explanation of why an IND is not necessary for the drug used in the clinical investigation. Investigators are required to contact FDA prior to submitting a project to the IRB if there is a question whether an IND if needed for the proposed clinical investigation (e.g. use of a marketed drug in a different population).

Validation of the IND number is done by the IRB Coordinator prior to IRB review of the clinical investigation. This will be done by evaluating the IND number on one of the

following materials supplied by the investigator: (1) sponsor protocol, (2) sponsor correspondence, (3) FDA correspondence, or (4) contract research organization correspondence. Research approval involving an FDA-regulated investigational drug or biologic will only occur after the IRB has received documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) **or** has formally determined that satisfactory justification has been provided by the investigator as to why an IND is not required.

(3) PI Responsibilities when Conducting Research using Investigational Drugs

(a) Supply documentation to the IRB of either (a) source documentation of the IND number for IND validation by the IRB Coordinator, or (b) explanation of why an IND is not necessary for the drug used in the clinical investigational.

(b) A VA "Investigational Drug Information Record" (VA Form 10-9012) must be completed by the PI and be forwarded to the VA Investigational Drug Service (IDS) upon approval of the study by the IRB and R&D Committee. VA Form 10-9012 must be part of the original submission packet to the IRB and must be signed by the IRB Chair and R&D Committee Chair when approval is granted. This form must also be modified and signed by the IRB and R&D Chairs if there are any changes to authorized prescribers or any other information on the form. A current copy of this form must also be submitted at the time of Continuing Review. VA Form 10-9012 is required for all drugs dispensed by the IDS for research purposes, including FDA-approved drugs, unless otherwise indicated by VA requirements.

(c) The PI must inform the Program Manager of the IDS, and the R&D Committee when a study involving investigational drugs has been suspended or terminated.

(d) All applicable requirements in VHA Handbook 1108.04 must be met.

(e) A copy of VA Form 10-1086, VA Research Consent Form, must be sent to the IDS to document each subject's consent to participate in the study. This will be provided to the IDS before or with the first written order for the investigational drug for each patient added to the protocol.

(4) Responsibilities of the Research Office when Approving Research Using Investigational Drugs

(a)The R&D Committee is responsible for informing the IDS that IRB and R&D Committee approval has been obtained for initial review. The R&D Office will forward the signed VA Form 10-9012, a copy of the IRB and R&D approval letters, Investigator's Brochures, and a copy of the approved protocol and consent form to the IDS.

(b) The IRB is responsible for informing the IDS of their approval of all continuing reviews, and all protocol amendments and modifications of research using investigational drugs. The IRB Office will forward the following items, as

applicable to the IDS, the signed VA Form10-9012; a copy of the IRB approval letter; VA Form 10-1223, Report on Subcommittee on Human Studies; a copy of the approved protocol; and a copy of the approved consent form.

(c)The IRB will notify the IDS of any suspensions or terminations in the research.

(d)The IRB must furnish the IDS with a copy of all updated protocols or Investigator's Brochures.

(5) Responsibilities of PI when Sponsor-Investigator holds IND

Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational drug or device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor. Sponsor-Investigators are required to be knowledgeable of the additional regulatory requirements of sponsors and know how to comply with them. In order to ensure the Sponsor-Investigator is knowledgeable about the additional regulatory requirements of sponsors and knows how to follow them, the Research Education and Compliance Office will conduct a Quality Assessment Interview. The Quality Assessment Summary Report must be submitted and reviewed before the IRB will grant final approval. If the study involves an IND, the Investigator is also required to submit this report to the IDS. The above are necessary prior to enrollment and/or participation of human subjects. The Investigator must document in the Data Safety and Monitoring Plan section of the protocol a description of who will be responsible for monitoring and a process for regular review of accrued research data and other relevant information so as to ensure the validity and integrity of the data and that there is no change to the anticipated benefit to risk ratio of study participation.

(6) Management of Investigational Drugs

The IDS is responsible for the receipt, storage, security, dispensing, and disposition of all investigational drugs.

(a) All investigational drugs will be delivered to the IDS, in the custody of the Program Manager of the IDS, and will remain under the control of the IDS until the time of dispensing.

(b) All investigational drugs will be stored in an appropriate and secure storage area, separate from other drug stocks.

(c) Investigational drugs will only be dispensed upon receipt of a properly written order from a practitioner authorized to use the drug.

(d) The IDS will be responsible for maintaining a log of all transactions involving the receipt, dispensing, and disposition of investigational drugs. The following information will be maintained on the log:

1. name of drug, dosage form and strength
2. manufacturer or other source
3. date of receipt of the drug
4. quantity received
5. expiration date, retest, or repass date
6. control number, lot number, or other identification (ID) number
7. name of site investigator
8. protocol name or number
9. name of subject or other subject identifier for individuals receiving the medication
10. quantity dispensed
11. balance of drug currently available (when amenable to protocol design)
12. patient identifier (<u>not</u> the patient's name)
13. recorder's initials
14. serial number of the patient and date the protocol was approved; and
15. a final entry is made when drug therapy for the entire study (at the site) has ended. This entry documents the date of termination of the use of the drug, the quantity remaining, the action taken to dispose of the balance on hand, and the agent or individual responsible for drug destruction or return. NOTE: When documentation by the clinical investigation sponsor demonstrates that the expiration date and control number (or lot number) of the medication(s) are monitored centrally, (to maintain blinding procedures or ensure continued stability) this information does not need to be maintained on the investigational drug log.

(e) Unused supplies of the investigational drug will be returned to the sponsor or properly disposed of in accordance with local IDS policies.

(7) Treatment Use of an Investigational New Drug (21 CFR 312.34 and 312.35)

During the clinical investigation of a drug used for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or therapy is available, FDA regulations indicate that it may be appropriate to use the drug in the treatment of patients not participating in clinical trials. If an experimental drug is to be provided under these circumstances, all of the FDA requirements set forth in 21 CFR 312.34 must be met:

(a) The drug is intended to treat a serious or immediately life-threatening disease;
(b) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
(c) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
(d) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

A Treatment IND is granted by the FDA and is added to an existing IND. The PI intending to initiate a Treatment IND protocol shall be the investigator of a study involving the test article, which has been reviewed and approved previously by the IRB. The investigator shall have received permission of the holder of the IND (sponsor of the research) to use the test article for treatment purposes. The investigator shall submit an application to the IRB prior to the initiation of the protocol, according to initial submission guidelines. The accompanying informed consent document shall be particularly explicit in regards to the use of a test article in a health care setting, and the assessment of the risk/benefit relationships.

(8) Humanitarian Use of an Investigational New Drug

There is not a regulation for humanitarian use of drugs. The terminology is often confused with treatment use and emergency use of investigational drugs.

B. Investigational Devices

The FDA definition of a “medical device” includes any instrument, apparatus, or other similar or related article that is intended for use in the diagnosis, treatment, or prevention of disease. Over 1,700 types of medical devices are regulated by the FDA. The Investigator is encouraged to review carefully relevant FDA information sheets concerning devices. The FDA defines an investigational device as “a device including a transitional device, that is the object of an investigation”.

(1) IDE Validation

Validation of the IDE number is done by the IRB Coordinator prior to IRB review of the clinical investigation. This will be done by evaluating the IDE number on one of the following materials supplied by the investigator: (1) sponsor protocol, (2) device description information, (3) sponsor correspondence, (4) FDA correspondence, or (5) contract research organization correspondence. Research approval involving an FDA-regulated investigational device will only occur after the IRB has received documentation that the research will be conducted under an applicable Investigational Device Exemption (IDE) **or** has formally determined that satisfactory justification has been provided by the investigator as to why an IDE is not required.

(2) Exempted IDE Investigations

The requirement to obtain an IDE, with the exception of Sec. 812.119 does not apply to investigations of the following categories of devices:

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

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

3) diagnostic device, if the sponsor complies with applicable requirements in
(i) Is noninvasive,
(ii) Does not require an invasive sampling procedure that presents significant risk,
(iii) Does not by design or intention introduce energy into a subject, and
(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

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

5) A device intended solely for veterinary use.

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

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

(3) Abbreviated requirements

The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under Sec. 812.20(a) that approval of an application is required:

1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:
(i) Labels the device in accordance with Sec. 812.5;
(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under Sec. 56.109(c).
(iv) Complies with the requirements of Sec. 812.46 with respect to monitoring investigations;
(v) Maintains the records required under Sec. 812.140(b) (4) and (5) and makes the reports required under Sec. 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by Sec. 812.140(a)(3)(i) and make the reports required under Sec. 812.150(a) (1), (2), (5), and (7); and
(vii) Complies with the prohibitions in Sec. 812.7 against promotion and other practices.

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

(4) Determination of Significant Risk and Non-Significant Risk Device Studies

If a study involves a device and the sponsor has not obtained an *investigational device exemption* (IDE) from the FDA, the IRB, prior to its initial review, must determine and classify whether the device constitutes a "Significant Risk" (SR) or a "Non- Significant Risk" (NSR) or if the protocol meets one of the FDA exemptions from the requirement to have an IDE. A Significant Risk Device study must have an IDE approved by FDA unless it meets one of the exemption categories listed above. A Non-Significant Risk Device study has an IDE, but the IDE is not approved by FDA. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated IDE requirements [21 CFR 812.2(b)].

(a) A <u>SR device</u> means an investigational device that (21 CFR 812.3.m.):

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

(b) A <u>NSR device</u> does not meet the above criteria. Examples of SR and NSR devices are listed in Appendix AA.

For studies involving devices classified by the sponsor as SR devices, the PI must provide the IRB with documentation of the Investigational Device Exemption (IDE) issued by the FDA. If the IDE is not provided and the IRB makes the determination of SR, the study cannot be approved by the IRB until one of the following occurs:

1) The sponsor obtains the IDE, it is forwarded to the IRB office and reviewed by the convened IRB, or
2) The IRB determines that the project meets the exempted IDE requirements. In this instance the IRB must report approval of the study to the FDA.

Where there is no IDE, a study that involves an investigational device classified by the study sponsor as NSR may be submitted for review. The sponsor must provide the IRB with a risk assessment and the rationale for making its NSR risk determination. The IRB must review this information from the sponsor and make its own assessment that the device is SR or NSR (see Investigational Device Checklist, Appendix BB).

(c) IRB assessment of risk is based on the following criteria:

1. an FDA Investigational Device Exemption (IDE) approval letter, if issued (a device that has an IDE is considered a significant risk device);
2. the proposed use of the device, as this may not be covered under an existing FDA approval, as well as its intrinsic design and construction;
3. reports of prior experience and investigations;
4. comparison with devices listed previously designated SR or NSR by FDA;
5. the study rationale, design, and subject selection criteria;
6. risk assessments and monitoring procedures used by a sponsor and/or an investigator;
7. discussion with FDA officials, if appropriate;
8. additional information from outside consultants, if appropriate.

If the IRB disagrees with the NSR assessment of the sponsor, then the study would be governed by the IDE regulations under 21 CFR 812 and an IDE must be obtained and approved by the FDA before the study can be approved. The IRB will notify both the investigator and the sponsor of its decision in writing, and the sponsor will need to submit an IDE application to the FDA. For any study involving a SR device as determined by the IRB, review of the study for approval will take place only after receipt of an approved IDE from FDA. IRB minutes document whether a study involves a SR or NSR device and the rationale for that determination. Studies involving SR devices do not qualify for expedited review at initial review.

(5) Responsibilities of PI when Sponsor-Investigator holds IDE

The requirements for expertise and training are similar to requirements for Investigational Drugs as described in Section 5.
Sponsor-Investigators are required to be knowledgeable of the additional regulatory requirements of sponsors and know how to comply with them. In order to ensure the Sponsor-Investigator is knowledgeable about the additional regulatory requirements of sponsors and knows how to follow them, the Research Education and Compliance Office will conduct a Quality Assessment Interview. The Quality Assessment Summary Report must be submitted and reviewed before the IRB will grant final approval.

(6) Storage, Security, Dispensing and disposition Investigational Devices

Prior to participating in research involving investigational device(s) the investigator will be required to meet with the Research Education and

Compliance Office to complete an educational session on local policy and procedure for the storage, security, dispensing and disposition of investigational device(s). Education will be documented in the protocol file in the form of a letter from the Research Compliance Officer. The investigator will dispense investigational devices only after obtaining written informed consent, unless such requirements are exempted or waived. The PI is responsible for the receipt, storage, security, dispensing, and disposition of all investigational devices in accordance with sponsor, manufacturer, and/or local guidelines. The investigator is required to describe within the protocol procedures for storage, security, and dispensing of investigational devices. The IRB assesses the plan and determines if procedures are appropriate to human subjects protections. The Research Compliance Office monitors investigational device studies.

(f) The PI is also responsible for maintaining a log of all transactions involving the receipt, dispensing, and disposition of investigational devices. The following information will be maintained on the log:

1. name of device
2. manufacturer or other source
3. date of receipt of the device
4. quantity received
5. expiration date, retest, or repass date
6. control number, lot number, or other identification (ID) number
7. protocol name or number
8. name of subject or other subject identifier for individuals receiving the device
9. patient identifier (<u>not</u> the patient's name)
10. recorder's initials
11. a final entry is made when device therapy for the entire study (at the site) has ended. This entry documents the date of termination of the use of the device, the quantity remaining, the action taken to dispose of the balance on hand, and the agent or individual responsible for device destruction or return.

(g) Unused supplies of the investigational device(s) will be returned to the sponsor or properly disposed of.

(7) Treatment Use of an Investigational Device

A device that is not approved for marketing may be under clinical investigation for a serious or immediately life- threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of the treatment investigational device exemptions (IDE) regulation. (§812.36)

FDA would consider the use of an investigational device under a treatment IDE if:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
4. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56.

(8) Humanitarian Use Devices

Similar to orphan drugs, an exemption approval route exists for an unapproved device that is meant to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4000 individuals in the United States. A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals per year in the United States. FDA regulations (21 CFR 814.124) provide for the submission of a Humanitarian Device Exemption (HDE) in which the manufacturer is not required to provide the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose prior to marketing.

Regardless of the intended use, a HUD requires <u>prospective</u> IRB review and approval by the full Committee. The use of a HUD does not constitute research unless the physician or health care provider intends to collect data from its use. HUDS also require continuing review by the IRB.

(9) Emergency Use of a Test Article (Investigational Drug, Biologic, or Device)

FDA regulations at 21 CFR 56.104(c) permits the emergency use of a test article without IRB review. Emergency use is defined as use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). Emergency use of an unapproved drug or biologic is research. For purposes of this policy, all persons receiving a drug, biologic, or device under FDA's emergency use of a test article regulations are considered to be participants. Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below. An exemption from IRB review is a prerequisite for the exception from the requirement for informed consent.

In order to meet these exemption requirements the activity cannot be a systematic investigation designed to develop or contribute to generalizable knowledge. Emergency use of a test article is intended to be a one-time only use. FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had time to convene a meeting. However, if subsequent use of the test article is contemplated, a complete IRB application must be submitted for full board review prior to any additional use of the test article.

The Chief of Staff must be notified prospectively and give authorization if a clinician is planning on administering a test article under the emergency use of a test article regulations. The Chief of Staff may consult with the IRB Chair to determine whether the circumstances follow FDA regulations prior to giving authorization if unsure whether use is authorized.

(a) Obtaining an IND or IDE

Investigational Drugs or Biologics

Emergency use of an investigational drug or biologic requires an IND (Investigational New Drug Application). The principal investigator must obtain an IND number from the manufacturer, if possible. If the manufacturer elects not to name the PI on the IND, the PI must then contact the FDA directly for an IND or obtain evidence of an IND Exemption.

Investigational Devices

Emergency use of an investigational device requires an IDE (Investigational Device Exemption). Therefore, the principal investigator must contact the manufacturer to determine if the product can be made available for use under the company's IDE. If an IDE does not exist, the FDA expects the principal investigator to determine the following:

- whether the criteria for emergency use have been met;
- assess the potential for benefits from the unapproved use of the device and to have substantial reason to believe that benefits exist; and
- assure the decision of the principal investigator that an "emergency" exists is not based solely on the expectation that IDE approval procedures may require more time than is available.

If an investigational device is being used, the investigator is responsible for assuring that the device sponsor/manufacturer notifies the FDA immediately after an unapproved device is shipped for emergency use.

(b) Obtaining Informed Consent

Even under emergency use of a test article, no subject may receive an investigational drug, biologic, or device without obtaining informed consent from the subject or the subject's legally authorized representative. An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

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

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB.

(c) Reporting Requirements

A written report from the clinician must be received to the IRB office within 5 days after the test article has been administered. The report should include at a minimum:

- Name of investigational drug, biologic, or device
- Condition of use (ex. administration schedule and dosage, device implantation)
- Date of Chief of Staff's authorization of emergency use request,
- Subject's diagnosis and outcome if known,
- Any adverse events or unanticipated problems occurring during or following test article administration,,
- Likelihood of needing to use the test article again,
- Copy of the signed informed consent (if applicable), or
- Copy of the progress note documenting exception to informed consent,

This reporting must not be construed as an approval for the emergency use by the IRB.

The IRB Chair or designated IRB member is expected to assess whether or not the conditions for the use have been met and document the determination. This is placed in the IRB files with a copy sent to the clinician. The IRB Administrator is responsible for maintaining this documentation in IRB records.