



**VA ANN ARBOR HEALTHCARE SYSTEM  
(VA AAHS)**

**SUBCOMMITTEE ON HUMAN STUDIES  
(VA IRB)**

**STANDARD OPERATING PROCEDURES**

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In this document, the term "VA IRB" is used to indicate the Institutional Review Board for Human  
Subject Research at the VA Ann Arbor Healthcare System (VA AAHS).

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## **I. THE INSTITUTIONAL AUTHORITY UNDER WHICH THE VA IRB IS ESTABLISHED AND EMPOWERED.**

The VA IRB is mandated to approve and disapprove any and all types of research, in which human subjects are involved. The VA IRB reports directly to the Research and Development Committee of the VA Ann Arbor Healthcare System (VA AAHS) and receives administrative support from the Research Service.

All research projects performed at the VA AAHS or involving patients of the VA AAHS must be approved by the Ann Arbor VA Research and Development Committee (VA R&D).

## **II. THE DEFINITION OF THE PURPOSE OF THE VA IRB: THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH.**

### **A. Primary Goal**

The primary goal of the VA IRB is to assure that, in research involving human subjects at the VA AAHS, the rights and welfare of the human subjects are adequately protected.

To achieve this goal,

- 1) The VA IRB will assist the investigators in designing their research projects in a manner to minimize potential harm to human subjects,
- 2) Review all planned research involving human subjects prior to initiation of the research,
- 3) Approve research that meets established criteria for protection of human subjects and
- 4) Monitor approved research to ascertain that human subjects are indeed protected.

### **B. Secondary Goals**

Secondary goals of the VA IRB are to inform and assist the VA AAHS and its researchers on ethical and procedural issues related to the use of human subjects in research, to facilitate compliance with relevant regulations of the United States Government and to provide a framework suitable for continued support by Government agencies, private foundations and the industry for research involving human subjects at the VA AAHS.

### **C. Research Activities Involving Humans as Participants Subject to the HRPP**

The VAAHS will follow the regulations of both the DHHS and the FDA for all activities that constitute "research" on "human subjects".

#### **1) DHHS DEFINITIONS**

"Research" as defined by DHHS regulations means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. [45 CFR 46.102(d)]

"Human Subject" as defined by DHHS regulations means 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. [45 CFR 46.102(f)]

"Intervention" as defined by DHHS regulations means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(f)]

"Interaction" as defined by DHHS regulations means communication or interpersonal contact between investigator and subject. [45 CFR 46.102(f)]

"Private information" as defined by DHHS regulations means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). [45 CFR 46.102(f)]

"Identifiable information" as defined by DHHS means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

#### **2) FDA DEFINITIONS**

"Research" as defined by FDA regulations includes any of these activities: (a) any experiment that involves any use of a drug other than the use of an approved drug in the course of medical practice; (b) the use of a medical device other than the use of a marketed device in the course of medical practice; (c) the results of

the activity will be submitted to the FDA or held for inspection by the FDA; (d) tissue specimens will be used to test the effectiveness of a medical device and the information will be submitted to the FDA for approval of the device; (e) the activity involves one or more of the following: FDA regulated articles: food or dietary supplement that bears a nutrient content or a health claim, a food or color additive for human consumption, infant formula, biological or electronic product for human use, or other article subject to the FD&C Act; AND individuals directed by a research protocol rather than by medical practice, when they are or become participants in research (either as recipients of an FDA regulated product (approved or experimental) or as controls) OR individuals participate in an investigation either as subjects or as controls where an investigational device is used on them or on their specimens.

The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

“Experiments” that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

“Experiments” that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a medical device. [21 CFR 812.2(a)]

“Human Subject” as defined by FDA regulations means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. [21 CFR 50.3(g), 21 CFR 56.102(e)] A human subject includes an individual on whose specimen a medical device is used. [21 CFR 812.3(p)]

#### D. Informed Consent of Human Subjects of Research

The process of obtaining informed consent has three components:

- 1) Providing the person, who is being recruited to become a subject of research, or that person's legally authorized representative, with the information necessary to give informed consent,
- 2) Obtaining the consent to participate in the research as a subject.
- 3) Documentation that informed consent has been obtained.

### **III. THE PRINCIPLES WHICH GOVERN THE VA IRB IN ASSURING THAT THE RIGHTS AND WELFARE OF SUBJECTS ARE PROTECTED.**

#### A. VA Ann Arbor Healthcare System (VA HHS), Department of Health and Human Services (DHHS), Office of Human Research Protections (OHRP) Federalwide Assurance (FWA), Office of Research Oversight (ORO), Department of Veterans' Affairs Research and Development Office (VA ORD).

- 1) The VA IRB operates within the principles set forth by the VA AAHS in the "OHRP Federalwide Assurance", enacted between the VA Ann Arbor Healthcare System and DHHS represented by OHRP and ORO on behalf of VA. The VA IRB assures that all of its activities related to human subject research, regardless of funding source, will be guided by the ethical principles in The Belmont Report.
- 2) The Medical Center Director is the responsible official for the Federalwide Assurance.

#### B. Ethical Principles

The VA IRB assures that all of its activities related to human subject research, regardless of funding source, will be guided by the ethical principles in the BELMONT REPORT, published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979)

#### C. Procedural Standards

The VA IRB assures that all of its activities related to Federally-supported human subject research will comply with the procedural standards in "Protection of Human Research Subjects" Title 45 Code of Federal Regulations (CFR) Part 46 of the United States Department of Health and Human Services.

#### D. Department of Veterans Affairs Regulations, Policies and Procedures

The VA IRB assures that all of its pertinent activities related to human subject research will comply with all requirements of Department of Veterans Affairs regulations in Title 38 Code of Federal Regulations Part 16 (38 CFR 16) (the VA implementation of the Common Rule and all other pertinent Department of Veterans Affairs policies and procedures), including policies and procedures of the Office of Research Oversight (ORO) and the Office of Research & Development (ORD), issued in Manuals, Handbooks and other relevant authorized

Directives.

#### **IV. THE AUTHORITY OF THE VA IRB.**

##### **A. Approve Exemption from IRB Review**

The VA IRB is responsible for final determination of Exemption based on 38 CFR 16, Section 101 and 1200.5. Notice of concurrence for all Exempt research will be promptly conveyed in writing to the VA R&D and to the investigator.

##### **B. Review of Non-exempted Projects**

The VA IRB will review all nonexempt research projects involving human subjects at the VA AAHS, in each of the following categories.

- 1) Research performed at the VA AAHS
- 2) Research projects that will recruit patients at the VA AAHS that are not performed on site
- 3) VA-funded research that is conducted by investigators of the VA AAHS.
- 4) Projects not funded by the VA or conducted at the VA, but carried out on investigators' VA time.

##### **C. Disapprove, Modify, Require Progress Reports, Suspend or Terminate Research Projects**

The VA IRB has authority in each of the following categories.

- 1) To require progress reports from the investigators and oversee the conduct of the study.
- 2) To suspend or terminate approval of a study.
- 3) To place restrictions on a study.

##### **D. Collaborating Institutions**

- 1) The VA-AAHS may enter into agreements with other VAMCs that allow the VA IRB to serve as the IRB of record for those institutions. Such agreements will require a Memorandum of Understanding (MOU) signed by the Director of the VA AAHS and the responsible official of the other institution.
- 2) The responsibilities of investigators affiliated with collaborating institutions in terms of education and reporting requirements for research projects will be the same as the responsibilities for Ann Arbor-based investigators.
- 3) Communication between the Ann Arbor Human Studies Committee and investigators at collaborating institutions will occur by mail, fax, electronic mail and phone conversations.
- 4) The specific procedures, including responsibilities of both the VA AAHS and the collaborating institution will be outlined in the MOU.

#### **V. THE VA IRB'S RELATIONSHIP TO THE INSTITUTION**

##### **A. The VA Research and Development Committee (VA R&D)**

The VA IRB functions as a sub-committee of the VA R&D. The VA R&D will approve or disapprove all IRB decisions. However, the VA R&D may not override IRB disapproval of a human studies project.

##### **B. The Medical Center Director**

- 1) The decisions of the VA IRB will be reviewed by the Medical Center Director and the Chief of Staff of the VA AAHS.
- 2) The Medical Center Director has the authority to approve and disapprove all IRB decisions. However, the Director may not override IRB disapproval of a human studies project.

##### **C. Research Investigators**

The VA IRB will assure adequate education of all research investigators and will also monitor investigator compliance with all VA IRB policies.

##### **D. The VA Research Service.**

The VA IRB receives administrative support from the VA Research Service, including: preparation of Agendas, Minutes and communications with investigators, the R&D Committee and outside agencies.

##### **E. Other institutions.**

- 1) The VA IRB will review and approve research to take place at non-affiliated institutions when funding is provided by the Department of Veterans Affairs (when the Ann Arbor VA is engaged in the research, including when it acts as a coordinating center for larger projects), or when non-VA funding is administered by the VA AAHS or its non-profit foundation, the Veteran 's Education and Research Association of Michigan (VERAM). This review is for the VA AAHS involvement in the research, and does constitute the VA AAHS

IRB's acting as the IRB of record for the non-affiliated institution.

- 2) The VA IRB will review and approve research that takes place at affiliated institutions that have an established Memo of Understanding (MOU) with the VA IRB (see section IV D)

#### F. Regulatory agencies.

In the case of an approval decision of the VA IRB, the Research Service of the VA Ann Arbor Healthcare System will act in behalf of the institution and certify the compliance of the project with the institutional Federalwide Assurance. In the case of disapproval, suspension or termination for cause, the Research Service will notify the relevant Federal regulatory agencies and sponsors of the research of the decision of the VA IRB.

## VI. THE MEMBERSHIP OF THE VA IRB.

### A. The Chairperson

#### 1) Selection and Appointment

The VA IRB will have a chairperson. The Chairperson will hold a VA appointment. The chairperson will be appointed by the ACOS/Research with the approval of the COS and the Hospital Director. The Chairperson of the VA IRB will have had experience in research involving human subjects and will be recruited from among active members of the staff of the VA Ann Arbor Healthcare System. The Chairperson will possess the professional competence necessary to review human subject research in all categories encountered at the VA AAHS and can judge the acceptability of the research in terms of institutional commitments and regulations, applicable law and standards of professional conduct and practice.

#### 2) Length of term/service

The chairperson will be appointed for a term of one-year; renewable for additional consecutive one-year terms.

#### 3) Duties

The Chairperson reviews all new project applications, selects primary and secondary reviewers based on protocol content and reviewer expertise, chairs the VA IRB meetings, reviews all documents submitted after VA IRB approval with pending requests for corrections and authorizes all approval letters for the VA IRB.

#### 4) Alternate Chairperson

Whenever the chairperson is not available, the chairperson will designate a senior scientist member of the VA IRB to assume the responsibilities of the chairperson during the period of his/her absence.

#### 5) Renewal/Removal

The process for the renewal of the term of appointment of the chairperson will be initiated by the ACOS/Research. The request for renewal will be submitted to the Director of the VA AAHS for approval. If the current chairperson is not eligible for reappointment, does not wish to extend his/her appointment, or the Director does not approve the reappointment, the procedures for the selection of a new chairperson will be activated.

### B. Number and Selection of IRB Members.

- 1) As mandated by Federal regulations, the VA IRB will have at least five regular, voting members, including the chairperson.

- a) At least one member will represent the VA R&D Committee.

- b) At least one member will be a scientist

- c) At least two mental health professionals**

- d) At least one member will be a non-scientist.

- e) At least one member will be a community representative.

- f) Non-voting members include the ACOS/Research, the AO/Research and the IRB Coordinator**

- g) A licensed physician must be a voting member for the IRB to review research involving an FDA-regulated article.**

- 2) To be effective and efficient in its operations and to be responsive to the needs of the research community it serves, at its discretion, the VA IRB may increase, above the Federally mandated minimum, the number of its members in any category. At its discretion, the VA IRB may also reduce its membership, as long as the membership conforms to the Federally mandated minimum and composition.

#### 3) Selection and Appointment

- a) In the case of selection and appointment of a new voting member, the Associate Chief of Staff for Research will solicit nominations and self-nominations from all members of the staff of the VA Ann Arbor Healthcare System for scientist members, from all members of the Staff of the VA Ann Arbor Healthcare System for non-scientist members and from research subjects or research subject advocates. These

solicitations for membership will include information on desired qualifications of the candidates in order to fill any gaps in expertise among the membership.

- b) The Associate Chief of Staff for Research will coordinate the process of selection and appointment. The recommendations for renewal of membership and nominations for new membership will be reviewed by the VA Chief of Staff and suitable candidates will be identified. The Director of the VA Ann Arbor Healthcare System will approve the selected candidates. The approved candidates will be appointed or reappointed by the Director or his/her designate.
- 4) Length of term/service and description of staggered rotation or overlapping of terms
- a) Scientist members will be appointed for three-year terms on staggered appointments. The term of membership will be renewable for a second, consecutive three-year period, as long as a member continues to possess the required qualifications. In case a member is chosen to become the chairperson, the duration of his/her membership will be extended automatically, to allow completion of the term of appointment as a chairperson. A member, who has served two consecutive three-year terms, will again become eligible for VA IRB membership no sooner than one year after being off the VA IRB; in the case of reappointment, the terms of membership will be reestablished.
  - b) Non-scientist members will be appointed for three-year terms, renewable for successive three year terms without limit, as long as a member continues to possess the desired qualifications.
- 5) Non-voting Members
- a) The Subcommittee on Human Studies, at its discretion, may recruit non-voting members from among the academic or administrative staff of the VA Ann Arbor Healthcare System, whose presence at the meetings of the VA IRB would aid the VA IRB in conducting its duties. These members may take part in all meetings of the VA IRB, participate in the discussions and make recommendations to influence decisions, but they may not vote on the decisions. Non-voting members will not be included in determining or establishing quorum at the meetings.
  - b) Non-voting members will be selected by the Associate Chief of Staff for Research; the duration of their membership will not be limited.

#### C. Qualification of members.

- 1) Scientist members of the VA IRB will have had experience in research involving human subjects and will be recruited from among active members of the staff of the VA Ann Arbor Healthcare System (includes physicians, dentists, PhD scientists, pharmacists, nurses, veterinarians and others with scientific training and experience).
- 2) The ACOS will ascertain that the VA IRB membership possesses the professional competence necessary to review human subject research in all categories encountered at the VA Ann Arbor Healthcare System and can judge the acceptability of the research in terms of institutional commitments and regulations, applicable law and standards of professional conduct and practice.
- 3) The IRB promotes respect for its advice and counsel in safeguarding the rights and welfare of human participants through its: Experience, Expertise, Diversity (including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes.).
- 4) When the IRB reviews research that involves a vulnerable category of participants, consideration is given to the participation of one or more individuals who are knowledgeable about and experienced in working with those participants: The IRB Chairperson will select appropriate IRB members to be primary and secondary reviewers of new projects that will involve vulnerable categories of participants. If appropriate IRB members are not able to review materials for the intended IRB meeting or if appropriate reviewers are not part of the IRB membership, the IRB Chairperson will consider the use of an internal or external consultant (see Section F).

#### D. Diversity of Members

- 1) Both men and women and persons of diverse races and cultural backgrounds will be eligible and represented on the committee. Every nondiscriminatory effort is made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender
- 2) Persons with a wide variety of professional scientific training will be eligible and represented on the committee.
- 3) Non-scientist members (without scientific training or experience) who have had expertise in human rights issues and/or ethical or legal issues considered to be relevant to human subject research) will be recruited from among the staff or local community. Non-scientist members may include lawyers, clergy and ethicists.
- 4) Community representatives will be recruited from the community of Ann Arbor and its vicinity. Community representatives (non-scientists including clergy, teachers, attorneys or veterans) and their families will not have any affiliation with the VA AAHS.

#### E. Alternate Members

- 1) The VA IRB, at its discretion, may recruit alternate members to substitute for certain regular members of the VA IRB. The appointment of alternate member(s) will be based on expertise similar to that of the regular voting member(s).
- 2) The IRB roster should identify the primary member(s) for whom each alternate member may substitute. An alternate member may vote only when the regular voting member is absent.
- 3) Alternate members will have full voting rights and they will be included in determining or establishing quorum at VA IRB meetings.
- 4) Alternate members may not vote on IRB actions if all regular voting IRB members are present at the meeting of the convened IRB.
- 5) Ad hoc substitutes are not permissible as voting members of the VA IRB.

#### F. Use of Consultants

The VA IRB, at its discretion, may invite scientists or non-scientists from within or outside the VA Ann Arbor Healthcare System, who are not members of the VA IRB, with competence in special areas to assist in the review of protocols which requires expertise beyond or in addition to that available on the IRB. Their identity will be kept confidential from the research study team that submitted the project application.

- 1) The IRB Chair evaluates each research proposal to decide whether there is a need for consultants with additional expertise.
- 2) The IRB Chair and/ or the ACOS/ Research will arrange for selection of a special reviewer with competence in special areas to assist in the review of protocols, which requires expertise beyond or in addition to that available on the IRB.
- 3) The consultant will be subject to the same conflict of interest policies as IRB members.
- 4) The consultant will have access to all documents submitted to the VA IRB relevant to the specific project under review.
- 5) The IRB Chair will make IRB members aware of information provided by the consultant. The consultant may submit a written report to the IRB and/or may attend the IRB meeting to participate in the deliberations and make recommendations on the project.
- 6) The IRB Coordinator will document in the IRB Minutes the key information provided by the consultant.
- 7) The consultant may not vote with the VA IRB.

#### G. Training of VA IRB Chair and Members

- 1) Orientation  
Orientation of new members will be conducted by the VA IRB Coordinator prior to attendance at a meeting of the IRB.
- 2) Continuing education
  - a) The VA IRB Coordinator will maintain procedures for training and educating IRB members and staff and investigators related to use of human subjects in research and ethics in research. The IRB Coordinator will inform IRB members of relevant issues and make committee members aware of applicable Federal regulations.
  - b) The VA IRB Coordinator will distribute IRB policies and essential information about the VA Medical Center to ensure that the IRB and staff and investigators possess sufficient knowledge of the local research context.

#### H. Compensation of VA IRB Members.

Non VA Staff members of the VA IRB will be compensated with a financial stipend, as determined by the VA ACOS/ Research.

#### I. Liability coverage for VA IRB Members.

VA IRB members, as persons acting on behalf of a federal agency in an official capacity, temporarily or permanently in the service of the United States, whether with or without compensation, will be protected from personal liability under the Federal Tort Claims Act (FTCA).

#### J. Resources

The VA IRB will conduct meetings at the VA AAHS. The Medical Center will provide filing space, reproduction equipment and computers, as needed by the VA IRB.

#### K. Conflict of Interest Policies

- 1) Conflict of Interest of IRB Members and Consultants
  - a) IRB Members will be surveyed for conflicts of interest (including financial and non-financial conflicts) at the beginning of each convened meeting and prior to review of each project. The current version of VA IRB Doc. 118 (Checklist for COI) will be used to define when an IRB member has a conflicting interest. The Checklist for each voting member attending the meeting must be submitted to the IRB Coordinator by the start of the meeting.
  - b) Consultants will be surveyed for conflicts of interest by the ACOS/ Research prior to submitting their review of each project (using VA IRB Doc 118). The ACOS/ Research will submit these disclosures to the IRB at the time of the IRB meeting.
  - c) Non-voting members of the IRB who are asked to assist in the review of research will be surveyed prior to contributing to the review of each project (using VA IRB Doc 118). The Checklist for each non-voting member attending the meeting must be submitted to the IRB Coordinator by the start of the meeting.
  - d) Financial and Non-Financial Conflicts of IRB Members, non-voting IRB Members and Consultants are the same as applied to research investigators. (See Doc. 107, R&D Application).
  - e) All persons with an identified conflict of interest will be absent from the meeting room during the discussion and vote on all types of reviews, including: Initial review (including requests for Exemption), Continuing review, Review of modifications, Review of unanticipated problems involving risks to participants or others, Review of non-compliance with the regulations or the requirements of the IRB (except to provide information when requested by the IRB). Voting members who are absent from the meeting room are not counted towards quorum.
  - f) The absence of IRB Members (voting and non-voting) and Consultants during the discussion and vote due to a specific conflict will be noted in the IRB Minutes. The specific reason for the conflict will be noted before the listing of IRB comments and concerns about the research application.

2) Conflict of Interest of Investigators

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 the research protocol should not be conducted at the institution. In making their determination, the IRB will consider the actions and recommendations of the Conflict of Interest Administrator/Committee and the investigator's Conflict of Interest Statement.

- a) In initial or continuing review of protocols, the IRB will consider the impact of the conflict of interest on the subject, the risk to the subject and the subject's willingness to participate in the research after disclosure of the conflict. The IRB will also consider the impact on the research and the research results.
- b) In reviewing protocols, the IRB should be aware 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.
- c) 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 recruit subjects and obtain the consent, or have the investigator recuse him or herself from decision making that may influence the outcome or reporting of the research results. (Sponsor payment arrangements designed to accelerate recruitment or are tied to the rate or timing of enrollment are not allowed by the VA IRB.)
- d) The IRB will determine if actions in addition to those required by the Conflict of Interest Administrator/Committee should be taken to manage, reduce or eliminate the conflict of interest.

## VII. PURPOSE OF THE VA IRB.

VA IRB will monitor all active research projects involving human subjects to ascertain that the subjects are being protected adequately from research risks and from any other breaches of human rights.

### A. Project Reviews

The VA IRB will conduct initial reviews of all proposed research projects and continuing reviews of all non-exempt research projects that include human subjects. The VA IRB will employ a review process which conforms to the Federal Policy for Protection of Human Subjects, the regulatory codes 38 CFR 16 of the HHS and 21 CFR 50, 56, 312 & 412 of the FDA. 38 CFR 16 and the current Federalwide Assurance, enacted between the VA Ann Arbor Healthcare System and the HHS and ORO. In addition, the IRB review requirements described in VHA Handbook 1200.5 will be met. The review process will be the same for all research involving human subjects, supported or

otherwise.

Specifically, the VA IRB will:

- 1) Review all research projects involving human subjects, before the involvement of human subjects may begin
- 2) Require from investigators revisions in research protocols and informed consent documents as a condition for initial or continuation approval
- 3) Approve or Disapprove new research projects and continuation of previously approved projects.
- 4) Monitor the activities in approved projects, in any way deemed necessary, including regularly scheduled continuing review at least every 365 days.
- 5) Verify investigator compliance with approved research protocols and informed consent procedures
- 6) Require reporting to the VA IRB of any planned changes in approved projects-
- 7) Report suspensions or terminations of IRB approval, serious or continuing non-compliance, and unanticipated problems involving risks to participants or others according to the VA AAHS Research Noncompliance Management Policy (section 10 in the Research Investigator Manual).
- 8) Suspend or terminate a previously approved project if deemed necessary. The IRB will assure that appropriate plans are in place to maximize subject safety (e.g. continuation of research participation, subject withdrawal or transition to standard of care).
- 9) Review and monitor the use of test articles (investigational drugs, biologicals and devices) for the purpose of treatment of serious or life-threatening illnesses (compassionate use).
- 10) The IRB will determine if the patient's medical record (electronic or paper) must be flagged to protect the participant's safety by indicating the participant's participation in the study, and the source of more information on the study. The IRB may not want to require the medical record to be flagged if the participant's participation in the study involves:
  - (a) Only one encounter
  - (b) Only the use of a questionnaire
  - (c) The use of previously collected biological specimens.
  - (d) The identification of the patient as a participant in a particular study (if the study is not greater than minimal risk) would place the participant at greater than minimal risk.

**B. Prompt Reporting of Findings and Actions**

- 1) The VA IRB will notify the investigator of the project and the R&D Committee, of its decisions to approve, request additional information, request corrections, discontinue, disapprove, suspend or terminate research projects. In the case of disapproval, suspension or termination, the notification statement will include clearly defined reasons for the decision.
- 2) The investigators will be informed and reminded of these conditions of approval, using two methods of communication:
  - a) Printed correspondence mailed to the principal investigator
  - b) Electronic mail sent to the principal investigator and other study team members.
- 3) The IRB Coordinator will review and transmit investigator responses to appropriate members of the IRB and to the whole IRB at the time of the next regularly scheduled meeting.
- 4) The IRB Coordinator will transmit, within 7 days of a VA IRB action, printed correspondence to the principal investigator and the appropriate institutional officials (including the institutional official responsible for the HRPP) any:
  - a) serious or continuing noncompliance with 21 CFR parts 50 and 56 , 38 CFR 16 or the requirements or determinations of the VA IRB
  - b) suspension or termination of VA IRB approval.
- 5) The ACOS/ Research will report all of the following events (within 10 working days of the IRB's determination to take such actions), through the Chief of Staff and the Medical Center Director, to the VA IRB, the Privacy Officer (when the report involved unauthorized use, loss, or disclosure of individually identifiable patient information), the Information Security Officer (when the report involved violations of information security requirements), the medical center directors of the component VA medical centers, and to the regional office of VA ORO and VA Central Office. **[What to Report to ORO, 9/08/2005 and 12/06/2006]**
  - a) Any adverse event (i.e., an untoward physical, psychological, social, or economic occurrence) in a human subject, or an imminent threat of an adverse event, that results in a substantive action by the Institutional Review Board (IRB) under VHA Handbook 1058.1 (*Reporting Adverse Events in Research*).
  - b) Any unexpected death of a human subject under VHA Handbook 1058.1 NOTE: Such deaths must be reported within 24 hours of the IRB's determination that the death was unexpected or within 10 working days if the IRB has not yet made a determination about whether the death was unexpected.

- c) Any unanticipated problem involving risks to subjects or others that results in a substantive action by the IRB.
  - d) Any for-cause suspension or termination of VA human subject research by the IRB, the VA facility, or a VA affiliate institution. NOTE: This does NOT include suspensions or terminations resulting solely from the expiration of the IRB approval period.
  - e) Any serious or continuing noncompliance with federal regulations or VHA policies for the protection of human subjects (including 38 CFR Part 16; 45 CFR Part 46; 21 CFR Parts 50, 56, 312 or 812; and VHA Handbook 1200.5).
  - f) Any serious or continuing noncompliance with IRB requirements or determinations.
  - g) Any findings of noncompliance in human research protections from the VHA Office of Research and Development (ORD) or other VA office. NOTE: The report to ORO should include a copy of the official findings. The facility should promptly provide ORO with copies of all subsequent correspondence between the office and the facility until the issue is resolved.
  - h) Any findings of noncompliance in human subject protections from external oversight agencies such as the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), etc. NOTE: The report to ORO should include a copy of the official findings (e.g., FDA Form 483, *Inspectional Observations*). The facility should promptly provide ORO with copies of all subsequent correspondence between the agency and the facility until the issue is resolved.
  - i) Any change in the facility's accreditation status from a VA-recognized accreditation organization for human research protections, or in the accreditation status of an affiliate institution or other VA facility upon which the facility relies.
  - j) Any change in the facility's Federalwide Assurance (FWA) or designated IRB(s) as filed with OHRP. NOTE: Report such changes directly to ORO Central Office and simultaneously copy the ORO Regional Office.
  - k) Any significant change in the facility's Memorandum of Understanding (MOU) with an affiliate institution or other VA facility regarding the designation of IRB(s) or other human research protection function. NOTE: Report such changes directly to ORO Central Office and simultaneously copy the ORO Regional Office.
- 6) The ACOS/ Research is responsible for preparing the report (with assistance from IRB staff). The report will include the following information:
- a) The nature of the event
  - b) Name of the institution conducting the research.
  - c) Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)
  - d) Plans, if any, to send a follow-up or final report by the earlier of:
    - iv. A specific date.
    - v. When an investigation has been completed or a corrective action plan has been implemented.
- 7) The ACOS/ Research will report suspensions or terminations of IRB approval, serious or continuing non-compliance, and unanticipated problems involving risks to participants or others according to the VA AAHS Research Noncompliance Management Policy (section 10 in the Research Investigator Manual).
- 8) The IRB coordinator will ensure that all steps of this policy will be completed within 15 days of the initiating action. For more serious actions, the IRB coordinator will expedite reporting.

#### C. Approval of Modifications to Research Activities

- 1) The VA IRB will ensure that changes in approved research are not initiated without committee review and approval except where necessary to eliminate apparent immediate hazards.
- 2) The IRB Coordinator will address this requirement through a variety of measures:
  - a) Training materials prepared for investigators
  - b) Specific directives included in project approval letters
  - c) Random audits of research records

#### D. Monitoring Safety

- 1) The VA IRB must review the data and safety-monitoring plan in the protocol developed by the investigator.
- 2) The VA IRB requires all Clinical Trials that are Phase III, or Multicenter, or recruiting subjects at risk (blinded, high-risk interventions, or vulnerable populations) to establish a Data Safety and Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) as required by DHHS or FDA policy and a plan for reporting DSMB

or DMC findings to the IRB.

#### E. Device Studies

- 1) VA IRB Risk Assessment Definitions:
  - a) The VA IRB will determine which device studies pose significant or non-significant risk in accordance with VA and Federal policies and regulations (VHA Handbook 1200.5 and FDA 21 CFR parts 50 and 56) and as described in the FDA "Blue Book Memo - Significant Risk and Nonsignificant Risk Medical Device Studies". <http://www.fda.gov/cdrh/d861.html>
  - b) The IRB will determinate the risk level based on the proposed use of the device and not the device alone.
  - c) Significant risk device means an investigational device that:
    - i) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
    - ii) 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;
    - iii) 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
    - iv) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
  - d) If the sponsor considers that a device is Non-Significant Risk, the sponsor must provide the IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The IRB may ask the sponsor for information such as a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The IRB will ask the sponsor whether other IRBs have reviewed the proposed study and what determination was made. The sponsor should inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.
- 2) The IRB may agree or disagree with the sponsor's assessment of significant risk or non-significant risk.
  - a) The IRB will notify investigator of the IRB decision of significant risk within 7 days after the date of the convened meeting of the VA IRB. The rationale will be documented in the IRB Minutes. (It is the investigator's responsibility to notify the Sponsor of the IRB determination of significant risk.)
  - b) The IRB will determine if the device study meets the abbreviated IDE requirements of [21 CFR 812.2(b)]; OR meets one of the exemption categories for an IDE [21 CFR 812.2(c)]
  - c) The VA Research Compliance Officer is responsible for determining whether a device has an IDE from the FDA;
  - d) The IRB will not conduct expedited review of any protocols including protocols that involve significant risk devices.
- 3) Investigational devices can only be used after:
  - a) Appropriate approvals of the protocol and informed consent for use of the device have been obtained, and
  - b) The original copy of the signed VA Research Consent Form (VA Form 10-1086) has been documented and recorded in the patient's medical record.
  - c) The Principal Investigator is responsible for storing the investigational devices in a locked, secure area.
  - d) Investigational devices are dispensed as outlined in the approved protocol and after the research subject has read and signed the IRB approved informed consent (Form 10-1086).
  - e) The Principal Investigator is responsible for maintaining records and tracking of investigational devices per 21CFR 812.140
  - f) The R&D Committee and the IRB are responsible for initial and ongoing review of risk/benefit ratio and approval of use of investigational devices with human subjects.
- 4) The VA IRB is responsible for reviewing and approving the device management plan. The Primary Reviewer and the IRB Chair will receive copies of the R&D Application, Scientific Protocol, Investigator Brochure and IRB Application. All members will receive copies of the IRB Application and the Device Management Application Form. [VA IRB Doc. 116]

#### F. Vulnerable Populations

- 1) The VA IRB will not allow research to be conducted on the following populations or procedures:
  - a) Children (*VHA Directive 2001-028*)

*A child is defined as any person who has not attained the legal age for consent to treatments or procedures involved in the research, under the applicable laws of the jurisdiction in which the research will be conducted (less than 18 years old in Michigan)*

*It is VHA policy that children can not be included in VA-approved research conducted by VA investigators while on duty, or conducted at VA facilities or approved off-site locations, unless a waiver has been granted by the CRADO.*

- b) Fetuses
- c) In vitro fertilization
- d) Prisoners

If a research subject, who is enrolled in an approved research study at the VAAHS, becomes a prisoner in a federal, state, county or local municipal facility, the subject must be withdrawn from the study unless there is a risk to the subject's health associated with withdrawal. If the investigator determines there is a risk associated with the withdrawal this should be submitted to the VA IRB for review and approval.

- 2) The VA IRB will consider certain groups of human subjects to be particularly vulnerable to coercion or undue influence in a research setting, to include the following populations:
  - a) **Pregnant women and fetuses**
  - b) Mentally disabled persons (impaired decision making capacity)
  - c) Economically or educationally disadvantaged persons.
  - d) Other vulnerable populations
- 3) In reviewing research projects involving these vulnerable groups, the VA IRB will ascertain that their use is adequately justified and that additional safeguards are implemented to minimize risks unique to each group.
- 4) The VA IRB will consider approval of research projects involving vulnerable populations if at least one of the following conditions is met:
  - a) The research does not involve more than minimal risk to the subject. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.
  - b) The research is likely to benefit the subject directly, even if the risks are considered to be more than minimal.
- 5) The VA IRB will not approve any research project that exposes vulnerable populations to significantly greater than minimal risks.
- 6) The IRB documents its consideration of the inclusion of vulnerable subjects where applicable in reviewer Check Lists (signed by the primary reviewer) and in the IRB Minutes.
- 7) • If the IRB is requested to review research that involves other vulnerable populations, the IRB Chair will decide if the population is appropriate for study at the VA AAHS and whether the protocol requires the scientific or scholarly expertise of a consultant with appropriate expertise to perform an in-depth review.

#### G. Activities Related to Pregnant Women

- 1) Activities related to pregnant women must not be undertaken unless:
  - a) Appropriate studies on animals and non-pregnant individuals have been completed and data for assessing potential risks to pregnant women and fetuses is provided.
  - b) The purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.
  - c) Individuals engaged in the activity will have no part in:
    - 1. Any decisions as to the timing, method and procedures used to terminate the pregnancy; or
    - 2. Determining the viability of the fetus at the termination of the pregnancy.
    - 3. Introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy.
- 2) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of research activity
- 3) No pregnant woman may be involved as a subject in a research activity unless:
  - a) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or
  - b) The risk to the fetus is minimal.
  - c) The mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if:
    - 1. The purpose of the activity is to meet the health needs of the mother,
    - 2. His identity or whereabouts cannot reasonably be ascertained,
    - 3. He is not reasonably available, or
    - 4. The pregnancy resulted from rape.

- 4) For research involving the participation of pregnant women as research subjects, the IRB must:
  - a) Determine that the proposed research meets the requirements outlined in this section;
  - b) Determine that adequate provision has been made to monitor the risks to the subject and the fetus.
  - c) Determine that adequate consideration has been given to the manner in which potential subjects are going to be selected, and that adequate provision has been made to monitor the actual informed consent process such as:
    1. Overseeing the actual process by which individual consents required by this appendix are secured either by approving enrollment of each individual into the activity, or by verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed, and
    2. Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.
  - d) These determinations must be documented in the IRB minutes.

#### H. Activities Related to Persons with Impaired Decision Making Capacity

- 1) The VA IRB membership must include at least one member who is an expert in the area of the research.
  - a) Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.
  - b) The VA IRB may utilize ad hoc members as necessary to ensure appropriate expertise.
- 2) Research involving persons with impaired decision-making capability may only be approved when the following conditions apply: (as defined in section 11 and appendix D of VHA Handbook 1200.5)
  - a) Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. The investigator must demonstrate to the VA 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) The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
  - c) Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.
  - d) Individuals with impaired cognitive judgment but able to understand the research must give their **assent** to participate in the study. Persons are capable of assent if they "know what procedures will be performed in the research, choose freely to undergo those procedures, communicate this choice unambiguously, and [know that they] may withdraw from participation.
  - e) The "mere absence of objection" ought not be interpreted as assent. The consent of a potential subject's legal guardian to authorize greater than minimal risk research involving non-objecting persons incapable of assent.
- 3) The IRB must make a determination in writing of each of the criteria listed in paragraph 2. 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.
- 4) Both investigators and VA IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.
- 5) Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

#### I. Recruitment and Subject Selection

- 1) The VA IRB policies and procedures to define acceptable recruitment practices, consistent with regulatory guidance, include the following activities:
  - a) Payments to subjects including payment terms and schedule must be disclosed in the proposed consent

form. Payments to subjects are evaluated during IRB review of the research consent form. The IRB will not approve amounts or terms of payment that are felt to be inappropriate or coercive. Subject payments must be pro-rated on a visit by visit basis.

- b) Research recruitment advertisements must be approved by the IRB. 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:  
The name and address of the clinical investigator and/or research facility
    - i. The condition under study and/or the purpose of the research.
    - ii. In summary form, the criteria that will be used to determine eligibility for the study
    - iii. The time or other commitment required of the subjects.
    - iv. The location of the research and the person or office to contact for further information.
    - v. (A clear statement that this is research and not treatment.
  - c) Advertisements should not include following items:
    - i. Promise of "free medical treatment."
    - ii. Terms such as "new medication," or "new drug" without explaining that the test article is investigational.
    - iii. Phrases such as, "receive new treatments."
    - iv. Language that explicitly or implicitly says that the article under investigation is safe or effective.
- 2) Compensation for identifying and/or enrolling subjects.
- a) The VA IRB will not allow direct compensation to investigators, physicians and other health care providers for identifying and/or enrolling subjects ("finders fees"). The VA IRB will not allow payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments"). (The IRB may grant an exception if the investigator can present a compelling reason for the exception.)
  - b) When a clinical trial is funded by an industrial sponsor, the research subject must be informed. One of these statements should be included in the Special Circumstances section:
    - i. *"The sponsor funds the VA hospital based on the number of research subjects enrolled."*
    - ii. *"The sponsor provides a fixed payment to the VA Hospital for performing the study."*
- 3) The VA IRB policies and procedures for evaluating protocols regarding the equitable selection of subjects include consideration of the following:
- a) Purposes of research.
  - b) Setting in which research occurs.
  - c) The proposed research should specify the gender and racial/ethnic composition of the subject population.
  - d) The scientific and ethical justification for including vulnerable populations such as pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
  - e) The scientific and ethical justification for excluding classes of persons who might benefit from the research.
  - f) Special efforts shall be made to include women and members of minority groups in studies of diseases, disorders and conditions that disproportionately affect them. (VHA Handbook 1200.9)
- 4) The VA IRB considers subject selection criteria in its review of research to ensure that subject selection criteria are appropriate to the purposes of research, consistent with VA and DHHS policies and fairly distributes the burdens, risks and benefits of the research. The IRB evaluates the following:
- a) The purpose of the research.
  - b) The burdens and risks of the research.
  - c) Potential benefits of the research.
    - i. Probable benefits to the subjects.
    - ii. Importance of the knowledge that may be reasonably expected to result from the research.
  - d) Inclusion criteria.
  - e) Exclusion criteria.
- 5) Whenever employees or volunteers of the VA Ann Arbor Healthcare System are to be used as "healthy subject pools" in research, the VA IRB will scrutinize the recruitment process, to ascertain that consent for participation is sought only under circumstances that minimize the possibility of coercion or undue influence and that public advertisement is employed to facilitate participation of equivalent healthy subjects not susceptible to coercion.
- 6) A VA investigator may not recruit employees they supervise for a human studies research project that includes the VA investigator as a study team member.

#### J. Provisions to protect Privacy and Confidentiality

The VA IRB systematically evaluates research proposals for provisions to protect privacy and confidentiality, including the following elements:

- 1) The methods used to obtain information about individuals who may be recruited to participate in studies
  - a) VA personnel may obtain and use medical, technical and administrative records from this or other VA facilities for research purposes. Requests for records from other facilities must be approved by the IRB and the Medical Center Director before being submitted to the appropriate Service Director in VA Central Office (VHA Handbook 1200.5).
  - b) 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. Requests for such documents must be submitted to the VA IRB and 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.
- 2) Methods used to obtain information about research subjects with informed consent:
  - a) Verbal or written inquiry from subjects, in person or through telephone, mail or electronic means;
  - b) Verbal or written inquiry about subjects from others associated with subjects (i.e. physicians, nurses, spouses), only with prior consent from subjects;
  - c) Physical interaction with subjects, through tests, measurements, procedures;
  - d) Observation of subjects, including eyewitness, videotaping, audiotaping and, photography.
- 3) Nature of information that may be sought.
  - a) Research proposals should state the kinds of information that are being collected. Protocols should include all questionnaires, data collection forms and descriptions of the content of other data formats to be used.
  - b) The nature of some information to be accessed or used may be "sensitive", such as involving use of illegal substances, sexual practices, spiritual or political beliefs. The VA HS-IRB may determine that additional means to ensure privacy are indicated if such information is collected.
- 4) Use of personally identifiable records.
  - a) Access to research data should be limited. Only investigators and designated research staff are authorized to use personally identifiable records. Only specified protected health information may be used or disclosed for specified purposes.
- 5) Methods to protect the confidentiality of research data
  - a) Investigators must design studies to maximize data confidentiality and to avoid unintentional release or other disclosures, as well as minimize the loss of privacy. It may be necessary to utilize original medical or administrative records that contain identifiable information. However data collection processes should be designed to encode information in such a way that linkage with original records or persons can be broken.
  - b) Research data and records should be stored in secure locations. If keys or other linkages exist that identify subjects, these should be stored separately from the records and destroyed at the earliest time, as the research will allow. Research proposals should describe the methods that will be employed to protect the confidentiality of research data.
  - c) Investigators should use measures such as coding, removal of identifying information and limiting access to data.
- 6) The investigator's disclosures to participants about confidentiality.
  - a) The extent of confidentiality that a research subject can expect should be explained at the time of the informed consent process. Details should be included in the informed consent document. If records are subject to audit by sponsors or agencies like the FDA, then explicit statements should be made in the consent document.
- 7) Determination of whether a Federal Certificate of Confidentiality should be obtained.
  - a) A Certificate of Confidentiality is a means to protect against being compelled to disclose identifying information about subjects of biomedical, behavioral, clinical and other research. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.
  - b) A Certificate of Confidentiality will be granted only when the research is of a sensitive nature where the protection is judged necessary to achieve research objectives. Sensitive research involves the collection of information in any of the following categories:
    - i. information relating to sexual attitudes, preferences, or practices;
    - ii. information relating to the use of alcohol, drugs or other addictive products;
    - iii. information pertaining to illegal conduct;
    - iv. information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community;
    - v. information that would normally be recorded in a patient's medical record and the disclosure of which could reasonably lead to social stigmatization or discrimination;
    - vi. information pertaining to an individual's psychological well being or mental health; and,

- vii. genetic information.
- c) A Certificate of Confidentiality must be obtained from DHHS.
- 8) Reporting Loss of Privacy or Violation of Information Security
  - a) The VA IRB Coordinator will report to the Privacy Officer any unauthorized use, loss or disclosure of individually-identifiable patient information.
  - b) The VA IRB Coordinator will report any violations of VA information security requirements to the VHA Information Security Officer.
- 9) Termination or Deletion of Human Use in a research study
  - a) Investigators must destroy or de-identify all research data that includes direct patient identifiers once the data is no longer needed.

#### K. Questions, Complaints and Feedback

The VA IRB process that enables research subjects and others to ask questions or to voice concerns, complaints and allegations of noncompliance with VA IRB policies includes the following factors:

- 1) The Research Compliance Officer or IRB Coordinator will have responsibility for responding to all questions, concerns or complaints regarding an individual's rights as a research subject.
- 2) The Research Compliance Officer or IRB Coordinator will document and ensure an investigation into each question, concern or request for information. Any issue that cannot be resolved will be addressed by the ACOS or the IRB.
- 3) The VA IRB will be responsible for implementing or recommending remedial or disciplinary actions in response to noncompliance with HRPP and IRB policies.
- 4) The institution actively seeks feedback about its research program through surveys, focus groups, interviews or other methods.
- 5) The Research Compliance Officer or IRB Coordinator will conduct annual surveys and present the results to the R&D and IRB. Groups to be surveyed may include the following:
  - a) Current research subjects.
  - b) Former research subjects.
  - c) Potential research subjects (e.g., patients, whether or not eligible for a specific protocol).
  - d) Research subject advocates.
- 6) The results of the Feedback Surveys will be presented in an annual report to the VA IRB and the VA R&D Committee.

### VIII. OPERATIONS OF THE VA IRB.

#### A. Scheduling of Meetings.

- 1) Regular Meetings
  - a) VA IRB members will convene regularly to fulfill their mandate to oversee research involving human subjects at the VA AAHS.
  - b) VA IRB meetings will be held at least once a month; generally on the 2<sup>nd</sup> Thursday.
  - c) The VA IRB Coordinator is responsible for scheduling an alternate date and time for a convened meeting if several voting members cannot attend the planned meeting date. The rescheduled meeting may only be held if a majority of voting members and at least one laymember and one non-affiliated member can participate.
- 2) Emergency Meetings
  - a) The Chairperson of the VA IRB may call for an emergency meeting of the committee.
  - b) The meeting may only be held if a majority of voting members and at least one laymember can participate.
  - c) Members must participate in person

#### B. Selection of Reviewers

- 1) Upon receipt of the documents for an initial review, the VA IRB Coordinator will prepare a copy of the IRB and R&D Application for the IRB Chairperson.
  - a) The IRB Chairperson will assess the scientific or scholarly expertise required for an appropriate and in-depth review of the research protocol
  - b) The IRB Coordinator will inform the IRB Chairperson which regular voting members of the IRB are planning to attend the meeting where the reviews will take place.
  - c) The IRB Chair will identify one of the regular members of the VA IRB, consistent with protocol content and reviewer expertise, to function as the "Primary Reviewer". The Chair will also assign a second member to function as the "Secondary Reviewer."
  - d) The Chairperson will also decide if a research protocol submitted for review requires the scientific or scholarly expertise of a consultant with appropriate expertise to perform an in-depth review. [See description of use of consultants in Section VI.F.]

- 2) Prior to the VA IRB meeting, the primary reviewer will have the authority to request from the applicant investigator, either directly or via the VA IRB office, revisions or additional information or documents. Upon completing his/her review, the primary reviewer will present the project to the VA IRB membership at a meeting of the VA IRB.
- C. Pre-meeting distribution to members, of place and time of meeting, agenda and study material to be reviewed.
- 1) The VA IRB Coordinator will prepare an agenda for each of its meetings. The agenda will include listing and identifiers for all research project applications awaiting action by the Subcommittee on Human Studies. At least five days in advance of the scheduled meeting date, the agenda will be made available for review by members of the VA IRB by distribution to all members. (The VA IRB Chair, or designee will contact the ACOS/ Research if the agenda is not distributed within five days of the planned meeting to discuss alternate plans for distribution of materials or possible rescheduling of the meeting.)
  - 2) For new projects, Primary, Secondary Reviewers (including Alternate Members selected as reviewers) and the IRB Chair will receive the following materials.
    - a) Full protocol.
    - b) Informed consent form or request of Waiver.
    - c) Any relevant merit review or grant applications.
    - d) Investigator's brochure (if applicable).
    - e) Advertisements or subject recruitment information (if applicable).
    - f) Surveys or questionnaires (if applicable).
    - g) The DHHS-approved sample consent document (when one exists). The complete DHHS-approved protocol (when one exists)
  - 3) For new projects, all IRB members (including Alternate Members) will receive at least the following materials
    - a) Protocol summary.
    - b) Informed consent form or request of Waiver.
    - c) Advertising material, (if applicable)
    - d) Surveys or questionnaires (if applicable).
- D. Meeting of the Convened IRB
- 1) The VA IRB Chairperson (or designee of the Chairperson) will determine that the meeting of the IRB is properly convened, including:
    - a) At least one non-affiliated member is present.
    - b) At least one non-scientific member is present.
    - c) More than half of the total number of voting members must be present (a quorum) in order to transact business. (If the IRB has 11 members, then six members present will constitute a quorum.)
- E. Analysis of Risk and Benefits of Research
- 1) The IRB consistently identifies and analyzes potential sources of risk, the measures to minimize risk and the anticipated benefits. The evaluation of research proposal risk includes consideration of the following:
    - a) Study design and scientific rationale.
    - b) Identification of the risks associated with research (including physical, psychological, social, **legal** and economic).
    - c) Assessment of procedures to minimize risk.
    - d) A determination that risks to participants are minimized or is their magnitude reduced by using procedures that are consistent with sound research design and do not unnecessarily expose participants to risk.
    - e) A determination that risks to participants are minimize by using procedures already being performed on the participants for diagnostic or treatment purposes. (if applicable)
    - f) Determination of the level of risks of the research (e.g., minimal, greater than minimal).
    - g) The process for monitoring and reporting unanticipated risks to participants or others.
    - h) Scientific training and human subject protection qualifications of investigators and research staff.
  - 2) The IRB evaluates each research proposal to identify the probable benefits of the research.
    - a) The IRB considers the probable benefits to the subject that may be reasonably expected to result from the research.
    - b) The IRB considers the importance of the knowledge that may be reasonably expected to result from the research.
  - 3) The IRB reviews the plan for data and safety monitoring and determines that the plan provides adequate protection for participants (when applicable).
    - a) **Protocols in which reports of serious harms are expected usually require a plan for monitoring**

**the data for the safety of participants.**

- b) Monitoring might occur at specific points in time, after a specific number of participants have been enrolled, or upon recognition of harm. Monitoring might be conducted by the investigator, the sponsor (e.g., medical monitor, safety monitoring committee), or by an independent monitoring board. The monitoring person might compare the character, incidence and severity of actual harm to that expected, comparing the magnitude and probability of benefits to that expected, or to determine the causality of unexpected harm.
- c) The IRB should evaluate a written plan. The plan might include the information evaluated, harm and benefit to be monitored, study endpoints, timing of monitoring, and decisions to be made by the monitoring process.
- d) The IRB must determine that all of the following requirements are satisfied: [VHA Handbook 1200.5 7.a]
  - (1) The research plan must make adequate provisions for monitoring the data collected to ensure the safety of participants.
  - (2) The plan may include establishing a Data Safety and Monitoring Board (data and safety monitoring board) or a Data Monitoring Committee (data monitoring committee) as required by DHHS or FDA policy, and a plan for reporting data and safety monitoring board or data monitoring committee findings to the IRB. [VHA Handbook 1200.5 7.a(6)]
  - (3) The IRB must review the data and safety-monitoring plan in the protocol developed by the investigator. [VHA Handbook 1200.5 7.a(6)]
  - (4) In addition, for studies that do not have or are not required to have a data and safety monitoring board or data monitoring committee and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, the IRB needs to carefully review the data and safety-monitoring plan. [VHA Handbook 1200.5 7.a(6)]. (For example, a study design comparing two or more interventions in which the investigators, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects; it is sometimes called a masked study design.) [VHA Handbook 1200.5 3.c]
- e) If the IRB reviews all safety information as the research protocol's data monitoring plan, the IRB should make sure it has the necessary clinical, scientific, and biostatistical expertise to provide for the safety of participants.
- f) If the data monitoring plan provides for a DSMB or DMC to review the safety of participants, the IRB is not obligated to perform a duplicate or parallel review.

**F. Criteria for VA IRB approval**

In consideration of approval of a new research application, a request for continued approval, or a request for an amended protocol for research projects involving human subjects, the Subcommittee on Human Studies will review the application and supplied materials to determine that all of the following criteria are met. **[38 CFR 16.111] and [21 CFR 56.111]**

- 1) Risks to subjects are minimized:
  - a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
  - b) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- 2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. 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 therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- 3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- 4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 38 CFR 16.116
- 5) Informed consent will be appropriately documented, in accordance with, and to the extent required by 38 CFR 16.117.
- 6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- 7) 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, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

- 8) In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research) [38CFR16.111(a)(2)].
- 9) The documentation that demonstrates compliance with these criteria will include: IRB applications, IRB reviewer check-lists (signed by the primary reviewer), IRB meeting minutes and IRB correspondence with investigators.

#### G. Voting Requirements

The VA IRB membership will determine the outcome of its review of research project applications at convened meetings, where quorum has been established, in accordance with applicable regulations. [38 CFR 16.108(b)](

- 1) More than half of the total number of voting members must be present (a quorum) in order to transact business. (If the IRB has 11 members, then six members present will constitute a quorum.)
- 2) The chairperson, or in his/her absence an experienced member of the VA IRB, will chair the meetings.
- 3) At least one non-scientist member must be present (diversity of a quorum).
- 4) Greater than 50% of attending members are needed to approve or disapprove a study.
- 5) Only members with full voting rights may vote to approve or disapprove a study.
- 6) Should the quorum fail during a meeting (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored.
- 7) Proxy voting (written or telephone) is not permitted
- 8) Prohibition against conflict-of-interest voting
  - a) When a research project application is reviewed in which a member of the VA IRB may have a conflict of interest, that member will leave the site of the VA IRB meeting for the duration of the review of that application, will not participate in the discussions in any way (except to provide information requested by the IRB) and will not vote on the application.

#### H. Possible IRB Actions

- 1) Approved
- 2) Approved, Pending

When the convened IRB stipulates specific minor revisions requiring simple concurrence by the investigator, the IRB Chair or another IRB member designated by the Chair may subsequently approve the revised research protocol (including a revised VA Consent Form) on behalf of the IRB upon completion of these tasks. The date of continuing review will be based on the date of IRB approval by the convened IRB. [38 CFR 16.111]
- 3) Deferred.

When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB, approval of the proposed research will be deferred, pending subsequent review by the convened IRB of responsive material. [38 CFR 16.111]
- 4) Disapproved.

The project will not be reconsidered in the current design.
- 5) The convened IRB may decide to approve a "closure" of a protocol when the protocol had been reviewed by the IRB and the IRB requested changes but the investigator did not respond. (This is not considered to be a termination of IRB approval "for cause", since the study was not started.)

#### I. Frequency of Continuing Review

- 1) At the time of initial review and at the time of each continuing review, the VA IRB will establish the interval until the next continuation review by taking into consideration the presumed level of research risk in combination with the anticipated benefits. However; the higher the risk, the sooner the date for continuing review will be scheduled. All approved studies will be subject to continuing review at least every 365 days. (The expiration date is the last date on which the research may be conducted.) .The VA IRB will use the following guidelines when determining the appropriate approval period.
  - a) MINIMAL OR LOW RISK = 365 day approval
  - b) MODERATE RISK = 6 month – 365 day approval
  - c) HIGH RISK = 3 month – 6 month approval
  - d) The VA IRB may decide to conduct continuing review before 365 days after a specified number of

subjects have been enrolled.

- 2) The VA IRB may decide not to follow these general guidelines for a particular project. In this case the IRB will document a full discussion of the reasons for making an alternate assignment in the IRB Minutes.

J. Communications to Investigators from the VA IRB.

- 1) The IRB Coordinator will promptly transmit to the principal investigator in writing correspondence conveying actions taken by the IRB including requests for clarifications and modifications required by the IRB
- 2) In general, VA IRB members are advised not to communicate directly with investigators during the IRB review process to protect their anonymity and preserve the status of their professional and personal relationships.

K. Further review/approval of VA IRB actions by others within the institution.

- 1) Minutes of an IRB Meeting will be written and reviewed by the IRB Chair (or designated senior member of the IRB) and the contents will be available for review within 1 week of the meeting date. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority.
- 2) All decisions of the VA IRB are transmitted to the ACOS/Research and the VA R&D Committee by means of the contents of approved VA IRB Minutes.
- 3) The VA IRB Minutes may be reviewed by the Medical Center Director and the Chief of Staff.
- 4) No institutional office or official of the VA AAHS may approve human subjects research that has not been approved by the VA IRB. [38 CFR 16.112]
- 5) No external body or official of the VA AAHS may override a VA IRB decision to disapprove a human subjects research project.

L. Appeal of VA IRB decisions.

- 1) In case of disagreement between the VA IRB and the investigators of a project under review in regards to requested revisions or a decision to disapprove the project, the VA IRB will provide the opportunity of rebuttal for the investigators, either in writing, or by appearing at a meeting of the VA IRB, to defend their cases.
- 2) Mechanism for appeal  
The investigator may submit a revised protocol, revised Consent Form and correspondence that includes further clarifications and justifications
- 3) To whom appeal is addressed  
The appeal should be addressed to the committee chair.
- 4) How appeal is resolved
  - a) The appeal will be discussed as a agenda item at a regular monthly meeting of the committee

M. Modifications to Ongoing Research (including Completion of the study)

- 1) The VA IRB monitors ongoing research during the period for which the research is authorized, including consideration of the following:
  - a) Changes to the research, including changes of principal and co-investigators.
  - b) Reports of unanticipated problems that represent risks to participants or others
- 2) Safety reports, including IND, IDE and MedWatch.
  - c) Protocol violations and/or deviations.
  - d) Investigator non-compliance.
- 3) Investigator requests to modify the research may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant.
  - a) All official letters of correspondence to investigators from the VA IRB include a reminder of this policy. "All changes or deviations from the project protocol, consent form or IRB policies must first be approved by the IRB."
- 3) Upon receipt of the documents for a Modification review, the VA IRB Coordinator will prepare a copy of the application for the IRB Chairperson.
  - a) The IRB Chairperson will assess the scientific or scholarly expertise required for an appropriate and in-depth review of the research protocol
  - b) The IRB Coordinator will inform the IRB Chairperson which regular voting members of the IRB are planning to attend the meeting where the reviews will take place.
  - c) The IRB Chair will identify one of the regular members of the VA IRB, consistent with protocol content and reviewer expertise, to function as the "Primary Reviewer".
  - d) The Chairperson will also decide if a research protocol submitted for review requires the scientific or scholarly expertise of a consultant with appropriate expertise to perform an in-depth review. [See description of use of consultants in Section VI.F.]
- 4) The primary reviewer will receive at least the following materials:

- a) The Application for Modification and all attached documents
  - b) The current approved Consent Form (VA or other form) and any newly proposed consent document.
  - c) Copies of items previously reviewed by the IRB or submitted by the investigator at the time of continuing review that are relevant to the Modification Application, including: Amendments, Reports of **Unanticipated Problems that indicate increased risks to participants or other**, Safety Reports (including IND, IDE and MedWatch), DSMB reports, reports of any withdrawal of subjects from the research) and reports of protocol violations, investigator non-compliance or complaints about the research.
- 5) All IRB members will receive at least the following materials:
- a) The Application for Modification and all attached documents
  - b) The current approved Consent Form (VA or other form) and any newly proposed consent document.
- 6) All amendments to the project or changes in the informed consent must be reviewed and approved by the IRB prior to initiating the changes, except when necessary to eliminate immediate hazard(s) to the participant(s). If the amendment addresses an issue related to biosafety or radiation safety, the appropriate committee or subcommittee must first approve the amendment.
- 7) The completion of the study is a change in activity and should be reported to the IRB.
- 8) In consideration of a request for modification of a previously approved project, the Subcommittee on Human Studies will review the application and supplied materials to determine that all of the following criteria are met: [38 CFR 16.111]
- a) Risks to subjects are minimized:
    - i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
    - ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
  - b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. 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 therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
  - c) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
  - d) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 38 CFR 16.116
  - e) Informed consent will be appropriately documented, in accordance with, and to the extent required by 38 CFR 16.117.
  - f) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
  - g) 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, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
  - h) In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research) [38CFR16.111(a)(2)].

#### **N. Review Reports Unanticipated Problems (UPR)**

- 1) A complete description of definitions, investigator reporting responsibilities, IRB review procedures, and possible IRB actions is found in a separate policy document [**Doc. 110**]  
[VA AAHS Policies and Reporting Form for Unanticipated Problems (UPR) In Human Subjects Research]

#### **O. Conduct Continuing Review**

All approved studies will be subject to continuing review at least every 365 days, starting from the initial IRB approval date. (The expiration date is the last date on which the research may be conducted.)

- 1) The principal investigator of an active research project shall be responsible for submitting to the VA IRB

- office the Application For Continued Use of Human Subjects at least six weeks in advance of the expiration date of the current period of approval.
- a) The VA IRB will send a reminder notice and application template starting at least two months in advance of the date of expiration of the approval period. The VA IRB will continue to send reminders at least once a week until investigator submits a completed application. The reminder notice will include the required date of submission to avoid a lapse in IRB approval.
  - b) If approval for continuation has not been issued by the VA IRB prior to the expiration date, the investigator is obligated to suspend all research activity on the project. Exception may be granted only if the IRB determines there is potential harm to individuals removed prematurely from the study.
  - c) The VA IRB will not conduct expedited review of Applications for Continued Use of Human Subjects
- 2) Upon receipt of the documents for a continuing review, the VA IRB Coordinator will prepare a copy of the application for the IRB Chairperson.
- a) The IRB Chairperson will assess the scientific or scholarly expertise required for an appropriate and in-depth review of the research protocol
  - b) The IRB Coordinator will inform the IRB Chairperson which regular voting members of the IRB are planning to attend the meeting where the reviews will take place.
  - c) The IRB Chair will identify one of the regular members of the VA IRB, consistent with protocol content and reviewer expertise, to function as the "Primary Reviewer".
  - d) The Chairperson will also decide if a research protocol submitted for review requires the scientific or scholarly expertise of a consultant with appropriate expertise to perform an in-depth review. [See description of use of consultants in Section VI.F.]
- 3) The primary reviewer will receive at least the following materials:
- a) The Application for Continued Approval
  - b) The Human Subjects Enrollment Survey, including the following information about subjects recruited:
    - i. Number of subjects accrued since last approval (using VA or other approved Consent Form),
    - ii. For subjects recruited using a VA Consent Form: name and SSN, gender, pregnancy status, minority status and decision-impaired status.
  - c) The Human Studies Research Application updated with all protocol changes**
  - d) The current approved Consent Form (VA or other form) and any newly proposed consent document.
  - e) Advertisements or subject recruitment information (if applicable).
  - f) Subject surveys or questionnaires (if applicable).
  - g) Copies of items previously reviewed by the IRB or submitted by the investigator at the time of continuing review, including: Amendments, Safety Reports (including IND, IDE and MedWatch), DSMB reports, reports of unanticipated problems involving risks to subjects or others reports of subjects that are withdrawn from the research, and reports of protocol violations, investigator non-compliance or complaints about the research.
  - h) The investigators Progress Report submitted as part of the yearly (or more frequent) application for Continued Approval that must include summaries of events that occurred since the last IRB review: Unanticipated problems involving risks to participants or others, participant withdrawals, reasons for withdrawals, complaints about the research, subject benefits, amendments, relevant recent literature, relevant multi-center trial reports, a current risk-potential benefit assessment, assurance that all UPR have been reported as required: and any other information that may impact on the risk/benefit evaluation and the IRB's approval for the research to continue.
    - i) Any relevant multi-center trial reports.
    - j) Any other relevant information, especially information about risks associated with the research. I
    - k) Determination if tissue samples or genetic material will be stored for future, unspecified purposes. (See section X, item O and VHA Directive 2000-043)
- 4) When investigators submit a newly proposed consent document and/ or any modification to the initial application at the same time as continuing review, these items are always reviewed as Modification to Ongoing Research as a separate item in the amendment section of the VA IRB Agenda.
- 5) All IRB members will receive and be encouraged to review all of the following materials.
- a) The Application for Continued Approval. The application includes the number of subjects accrued, total number of subjects planned to be recruited
  - b) The original VA IRB Application with all subsequent approved changes (including the current approved version of the informed consent document).**
  - c) The investigator's summary of findings obtained to date and new scientific findings in the literature or other relevant findings that may impact on the research, the risk/benefit evaluation and the IRB's approval for it to continue
  - d) All \*new\* items submitted at the time of submission of the continuing review application will be reviewed by all IRB members within the corresponding standard sections of the VA IRB Agenda,**

**including: responses to deferred items; Amendment Requests to the protocol (with revised IRB Application), Reports of Unanticipated Problems (that indicate increased risks to participants or others) Reports, Data Safety Monitoring Reports, Other Reports and Communications. Printed copies of these items will be distributed to all IRB members.**

- 6) In consideration of a request for continued approval, the Subcommittee on Human Studies will review the application and supplied materials to determine that all of the criteria are met in [38 CFR 16.111] and [21 CFR 56.111] (See VA IRB Check-Lists for Primary Reviewers.)
- 7) The range of possible actions taken by the IRB for protocols undergoing continuing review includes one of the following actions:
  - a) The research may continue.
  - b) The research may continue with modifications to protocol and/or consent form
  - c) The research will be suspended.
  - d) The research will be terminated.
- 8) The VA IRB requires investigators to maintain approval for continued use of human subjects as long as 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 participants have completed research-related interventions, or when the remaining research activities are limited to analysis of private identifiable information.
- 9) At the time of each continuing review, the VA IRB will establish the interval until the next continuation review by taking into consideration the presumed level of research risk in combination with the anticipated benefits. However; the higher the risk, the sooner the date for continuing review will be scheduled. All approved studies will be subject to continuing review at least every 365 days. (The expiration date is the last date on which the research may be conducted.) .The VA IRB will use the following guidelines when determining the appropriate approval period.
  - a) MINIMAL OR LOW RISK = 365 day approval
  - b) MODERATE RISK = 6 month – 365 day approval
  - c) HIGH RISK = 3 month – 6 month approval
  - d) The VA IRB may decide to conduct continuing review before 365 days after a specified number of subjects have been enrolled.
- 10) The VA IRB may decide not to follow these general guidelines for a particular project. In this case the IRB will document a full discussion of the reasons for making an alternate assignment in the IRB Minutes.
- 11) The minutes of the IRB meeting will document separate deliberations, actions and votes for each protocol undergoing continuing review by the convened IRB.

#### P. Protocols with Lapsed Approval.

- 1) The VA IRB requires that any project with lapsed approval must be stopped.
- 2) The investigator may not recruit new subjects, continue research treatments, follow current subjects, or analyze data that is linked to the identity of current subjects.
- 3) The investigator must notify the IRB if a suspension of medication might endanger subject health and treatment must continue off-study. The IRB Chair, with appropriate consultation with the COS, will determine if the subject may continue in the research.
- 4) The VA IRB Chair will report the expiration of approval to the study sponsor.**
- 5) The investigator may apply to re-initiate the project by submitting a new Human Studies Application (using the most recent version). The application to reactivate the project must be reviewed by a convened meeting of the VA IRB.

#### Q. Quality Assessment / Quality Improvement Activities

- 1) In order to attain and sustain excellence in the institution's Human Research Protection Program (HRPP), the Research Service at the VA Ann Arbor Healthcare System will maintain an active Performance Improvement Program (PIP). The primary goal of the program is to systematically plan, design, measure, assess and improve performance in an ongoing fashion.
- 2) The institution annually evaluates investigator compliance with HRPP and IRB requirements. The institution will audit samples of investigators files on protocols that are greater than minimal risk on an ongoing basis, such as quarterly but dependent on the number of greater than minimal risk protocols.

#### R. Additional IRB Reporting Activities

The IRB documents the following, if applicable:

- 1) Assessment of additional safeguards to protect vulnerable populations if entered as study subjects.
- 2) The basis for allowing a protocol to be exempt from IRB review.
- 3) The basis for allowing waiver or alteration of required elements of the informed consent process,

- documentation of consent, or Waiver of Patient Authorization for Access to Protected Health Information.
- 4) The determination of risk level of investigational devices.
  - 5) When reviewing a research proposal with elements warranting special attention (e.g. placebos, challenge studies, radiation exposure, deviations from standards of care) the IRB documents its consideration of the appropriateness of and rationale for, such elements.

#### S. Sponsored Research

- 1) Sponsored research is any human research involving an external company, institution, individual donor, or organization that is responsible for the initiation, management, or financing of a research study. It includes those funded by government funding agencies, such as NIH, as well as those managed by pharmaceutical companies.
- 2) The Cooperative Research and Development Agreement (CRADA) is used by federal labs to engage in collaborative efforts with non-federal partners to achieve goals of technology transfer. CRADAs establish the terms of sponsored collaborative research, generally with non-federal industry partners and are specifically designed to protect the parties' prior inventions while allowing the government and private sector research partner(s) to negotiate management of any new discovery or intellectual property that may result from the collaboration. CRADAs are governed by Title 15 Commerce and Trade, Chapter 63, Technology Innovation, Section 3710a Cooperative Research and Development Agreements. Related statutes are found in other parts of Title 15 and Title 35 Patents, Chapter 18, Patent Rights in Inventions Made with Federal Assistance.
- 4) In circumstances where a CRADA cannot be used the VAAHS enters into a Clinical Trial Agreement with the Sponsor. Clinical Trial Agreements follow the same principles as are outlined in the CRADA regulations. The VA IRB requires CRADA or a Clinical Trial Agreement whenever sponsored research is carried out at the VAAHS.

#### T. Multi-Site Studies

- 1) For research performed at multiple locations, the VA IRB expects that each institution will review and approve its own participation in the research.
- 2) The VA IRB will not cede to the review of another organization's IRB when any part of a multi-site research study takes place within the VAAHS. The VA IRB will not enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort for the review.
- 3) When the overall principal investigator of research conducted at multiple locations is affiliated with the VAAHS, or the VAAHS is otherwise involved as the primary or coordinating center, the PI must assure the VA IRB that each performance location involved in the research has been properly approved at that location before the research is initiated there and must notify the VA IRB if any lapse or other change in approval status occurs. The VA IRB may take any steps it deems appropriate to verify the information provided by the PI.
- 4) The VA IRB may decide to designate a voting member or staff member to communicate with the IRB at another site in the multi-site study about unanticipated problems for study subjects or non-compliance of investigators. Reports of these communications will be reviewed at the next convened meeting of the VA IRB.

#### U. Suspensions and Terminations of IRB Approval

##### 1) Definitions

a) Suspension: The temporary closing of a human research project or discontinuing an investigator's or key personnel's privilege to conduct or to participate in the conduct of human research. The suspension may be partial in that certain activities may continue while others may stop or it may be complete in that no activity related to the human research or related to the privilege to conduct or participate in the conduct of human research may proceed. The IRB will make this determination.

For suspended research, enrollment for new subjects cannot occur; continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB or IRB Chairperson finds that it is in the best interest of individual subjects to do so. Once suspended, IRB review and re-approval must occur prior to re-initiation of the research

b) Termination: The permanent closing of all activities related to a human research project or an investigator's or key personnel's privilege to conduct or to participate in the conduct of human research, except the continuation of follow-up activities necessary to protect subject safety.

- 2) The IRB may suspend or terminate approval of research at any time if it determines that research activities are not being conducted in accordance with federal regulations or that the research has been associated with

unexpected serious harm to subjects [21 CFR 56.113]. The concerns of the IRB will be conveyed to the Principal Investigator in writing and will include a statement of the reasons for the IRB's action and procedures to be followed. A written response addressing IRB concerns may be required from the Principal Investigator.

- 3) Once notified of the suspension, the PI must immediately submit to the IRB Chair, a list of research subjects for whom suspension of the research would cause harm. The IRB Chair, with appropriate consultation with the COS, determines if the subject may continue in the research.
- 4) When study approval is suspended or terminated by the IRB:
  - a) Current participants are notified that the study has been suspended or terminated.
  - b) Procedures for withdrawal of enrolled participants consider the rights and welfare of participants.
  - c) When follow-up of participants for safety reasons is permitted/required by the IRB, the participants should be so informed.
  - d) When follow-up of participants for safety reasons is permitted/required by the IRB, any outcomes or unanticipated problems (that indicate increased risks to participants or others) should be reported to the IRB and the sponsor.

## **IX. VA IRB DOCUMENTATION AND RECORD RETENTION REQUIREMENTS.**

### **A. VA IRB Membership Roster**

- 1) The IRB roster will include the following information:
  - a) Name
  - b) Earned Degree
  - c) Scientific Status
  - d) Representative Capacity (knowledge about or experience in working with specific vulnerable populations)
  - e) Indications of Experience
  - f) Employment Relationship to the organization
  - g) Affiliation Status
  - h) IRB Position
  - i) Membership Status and term of appointment.
- 2) The IRB roster must include the primary members or class of primary members for whom each alternate member can substitute

### **B. Written procedures and guidelines (including this document)**

### **C. Minutes of IRB Meetings.**

- 1) The VA IRB office will prepare minutes of each meeting of the VA IRB, during which research projects are being reviewed. The minutes will be made available for review by the VA IRB members and the Research Development Committee by distribution to each member at the next regularly scheduled meeting of each committee.
- 2) The VA IRB Minutes may not be altered by anyone including a higher authority once approved by the members at a subsequent IRB meeting.
- 3) The IRB Minutes will be in sufficient detail and will include the following:
  - a) Members present (any consultants/ guests/others shown separately) and absent; documentation that quorum was maintained with a non-scientific member present.
  - b) Summary of separate discussions on debated issues and a record of VA IRB actions and decisions on each protocol undergoing review by the convened IRB.
  - c) Record of voting (showing votes for, against and abstentions)
  - d) Identification of members who did not participate in a discussion and vote due to conflict of interest.
  - e) Reasons for requiring changes in a project, or disapproving, suspending or terminating a project
  - f) If vulnerable groups of subjects were included in the research, the justification for their inclusion and adequacy of special precautions taken to minimize risks
  - g) Specific documentation of findings when approving an alteration or waiver of some or all the required elements of the informed consent procedure or a Waiver of Patient Authorization for Access to Protected Health Information
  - h) Determination of the level of risk and the date of next scheduled continuing review of a project
  - i) When an alternate member replaced a primary member.
  - j) A written summary of the discussion of controverted issues and their resolution.
  - k) Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.

- l) For initial and continuing review, the approval period.
- m) The names of IRB members who absented themselves from the meeting due to a conflicting interest along with the fact that a conflicting interest was the reason for the absence.
- n) Protocol-specific findings justifying determinations required by the regulations for waiver or alteration of the consent process.
- o) The rationale for significant risk/non-significant risk device determinations.
- p) The approval of research contingent on specific minor conditions by the chair or designee to be documented in the minutes of the first IRB meeting that took place after the date of the approval.
- q) The determination of the level of risk.
- r) Attendance at the meetings including those members or alternate members who participated through videoconference or teleconference, and documentation that those members received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.

#### D. Communications from the VA IRB.

- 1) The VA IRB Coordinator will prepare a notification document to inform the applicant principal investigator and the R&D Committee of the outcome of an IRB review. This document will include the following information:
  - a) The actions taken by the VA IRB and the date the decision was reached,
  - b) For approved projects, the determination of risk level, the expiration date of the approval, and the reporting requirements for the principal investigator;
  - c) For disapproved, suspended or terminated projects, the reasons for these decisions and the requirements for re-submission of new projects.
  - d) Terminations and suspensions, instances of serious or continuing noncompliance, and determinations that an event constitutes an unanticipated problem involving risks to subjects or others are reported to the institutional official responsible for the HRPP (the VA ACOS/Research).

#### E. Project History Folders

- 1) Currently approved protocols are maintained in individual investigator project files in the VA Research Office.
- 2) Each project folder will include the following types of documents:
  - a) Application Forms,
  - b) Research Protocol,
  - c) Investigator's Brochure for test articles,
  - d) Relevant grant and federal contract applications,
  - e) Certification Documents from other agencies of the VA AAHS, as mandated by federal regulatory agencies or by the VA AAHS to review and approve a project of a specific type,
  - f) Texts of Advertisements and brochures for subject recruitment,
  - g) Approved and date-stamped versions of informed consent documents,
  - h) Reports of unanticipated problems involving increased risks to subjects or others, DSMB reports
  - i) Notifications of VA IRB decisions
  - j) Requests for approval of Continued Use of Human Subjects
  - k) Primary reviewer check-lists
  - l) Requests for amendments to the protocol and Consent Form,
  - m) Statements on significant new findings
  - n) Records of all IRB review activities
  - o) Correspondence between VA IRB and investigators of the research project.
  - p) Scientific evaluations.
  - q) DHHS-approved sample consent documents.
  - r) Progress reports submitted by investigators.
  - s) Reports of injuries to participants.
  - t) Records of continuing review activities.
  - u) Correspondence between the IRB and the Research and Development Committee.
  - v) Protocol violations submitted to the IRB.
- 3) VA IRB records are the property and the responsibility of the VA Research Office and are maintained and or stored as required to protect the privacy and confidentiality of subjects.

#### F. Record Retention and Accessibility

- 1) The investigator's research records must be retained for a minimum of 5 years after the completion of the study and in accordance with VHA's Records Control Schedule (RCS 10-1), applicable FDA and DHHS regulations, or as required by outside sponsors.
- 2) If a protocol is cancelled without participant enrollment, the R&D Office will retain IRB records for at least five years after cancellation.

- 3) Records of FDA-approved research will be kept for a period of at least 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
- 4) The records are maintained and/or stored in a secure manner to protect the confidentiality of research subject information.
- 5) The IRB controls access to all research project files. Only IRB members and research office staff may access the project files. The IRB and research office staff will provide copies of requested records to the appropriate investigator or study team member.
- 6) The IRB staff will make project records accessible for inspection and copying by authorized representatives of the Veterans Administration and appropriate Federal departments or agencies, at reasonable times and in a reasonable manner.

G. Budget and accounting records.

The VA R&D Committee will be responsible for budget and accounting records.

H. Emergency use reports.

(see Sections XII)

I. Statements of significant new findings provided to subjects.

- 1) The IRB continuously reviews new medical findings and decides if current subjects should be notified.
- 2) The IRB will also review the content of subject notification letters
- 3) The IRB will require the investigator revise the Consent Form for currently enrolled subjects and/or for enrollment of new subjects if significant new findings may affect the subjects willingness to participate in the study.

J. VA IRB Relational Database

- 1) To facilitate tracking of the steps involved in accepting, reviewing and monitoring research projects involving human subjects the VA IRB will maintain one or more databases on all research projects submitted for review.
- 2) The databases will provide adequate resources for tracking research project history, including the dates originally approved by R&D and IRB committees, the date of most recent IRB approval and the date of expiration of IRB continuing approval.

K. Records for VA-Sponsored Tissue Banks (see VHA Directive 1200, dated 3/31/03)

- 1) If human biological specimens are collected and stored for future research purposes not specified in the original VA IRB-approved protocol, then the specimens must be stored in a VA-Sponsored (on-site) or a VA-Approved (off-site) Tissue Bank.
- 2) The VA IRB will have oversight of the operation of the local facility-based Tissue Bank and its data management center.
- 3) The VA IRB will review applications for On-Site Tissue Banks as part of a new project application. The approved project will be subject to continuing review and approval according to standard IRB policies and procedures.
- 4) The ACOS/Coordinator for R&D shall maintain records for all new Tissue Banks within the facility. These records will include the location of the bank and the name of the investigator responsible for the oversight of the bank.

**L. A Resume for each IRB Member**

**X. INFORMATION THE INVESTIGATOR PROVIDES TO THE VA IRB.**

A. Professional qualifications to do the research (including a description of necessary support services and facilities).

B. Documents Required from the Investigator

- 1) An investigator who intends to initiate a research project involving human subjects shall be responsible for submitting the following documents:
  - a) Request to Review Research Proposal to the VA R&D Committee and
  - b) Human Studies Application to the VA IRB.
- 2) No aspect of use of human subjects in research may begin until both the VA IRB and the Research and Development Committee have granted approval.
- 3) Each application shall be accompanied by all documents necessary for an orderly review of the project,

particularly those aspects involving human subjects. The application shall be accompanied by copies of:

- a) Informed Consent documents, prepared by completing the "Informed Consent" template form issued by the VA IRB (may be substituted by the explanatory statement, if VA IRB is being requested to waive the documentation of the consent, as defined in Section XIV and XV).
  - b) Research Protocol (prepared by the investigator for investigator-initiated projects, or by the sponsor of the study) and (if applicable) the Grant Application.
  - c) Investigator's Brochure for investigational drugs or devices (if applicable),
  - d) Texts of advertisements for subject recruitment (if applicable) and
  - e) Any other supporting document that would facilitate a meaningful review.
- 4) Sponsors and Sponsor-Investigators at the VA AAHS
- a) The sponsor takes responsibility for and initiates a clinical investigation. The sponsor may be a pharmaceutical company, a private or academic organization, or an individual. An organization, other than an individual, that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.
  - b) A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed. The sponsor-investigator must meet the requirements FDA 21 CFR part 312 and 21 CFR parts 50 and 56.
  - c) The interrelationship and interaction between the research sponsor (e.g., drug, biologic and device manufacturers), the clinical investigator and the Institutional Review Board (IRB) may be very complex. The regulations do not prohibit direct sponsor-IRB contacts, although, the sponsor-IRB interaction customarily occurs through the investigator who conducts the clinical study. The clinical investigator generally provides the communication link between the IRB and the sponsor. Such linkage is agreed to by the sponsors and investigators when they sign forms FDA-1571 and FDA-1572, respectively, for drug and biologic studies or an investigator agreement for device studies. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The clinical investigator should be kept apprised of the discussion.

C. Study protocol which includes/addresses

- 1) Title of the study and the sponsor of the study
- 2) Purpose of the study (including the expected benefits obtained by doing the study).
- 3) Results of previous related research.
- 4) Subject inclusion/exclusion criteria.
- 5) Justification for use of any special/vulnerable subject populations
- 6) Study design (including as needed, to support an evaluation of sources and mitigators of risk).
- 7) Description of procedures to be performed, extra costs to subjects for their participation in the study
- 8) Identification of risks that may result from the research and steps taken to minimize risk.
- 9) Information about the probable benefits of the research, including the anticipated benefits to subjects and the importance of the knowledge that may be reasonably expected to result from the research.
- 10) Information about the reasons for inclusion of vulnerable subjects and additional safeguards to protect their rights and welfare.
- 11) The circumstances surrounding consent procedure, including subject autonomy concerns, language difficulties and vulnerable populations.
- 12) Advertisements and/or brochures used for subject recruitment and description of recruitment methods
- 13) Payment to subjects for their participation. *The VA IRB will not permit subjects to receive compensation for research that is integrated with a patient's medical care. The VA IRB will not permit subjects to receive compensation for research which makes no special demands beyond those of usual medical care. The VA IRB will not allow excessive payments to research subjects that may be a coercive influence on the subject's decision to participate in the research study. The nature and amounts of compensation must be fully described in the Consent Form.*
- 14) Compensation for injured research subjects. All necessary medical treatment (except in limited circumstances), will be provided in a VA medical facility. Subjects will be treated for the injury at no cost to them. However, no additional compensation has been set aside. Subjects will not be asked to waive any legal rights or released the hospital or its agents from liability for negligence by signing the research consent form.
- 15) The VA IRB will not allow investigators, physicians, or other health care providers to accept personal compensation for recruitment of research subjects. *The VA IRB will allow a study sponsor to reimburse the medical center for performing the study and/or the recruitment of research subjects. This condition must be described in the VA Consent Form.*

- 16) Procedures for documentation of informed consent, including any procedures for using witnesses, translators and document storage and provisions for protection of subject's privacy.

D. Investigator's Brochure (when one exists); relevant Grant Applications

E. Texts of Questionnaires, Survey Instruments, Advertisements and Recruitment Materials for subject recruitment (if applicable)

F. The informed consent document

A description of VA IRB policies and procedures for informed consent are found in the policy document: "How To Prepare a VA Consent Form and Obtain Informed Consent at the VA Ann Arbor Healthcare System" (part of the VA IRB Application Form)

G. Plan for Monitoring Safety of Clinical Trials

- 1) In 1998, NIH issued a policy states that data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III); etc. It includes all types of intervention studies, whether medication or non-medication (e.g., behavioral, prevention, diagnostic) trials. Monitoring should be commensurate with the study risks.
- 2) The VA IRB requires all Clinical Trials that are Phase III, or Multicenter, or recruiting subjects at risk (blinded, high-risk interventions, or vulnerable populations) to establish a Data Safety and Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) as required by DHHS or FDA policy and a plan for reporting DSMB or DMC findings to the IRB.
- 3) The investigator must develop a research plan that contains a description of the data and safety monitoring plan that includes the reporting mechanism of unanticipated problems (involving increased risks to participants or others) to the IRB, and when required to Office of Research Oversight, Office of Research and Development, and other Federal agencies or sponsors. [VHA Handbook 1200.5 10.b]
  - a) The plan may vary depending on the potential risks, complexity and nature of the study. [VHA Handbook 1200.5 10.b]
  - b) A data and safety monitoring board or data monitoring committee needs to be part of the monitoring plan when required by NIH or FDA. [VHA Handbook 1200.5 10.b]
  - c) The use of a data and safety monitoring board or data monitoring committee needs to be considered if there are multiple clinical sites, the study is blinded, interventions are particularly high-risk, or vulnerable populations are included. [VHA Handbook 1200.5 10.b]
  - d) If a data and safety monitoring board or data monitoring committee is used, all events must be reported to the data and safety monitoring board or data monitoring committee and a summary of the data and safety monitoring board or data monitoring committee findings must be reported to the IRB and other entities as required. [VHA Handbook 1200.5 10.f]
  - e) Unanticipated problems (involving increased risks to participants or others), as defined by the monitoring plan in the protocol, must be reported in accordance with the monitoring plan approved by the IRB and as defined in FDA regulations, or other applicable Federal regulations. [VHA Handbook 1200.5 10.f]

H. Requests for Modifications in approved research projects.

- 1) Protocol changes in approved research projects may not be initiated without review and approval by a meeting of the convened VA IRB, except when necessary to eliminate apparent immediate hazards to the subject [38 CFR 16.108(b)]
- 2) Investigators of a previously approved project must submit an Amendment Request Form to make amendments in various aspects of the project. The date of approval of an amendment does not change the date by which the next regularly scheduled continuing review of the project is to be completed.
- 3) An amendment may be in the content or the form of documentation. Types of amendments include the following:
  - a) Amendment for a change in the study protocol
  - b) Amendment in the investigator's brochure describing a test article
  - c) Amendment in the informed consent document
  - d) Amendment in the investigatorship.
- 4) Different types of amendments may be requested individually or in combination.
  - a) Information that may impact on the risk/benefit ratio should be promptly reported to and reviewed by, the IRB to ensure adequate protection of the welfare of the subjects.
  - b) A change in the study protocol or investigator's brochure may require a change in the informed consent

document. The VA IRB will scrutinize the amendment documents to determine the degree to which risks to human subjects may have changed, if there is any need to revise the consent document and if changes in the consent document are adequate. A copy of the current and the revised informed consent document shall accompany the amendment application.

### **I. Reports of Unanticipated Problems**

- 1) A complete description of definitions, investigator reporting responsibilities, IRB review procedures, possible IRB actions and IRB reporting policies and procedures is found in a separate policy document. **[Doc. 110 [VA AAHS Policy and Reporting Form for UPR in Human Subjects Research]].**

### **J. Progress reports and Targeted or Random Reviews to Monitor Active Research Projects.**

- 1) Monitoring of approved projects will occur in the form of data required for Continuing Reviews. Progress Reports submitted as part of the yearly (or more frequent) application for Continued Approval must include summaries of events that occurred since the last IRB review: Unanticipated problems involving risks to participants or others, participant withdrawals, reasons for withdrawals, complaints about the research, subject benefits, amendments, relevant recent literature, relevant multi-center trial reports, a current risk-potential benefit assessment, assurance that all AE or UPR have been reported as required.
- 2) Targeted (or random) monitoring of active research projects will include examinations of research records held by the principal investigator, contacts with former and current research subjects, dispatch of observers to the sites where research involving the human subjects is being conducted.
- 3) In targeting research projects to be subjected to these additional monitoring activities, the VA IRB will consider the level of risks of harm, the frequency and nature of unanticipated problems (that indicate increased risks to participants or others), the vulnerability of the subjects of research, and information provided by from other sources and any complaints received from the subjects.
- 4) Such criteria could include some or all of the following:
  - a) Randomly selected projects;
  - b) Complex projects involving unusual levels or types of risk to subjects;
  - c) Projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB.
- 5) If the information gained during the monitoring process indicates that human subjects of a research project are exposed to unexpected serious harm, or the requirements of the VA IRB are not being met, the VA IRB may suspend or terminate the research. In such instances, the VA IRB will provide the opportunity of rebuttal for the investigators, either in writing, or by appearing at a meeting of the VA IRB to defend their cases.

### **K. Final Report.**

Investigators of a previously approved project are obligated to notify the VA IRB of the completion of the project and to submit a final report of human subject enrollment and any unreported unanticipated problems (that represent increased risk to participants or others).

### **L. Institutional Forms/Reports**

Investigators of a previously approved project are obligated to complete all required institutional forms/reports to maintain compliance with local, state and federal regulations.

### **M. Device Management Plans**

- 1) The principal investigator is responsible for submitting a Device Management Plan that includes the following elements:
  - a) Where and how will the device be stored at the Ann Arbor VA Medical Center?
  - b) How will the device be secured?
  - c) Who will have access to the device?
  - d) Who will be accountable for the secure access and storage of the device?
  - e) How will the dispensing and utilization of the device be tracked?
  - f) How will the tracking records pertaining to the device be maintained?
  - g) Who will be responsible for proper dispensing, utilization and tracking records for the device?

## **XI. EXEMPTION FROM VA IRB REVIEW**

Federal regulatory agencies have recognized certain types of research as having negligible risk to the subjects and considered them to be eligible for exemption from review by institutional review boards. At the VA AAHS, the VA IRB is responsible for determination of exemption by investigators and for making the final determination based on

38 CFR 16, Section 101 and VHA Handbook 1200.5. Notice of concurrence for all exempt research will be promptly conveyed in writing to the investigator.

A. Procedure for IRB approval of exemption request by a VA investigator

- 1) The VA IRB will consider the approval of an exemption request at regularly scheduled meetings of the full committee. (The project proposal must also be submitted to the R&D Committee.)
- 2) The R&D Committee will be notified of the outcome of an exemption review at the next regularly scheduled meeting. The R&D Committee chair or the ACOS/Research may overrule the approval of exemption, but not the rejection of exemption.
- 3) The R&D Coordinator will prepare and transmit final notifications to investigators following reviews and decisions of the R&D and IRB Committees.
- 4) The R&D Project Database will maintain a list of all research projects that are approved for exemption from further review by the Committee.
- 5) Exemption determinations are not to be made by investigators or others who might have an apparent or real conflict of interest regarding the studies. **(Cannot be applied to FDA-regulated research)**
- 6) -Although most exempt research requires no further oversight to be conducted ethically, some exempt research raises ethical concerns or requires measures to protect participants. The VA IRB will evaluate whether exempt research fulfills the organization's ethical standards. The VA IRB has full authority not to grant exemption even if the proposed research meets statutory criteria for exemption. The VA IRB Minutes and the written correspondence to the investigator will include a detailed description of the IRB reasons for not approving an investigator's request for exemption of a proposed research study.
- 7) The R&D Committee Coordinator will inform the IRB Coordinator if amendments or other modifications to research determined exempt must be re-submitted to the IRB for re-review.

B. Categories of Exempt Research

- 1) Federal regulatory agencies have recognized certain types of research as having negligible risk to the subjects and considered them to be eligible for exemption from review by institutional review boards. (38CFR16.101(b))
- 2) The VA IRB will review and approve for exemption from continued review research activities in which the only involvement of human subjects will be in one or more of the following categories
  - a) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as ( i ) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
  - b) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: ( i ) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human 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, reputation **or loss of insurability.**
  - c) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: ( i ) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
  - d) Research, involving the collection 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, directly or through identifiers linked to the subjects.  
**(The IRB reviewer will determine that the cited materials existed at the time the research was proposed.)**

Definition of de-identified data from HIPAA Privacy Rule 164.514(a)-(c)

De-identified data does not contain the following information: name, address (including all geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their

equivalent geo-codes, except for the initial three digits of most zip codes), all elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death, age over 89 and all elements of dates (including year) indicative of age over 89, except that ages over 89 may be aggregated into a single category of "age 90 or older", telephone and fax number, e-mail address, social security number, medical record number, health plan beneficiary number or account number, certificate/license number, vehicle serial number, URL or IP address, biometric indicators such as finger or voice prints, full face photographic images, any other uniquely identifying characteristic.

(The investigator will not be able to re-link the data to the identity of the subject.)

- e) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.  
**(The IRB reviewer will determine that the protocol: will be conducted pursuant to specific federal statutory authority; will not have any statutory requirements for IRB review; will not involve significant physical invasions or intrusions upon the privacy interests of participant; the investigator will have authorization or concurrence by the funding agency.)**
- f) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

## XII. EMERGENCY SITUATIONS AND TREATMENT INVESTIGATIONAL NEW DRUG OR DEVICE EXCEPTIONS

### A. IRB Review of Research in Emergency Situations

- 1.) DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject and any data regarding such care may not be included in any report of a prospectively conceived research activity. (see 38 CFR 16.103(b) and 46.116(f))
- 2.) FDA regulations permits patients given emergency use test articles without prior IRB review and approval to be considered as research subjects and data from the emergency use may be used in research through reporting to the sponsor and the FDA.

### B. Treatment Investigational New Drug or Device Exceptions (Treatment IND)

- 1) The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.
- 2) There are four requirements that must be met before a treatment IND can be issued:
  - a) The drug is intended to treat a serious or immediately life-threatening disease;
  - b) There is no satisfactory alternative treatment available;
  - c) The information available must be sufficient to conclude that the test article may be effective for the intended use and would not expose the patient to an unreasonable risk (usually, this information becomes available early in Phase 3, or sometimes in Phase 2 of clinical trials); and
  - d) The trial sponsor is actively pursuing marketing approval.
- 3) Treatment IND studies require prospective IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.
- 4) Data obtained as a result of a drug or device use under 21 CFR 312.34 may be used for research, only with prior IRB approval.

### **C. Emergency use of Test Articles**

- 1) The investigator must report to the VA IRB any emergency use of a test article according to the FDA policy [21 CFR 56.104]. FDA requirements for emergency use of a test article include the following definitions:
  - a) Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. [21 CFR 56.102(d)]
  - b) Whenever possible, the VA IRB Chairperson and the VA Research Pharmacist must be notified prior to emergency use.
  - c) Emergency use of a test article may be exempted from IRB review provided that such emergency use is reported to the VA IRB Chairperson within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR 56.104(c)]
  - d) Under DHHS regulations, whenever emergency care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject and the data derived from use of the test article may not be used in a prospective systematic investigation designed to develop or contribute to generalizable knowledge.
  - e) Under FDA regulations, patients given emergency use test articles are considered research subjects and data from the emergency use may be used in research through reporting to the sponsor and the FDA.
- 2) If full IRB approval cannot be obtained and use of the investigational drug, biologic or device meets the criteria for single time emergency use, the following steps must be completed prior to the use:
  - a) The VA IRB Chairperson (or a designated IRB member) must be notified **prior** to the single time emergency use. This is usually accomplished by a phone call and submission of the Single Time Emergency Use Request Form [VA IRB Doc. 122]. Verbal or written approval from the VA IRB Chairperson must be obtained prior to use.
  - b) If the VA IRB Chairperson (or a designated IRB member) is not available before the use of the test article, both the investigator and a physician who is not otherwise participating in the single time use of the test article must complete the "Single Time Emergency Use Request Form" [VA IRB Doc. 122], to certify that all of the criteria for single time emergency use have been met.
  - c) The Investigator must submit to the VA IRB Chairperson a completed "Single Time Emergency Use of a Test Article Request Form", a copy of the informed consent or a written justification that informed consent could not be obtained, and any available documentation from the sponsor within five (5) days working days after the test article is used.
  - d) The VA IRB Coordinator will assure that all submitted materials are distributed to the IRB Chair (or a senior member of the VA IRB) as soon as they are received to be reviewed within the next 48 hours. The materials will also be included in the agenda for the next convened meeting of the IRB.
- 3) Even for an emergency use the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative. The 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.
- 4) If informed consent cannot be obtained from the subject or the subject's legally authorized representative, then the investigator and a physician not otherwise involved in the use [21 CFR 50.23(a)] must certify in writing all of the following:
  - a) The subject is confronted by a life-threatening situation necessitating the use of the test article.
  - b) Informed consent cannot be obtained because of an inability to communicate with or obtain legally effective consent from the subject.
  - c) Time is not sufficient to obtain consent from the subject's legal representative.
  - d) There is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.
- 5) If the four conditions above apply (4a – 4d), the clinical investigator should make the determination. If an independent physician is not available to certify that the criteria are met at the time of the use, the determination should be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation within 5 working days after the use of the test article. [21 CFR 50.23(cb)].
- 6) The IRB Chairperson (or a designated IRB member) will review the intent to invoke or the five-day report of the exception to the requirement to obtain consent for the use of a test article on an emergency basis to determine that the circumstances would follow or have followed FDA regulations.  
(The Emergency Use report will be reviewed at the next convened meeting of the VA IRB.)
- 7) All emergency use of investigational articles without prior IRB approval must be reported to the VA IRB

Chairperson within 5 days, even when informed consent was obtained. The IRB will review the emergency use report at the next convened meeting.

D. Exceptions from Informed Consent Requirements for Emergency Research (21CFR50.24)

- 1) The VA IRB will not review or approve requests for a waiver of the requirement for consent for planned emergency research.**
- 2) The VA IRB will not approve exceptions from informed consent for emergency research.**

**XIII. POLICIES FOR EXPEDITED REVIEW**

A. VA IRB Policies

- 1) The VA IRB will not conduct expedited review of new research project applications.
- 2) The VA IRB will not conduct expedited continuing review of projects previously approved by the VA IRB.
- 3) The VA IRB will not conduct expedited review of project amendments.
- 4) The VA IRB will not conduct expedited review of the addition of investigators to protocols. (Investigators are defined as individuals who are accountable for the overall conduct of a particular research protocol.)
- 5) The VA IRB will not conduct expedited review of the risk level of devices used in research.

**XIV. RESEARCH PROJECTS ELIGIBLE FOR WAIVER OF THE REQUIREMENT FOR SIGNED INFORMED CONSENT: WITH ORAL INFORMED CONSENT**

A. VA IRB Policy for Waiver of Signed Informed Consent

The VA IRB may waive the requirement for documentation of the informed consent (a signed written informed consent document), but not that of obtaining informed consent, under the following circumstances:

- 1) The investigator must provide a VA IRB-approved, printed document to the subject that includes the basic elements of informed consent [38 16.116(a)]
  - a) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
  - b) A description of any reasonably foreseeable risks or discomforts to the subject;
  - c) A description of any benefits to the subject or to others which may reasonably be expected from the research;
  - d) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
  - e) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
  - f) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
  - g) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
  - h) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

And,

- 2) The principal risk would be potential harm resulting from a breach of confidentiality and the only record linking the subject and the research would be the consent document. (In this case, each subject must be asked whether the subject will allow documentation linking the subject with the research, and the subject's wishes must govern).

Or,

- 3) The research presents no more than minimal risk of harm to subjects (i.e., the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests); and involves no procedures for which written consent is normally required outside of the research context.

[38 16.117(c)]

## **XV. HUMAN SUBJECT RESEARCH ELIGIBLE FOR WAIVER OF THE REQUIREMENT FOR INFORMED CONSENT OR ALTERATION OF ELEMENTS OF INFORMED CONSENT**

### **A. VA IRB Policy for Waiver or Alteration of Informed Consent**

To comply with the Common Rule (45 CFR 46) the IRB must determine the following before approving a Waiver or Alteration of informed consent:

- 1) The research involves no more than minimal risk to the subjects (i.e., the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests).
- 2) The alteration or waiver will not adversely affect the rights and welfare of the subjects.
- 3) The research could not practicably be carried out without the alteration or waiver of authorization.
- 4) Whenever appropriate, the subjects (including their physicians, as applicable) are provided with additional pertinent information after participation.

### **B. VA IRB Policy for Waiver of Informed Consent for Access to Protected Health Information for Patient Screening and Research Data Collection**

To comply with The HIPAA Privacy Rule [45 CFR 160 and 45 CFR 164], the VA IRB may waive the requirement for obtaining informed consent under the following circumstances:

- 1) The investigator must provide a specific description of the Protected Health Information (PHI) to be accessed.
- 2) The use of the PHI involves no more than minimal risk to the privacy of individuals, as explained below in items a, b and c
  - a) The investigators will protect the identifiable patient information from improper use or disclosure (including limitations to physical and electronic access.)
  - b) The investigators will destroy the patient identifiers at the earliest opportunity, consistent with conduct of the research (with an explanation if there is a health, research or legal justification for retaining the patient identifiers).
  - c) The identifiable information will not be reused or disclosed to any other person or entity outside the VHA other than those identified in the protocol, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB. (The investigator must justify the need to reuse or disclose the identifiable information.)
- 3) The investigator must explain why it will not be practicable to obtain patient authorization to access the PHI.
- 4) The investigator must explain why the research could not be practicably carried out without the waiver for access to the PHI.

## **XVI. WRITTEN INFORMED CONSENT**

### **A. Consent Form Requirements**

- 1) A VA Consent Form (Form 10-1086) must be used to recruit research subjects at the VA AAHS if the research will be conducted at the Ann Arbor VA site with direct contact with human research subjects **or** if the research will be conducted off-site and the research is funded by the VA (e.g. MERIT or VERAM).
- 2) An approved Consent Form from another research institution may be used to recruit research subjects if the research study is funded and administered by non-VA sources, research subjects will not be studied at the Ann Arbor VA and VA resources will not be used (informed consent may not be conducted on the VA site).
- 3) The VA IRB will not allow the use of a Short Form Consent document.

### **B. Basic Elements of Informed Consent (VA Form 10-1086)**

In obtaining informed consent, the investigators shall give the subject (or legally authorized representative) sufficient information about the study and how the study may affect the subject. The consent information must contain all the 8 basic elements of information set forth in The Common Rule (38CFR16.116(a 1-8)) and in FDA regulations (45CFR46.116(a 1-8)).

- 1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental;
- 2) A description of any reasonably foreseeable risks or discomforts to the subject;
- 3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

- 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- 5) A statement that the FDA and other regulatory and compliance agencies may inspect the records
- 6) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- 7) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

**The VA Ann Arbor Healthcare System will provide the same compensation and medical treatments in the case of a research-related injury to non-veteran participants enrolled in VA-approved research**

- 8) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject; and
- 9) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 10) A description of the amount (if any) and the schedule of payments to subjects.

#### C. Additional Elements of Informed Consent (VA Form 10-1086)

- 1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- 2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- 3) Any additional costs to the subject that may result from participation in the research.
- 4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- 6) The approximate number of subjects involved in the study
- 7) Describe the form of payments and how payments will be made to compensate subjects.

#### D. Informational Component of Informed Consent

- 1) Deliver the information in a comprehensible manner, using a language readily understandable by the subject or the subject's legally authorized representative.
- 2) The appropriate reading level of the consent form must be based on the education level of the potential population (6th grade education at the Ann Arbor VAMC).
- 3) Investigators may not recruit non-English speaking subjects without preparing validated translations of consent forms into the subject's native language.
- 4) The VA IRB prohibits any informed consent, whether oral or written, from including any exculpatory language through which the subject or the subject's 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.
- 5) The content of the Consent Form must be consistent with applicable laws of the State of Michigan.

#### E. Authorization to Release Protected Health Information

- 1) The IRB will ensure that the required language for a valid authorization to release health information (Health Insurance Portability and Accountability Act (HIPAA) Authorization) is included in the informed consent document.
- 2) The IRB may waive the requirement for an authorization or may alter the form or content of the authorization only in accordance with and as permitted by the HIPAA Privacy Rule (45 CFR 164.508). Such actions and the justification for them will be fully documented in the minutes of the IRB meeting where the action was taken.

#### F. Obtaining Informed Consent

- 1) If the IRB requires investigators to obtain informed consent prior to entering a subject into a study, the VA IRB approved version of the VA Consent Form must be used to recruit research subjects to participate in research studies at the VA AA HCS.
- 2) The VA IRB has the authority to determine who is eligible to inform the prospective subject about all aspects of

the trial and conduct the informed consent process.

- a) The person who conducts the consent interview should be knowledgeable about the study and be able to answer questions. (The FDA does not specify who this individual should be.)
- b) If someone other than the clinical investigator conducts the interview and obtains consent, this responsibility should be formally delegated by the clinical investigator and the person so delegated should have received appropriate training to perform this activity.

#### G. Documentation of Obtaining Informed Consent

- 1) The IRB requires informed consent to be documented by the use of a written consent form, VA Form 10-1086, approved by the IRB and signed and dated by the subject, by a witness to the subject's signature and by the investigator obtaining the consent (except in cases where the written documentation of informed consent is waived by the IRB). (VHA Handbook 1200.5)
- 2) Witness Requirements
  - a) The VA IRB requires a witness to the signature of the subject or the subject's representative.
- 3) Under appropriate conditions, the VA IRB may approve the investigators to obtain informed consent from a research subject's legally authorized representative (surrogate consent). Such consent may be required when the prospective research participant is incompetent as determined by two VA physicians (after appropriate medical evaluation) and there is little or no likelihood that the patient will regain competence within a reasonable period of time, or as established by a legal determination. The VA IRB may decide that the inclusion of incompetent subjects or persons with impaired decision making ability are suitable as research subjects in a study under the following conditions:
  - a) The investigator demonstrates a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects.
  - b) The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there is at least a greater probability of direct benefit to the participant.
  - c) Procedures are devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity.
- 4) A legally authorized representative may sign a VA Consent Form for a subject who is determined to be incapable of making an autonomous decision (according to FDA, VA policy, state and local law).

According to VHA Handbook 1200.5, sect 3(q), a legally authorized representative may include: a Health Care Agent appointed under a Durable Power of Attorney for Health Care (DPAHC), a court-appointed guardian, or next-of-kin in the following order of priority: Spouse, Adult child (18 years of age or older), Parent, Adult sibling (18 years of age or older).

[Michigan state law is silent on this issue, so deference is given to federal law.]  
[FDA defers to state and local laws regarding who is a legally authorized representative.] (FAQ 1998, #44)

  - a) Individuals with impaired cognitive judgment but able to understand the research must give their assent to participate in the study. Persons are capable of assent if they "know what procedures will be performed in the research, choose freely to undergo those procedures, communicate this choice unambiguously, and [know that they] may withdraw from participation.
  - b) The "mere absence of objection" ought not be interpreted as assent. The consent of a potential subject's legal guardian to authorize greater than minimal risk research involving non-objecting persons incapable of assent.
- 5) The documentation of informed consent shall be executed using the IRB-approved date-stamped version of the Consent Form (includes both the approval and expiration dates).
  - a) After fully understanding all the elements in the document, the subject must put his/her initials at the bottom of each page and then sign the Subject's Rights Page (last page)
  - b) If the subject has a legally authorized representative, the representative should also sign and enter the date on the Subject's Rights Page of the consent document. The subject should not begin participation in the study until the Consent Form is signed.
  - c) A witness to the signature of the subject or the subject's representative must also sign and date.
  - d) The principal investigator must also sign and date the Subjects Rights page
- 6) The investigator must then make at least one photocopy of the signed document.
  - a) The original signed copy must be kept in the investigator's case history files.
  - b) A photocopy must be given to the subject.
  - c) A scanned copy must be placed in a Research Enrollment Warning Note (REWN) in the Computerized Patient Medical Record (or a second photocopy must be placed in the patient's paper medical record). The REWN has an automatic template that includes fields for subject enrollment date and termination date.

#### H. IRB Observation of Informed Consent

- 1) The VA IRB has the authority to evaluate the research plan and to observe the process to obtain informed consent as a method to provide additional safeguards to adequately protect the rights and welfare of research participants. The evaluation and/ or observation may include:
  - a) Assessing the subject's capacity to consent to a research protocol, if applicable.
  - b) Ensuring that information is given to the subject, or the subject's legally authorized representative, in a language that is understandable to the subject or representative.
  - c) Providing the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate.
  - d) Ensuring that subjects give consent without coercion or undue influence.
- 2) Procedures
  - a) The VA IRB will determine when it is appropriate to observe the informed consent process for a specific investigator (or authorized study team member) and for a research specific study.
  - b) Protocols selected for consent observation may represent higher risk studies, studies that involve complicated procedures or interventions, studies involving potentially vulnerable populations or those involving study staff with minimal experience in administering consent to potential study participants
  - c) The ACOS/ Research or the VA IRB Chair will appoint a trained Research Service staff member (Research Compliance Officer or IRB Coordinator) to observe the consent process and to submit a written report of findings.

### **XVII. REQUIREMENT FOR APPROVAL OF CERTAIN TYPES OF HUMAN SUBJECT RESEARCH BY ADDITIONAL AGENCIES OF THE VA ANN ARBOR HEALTHCARE SYSTEM**

Certain types of research involving human subjects will have to be reviewed and certified by additional agencies of the VA Ann Arbor Healthcare System, as required by Federal regulatory agencies, sponsors, or the VA Ann Arbor Healthcare System itself. Depending upon the type of research, one or more certifications will be a requirement for approval by the VA IRB. To prevent delays in the total review process, at its discretion, the VA IRB may accept concurrent review by the VA IRB and the other agency, but defer the final decision until a notice of certification has been received.

#### A. Investigational Drug Service

As mandated by the administration of the VA Ann Arbor Healthcare System, the Pharmacy of the VA Ann Arbor Healthcare System will be responsible for safe-keeping, dispensing and monitoring of investigational drugs administered to human subjects within the confines of the institution. The same regulation will apply to studies involving marketed drugs and a placebo, being dispensed in a blinded or masked manner. For such drug studies, the VA IRB will require prior certification by the Pharmacy as a condition for approval.

- 1) The VA R&D Office will provide copies of the research Protocol, Investigator Brochure, Form 10-1223, Form 10-9012, and the Drug Management Form to the Investigational Drug Service.
- 2) The VA Research Pharmacist will serve as a voting member of the VA R&D and VA IRB Committees.

#### B. Subcommittee on the Human Use of Radioisotopes

The protocol of research studies involving the administration of radioactive substances to human subjects will be reviewed and approved by the VA AAHS Subcommittee on the Human Use of Radioisotopes (SHUR). When applicable, the VA IRB will require prior certification by this subcommittee as a condition for approval.

#### C. Hospital Biomedical Engineering Unit

- 1) As mandated by the administration of the VA AAHS, all devices, regardless of whether they are investigational or marketed devices, will be inspected by the Bioengineering Service of the VA AAHS. For studies involving devices to be used on or in human subjects, the VA IRB will require prior certification by the Bioengineering Service as a condition for approval.
- 2) The Bioengineering Service will advise the research investigator and the VA IRB on the appropriate procedures regarding the use of investigational devices that include storage, security and dispensing.

### **XVIII. CREDENTIALING & TRAINING OF IRB MEMBERS AND INVESTIGATORS INVOLVED IN HUMAN SUBJECTS RESEARCH**

- A. The VA IRB provides required educational training in Human Subject Protection to IRB Members, Research

Investigators and Team Members.

- 1) The VA IRB educates IRB Members, Research Investigators and Team Members about and holds them accountable for, protecting the rights, safety and well-being of human research participants. The VA IRB ensures that all individuals with responsibility for human subject protection have completed required training in human research subject protection and Good Clinical Practice.
  - 2) The VA IRB Coordinator will ensure that the type and scope of human subject education and training meets VA and Federal requirements.
  - 3) The VA IRB Coordinator will identify the individuals for whom training is required in compliance with VA and Federal requirements. (These will include all VA IRB members, Principal Investigators, Study Coordinators, Study Team Members and persons administering Informed Consent.
  - 4) Individuals must certify they have met training requirements by submitting a certificate of completion or the results of a test administered at the end of an authorized instruction program.
  - 5) The VA IRB requires that all VA IRB members, Principal Investigators, Study Coordinators, Study Team Members and persons administering Informed Consent must participate in human research protection training on an annual basis (within 365 days of the previous training) that is approved by VA ORD.
- B. The VA IRB maintains a tracking system for required educational training
- 1) The VA IRB Coordinator will maintain a log or tracking system of required training received by all individuals with responsibility for human research protection.
  - 2) The log or tracking system will include completion dates and certificate numbers of approved training in human subject research protection.
- C. Credentialing Non-VA Human Studies Research Workers
- The Ann Arbor VAMC complies with the "Stand-Down" order issued by VA Office of Research and Development on March 6, 2003.
- 1) The VA IRB will establish and maintain a program to verify the academic and professional credentials of all non-VA human studies research workers who conduct all or part of their research directly at a VA site.
  - 2) The VA IRB will establish and maintain a process to ensure that the VA Human Resources Office initiates and completes a background investigation on all non-VA human studies research workers who conduct all or part of their research directly at a VA site

## **XIX. REGULATORY & ADVISORY DOCUMENTS**

### **A. Federal**

1. "Protection of Human Research Subjects" Title 45 Code of Federal Regulations Part 46 (38 CFR 16), issued by the United States Department of Health and Human Services.
2. "Protection of Human Subjects" Title 21 Code of Federal Regulations Part 50 (21 CFR 50), issued by the United States Food & Drug Administration.
3. "Institutional Review Boards" Title 21 Code of Federal Regulations Part 56 (21 CFR 56), issued by the United States Food & Drug Administration.
4. "Investigational Drugs" Title 21 Code of Federal Regulations Part 312 (21 CFR 312), issued by the United States Food & Drug Administration).
5. "Investigational Devices" Title 21 Code of Federal Regulations Part 412 (21 CFR 412), issued by the United States Food & Drug Administration.
6. "Federal Policy for the Protection of Human Subjects", which represents a consolidation of related regulatory policies of all federal agencies, issued by the United States Department of Health and Human
7. "Protecting Human Research Subjects: Institutional Review Board Guidebook", prepared by the Office for Protection from Research Risks of the National Institutes of Health.
8. "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research", prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979).
9. "The Nuremberg Code", derived from the Trial of Criminals of World War II by the International Military Tribunal (1949).
10. "World Medical Association Declaration of Helsinki" (adopted in 1964; most recently amended in 1989).
11. Amendments to regulations and news releases by federal regulatory agencies.
12. "Protection of Human Subjects" Title 38, Code of Federal Regulations, Part 16 (CFR16), issued by the Department Of Veteran Affairs.
13. VHA Handbook 1200.5 (updated 6/28/05), "Requirements for the Protection of Human Subjects in Research"
14. VHA Handbook 1058.1 (11/19/04), "Reporting Adverse Events In Research To The Office Of Research Oversight"
15. VHA Handbook 1058.1 (9/08/05), "What to Report to the Office of Research Oversight"
16. VHA Handbook 1058.2 (5/04/05), "Research Misconduct"
17. VA Ann Arbor Healthcare System (8/23/05), "Policy and Procedures for Dealing with Research Misconduct"
18. VHA Directive 1200 (3/31/03), "Banking of Human Biological Specimens Collected from Veterans for Research"
19. VHA Directive 2005-050 (11/04/05), "Requirements for Conducting VA-Approved International Research Involving Human Subjects, Human Biological Specimens or Human Data"
20. VA Directive 6504, "Restrictions on Transmission, Transportation and Use of, and Access to, VA Data Outside VA Facilities" (6/07/06).
21. VA IT Directive 06-2, "Safeguarding Confidential and Privacy Act-Protected Data at Alternative Work Locations" (6/08/06).