



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

**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 (VAAHS).

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I. THE INSTITUTIONAL AUTHORITY UNDER WHICH THE VA IRB IS ESTABLISHED

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 (VAAHS) and receives administrative support from the Research Service.

II. 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 VAAHS, 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 VAAHS 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 VAAHS.

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 (also VA definitions in 38 CFR 16)

"Research" as defined by DHHS regulations means a systematic investigation, including research development, testing and evaluation, *[including hypothesis formulation, testing by experimentation or analysis, and a statement of logical conclusions]* designed to develop or contribute to generalizable knowledge *[knowledge that could be applied to populations outside the covered entity]*. [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 VAAHS 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 1200.05. 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 VAAAHS, in each of the following categories.

- 1) Research performed at the VAAAHS
- 2) Research projects that will recruit patients at the VAAAHS that are not performed on site
- 3) VA-funded research that is conducted by investigators of the VAAAHS.
- 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.
- 4) To observe or have a third party observe the consent process and the research.

D. Collaborating Institutions

- 1) The VAAAHS 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 VAAAHS 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 VAAAHS 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 VAAAHS.
- 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 VAAAHS or its non-profit foundation, the Veteran's Education and Research Association of Michigan (VERAM). This review is for the VAAAHS involvement in the research, and does not constitute the VAAAHS IRB's acting as the IRB of record for the non-affiliated institution.
 - a. The VA IRB only reviews and approves the part of the research that takes place at VAAAHS, not the part

that takes place elsewhere, unless it is off-site research done by VA employees on VA time.

b. The VA IRB has an obligation to ensure that the off-site collaborators have FWAs and have obtained their local IRB approval.

- 2) The VA IRB will also 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

a) The VA IRB will have a chairperson. The Chairperson will hold a VA appointment and will be recruited from among active members of the staff of the VA Ann Arbor Healthcare System.

b) The Chairperson may be recommended by the ACOS/Research with the approval of the COS. The chairperson will be appointed by the Medical Center Director

c) The Chairperson will possess the professional competence necessary to review human subject research in all categories encountered at the VAAHS 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 by the Medical Center Director for a term of 3 years and may be re-appointed indefinitely

3) Duties

The IRB Chairperson or designee 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 VAAHS 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) The VA Research Pharmacist will serve as a voting member of the VA R&D and VA IRB Committees.

e) At least one member will be a non-scientist (laymember).

f) At least one member will be a community representative (non-affiliated member).

(1) A laymember and a non-affiliated member can be the same person.

(2) The VA IRB encourages the involvement of its laymembers and community members in the design and implementation of research and, when appropriate, in the dissemination of results.

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

h) 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 additional, three-year periods, 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
- 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, WOC Employees, retired IRB Members, 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 VAAHS.

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 selection of alternate members by the Associate Chief of Staff for Research will be based on recent participation as a voting member in the VA IRB (appointed by the Medical Center Director) with 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. An alternate may substitute for more than one voting member, and a voting member may have more than one alternate.
- 3) Alternate members will have full voting rights and they will be included in determining or establishing quorum at VA IRB meetings. The IRB Minutes will identify for whom the alternate is substituting.
- 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. Training materials include mandatory training modules, procedural updates/guidance from ORO, educational articles provided by the Chair or IRB Coordinators, and any other material deemed appropriate.
 - 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

The Chairperson and laymembers 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). *[The VAAAHS can make a WOC appointment for non-affiliated members to provide this protection, as long as the appointment is only for IRB participation.]*

J. Resources

The VA IRB will conduct meetings at the VAAAHS. 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 may identify, review and require appropriate changes in protocols affected by conflict of interest for research involving human subjects when such conflicts are discovered during review. 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 1200.05 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 by reviewing audits/reports provided by the Research Compliance Office or when notified of issues by IRB office staff, study team members or others.
- 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 VAAHS 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 requirement of flagging Medical records is no longer required per VHA Handbook 1200.05 (11/12/14), but The IRB may determine that 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, such as the study is categorized as greater than minimal risk, or an investigational drug or device is being utilized in 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.
 - (e) A Certificate of Confidentiality has been obtained.

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 5 days of a VA IRB action, printed correspondence to the principal investigator and the appropriate institutional officials (including the Medical Center Director) 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.

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 by the Research Compliance Officer

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.
 - a) For projects of more than minimal risk that have a DSMB or DMC, the IRB will review a cumulative list of SAEs with each continuing review.
 - b) For projects with DSMB or DMC, the Principal Investigator should include copies of DSMB/DMC reports from the prior 12 months with each continuing review.

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 1200.05 and FDA 21 CFR parts 50 and 56) and as described in the FDA "Blue Book Memo - Significant Risk and Non-significant 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 IRB Coordinator 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) Fetuses or human fetal tissue
 - b) In vitro fertilization
 - c) Prisoners
 - i) Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the VA Chief Research and Development Officer (VA CRADO). If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). NOTE: Requirements for requesting a waiver may be obtained by contacting the Office of Research and Development at VA Central Office.
 - ii) 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. *There are special membership and procedural requirements for the IRB to approve this request. This request must also be approved by the VA CRADO.*
- 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.
- e) d) Children

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 cannot be included in VA-approved research conducted by VA investigators while on duty, or conducted at VA facilities or approved off-site locations, unless approval has been given by the Facility Medical Center Director and the IRB has the appropriate expertise to evaluate any VA research involving children and must comply with the requirements of 45 CFR 46.401 – 46.404 and 46.408..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 persons who are mentally disabled or who are at high risk for impaired decision making capacity 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 persons who are mentally disabled or who are at high risk for impaired decision making capacity 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 VAAHS 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.
- 5) For research involving the participation of pregnant women as research subjects, the Facility Medical Center Director must:
 - a) Certify that the VA Medical Facility has sufficient expertise in women's health to conduct the proposed research.
 - b) Provide a Memorandum of Approval stating that the VA Facility Medical Center Director is aware of and approves the request for his/her facility to participate in the research activity involving pregnant women.
 - c) If the research is greater than minimal risk, the VA Facility Director certification should include a statement that the VA Facility is able to respond to obstetric emergencies.
 - d) The VA Facility Medical Center Director's certification documentation will be kept in the Investigator's study files and in the Research & Development (R&D) file of the Research Office.

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 1200.05)
 - 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.
- 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) **Initial contact with potential subjects cannot be conducted by telephone.** The VHA does not allow "cold calling". [VHA Handbook 1200.12 §7.c.]
 - b) 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.
 - c) The VA IRB must receive and review the final copy of all research recruitment advertisements [printed or audio or video taped]. 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. Do not include exculpatory language.
 - vi. Do not emphasize the payment or the amount to be paid, by such means as larger or bold type. Advertisement includes a brief list of benefits to participants, if any. Advertisements do not allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
 - d) 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.
 - 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 promptly after detection or notification to the Privacy Officer any unauthorized use, loss or disclosure of individually-identifiable patient information.
 - b) The VA IRB Coordinator will report promptly after detection or notification any violations of VA information security requirements to the VHA Information Security Officer.

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. The VA IRB Coordinators contact information is provided on all consent forms.
- 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. [Any apparent serious or continuing noncompliance should be reported to the IRB within 5 days according to Handbook 1058.01.
- 3) The VA IRB will be responsible for implementing or recommending remedial or disciplinary actions in response to noncompliance with HRPP and IRB policies.

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 VAAHS.
- b) VA IRB meetings will be held at least once a month; generally on the 2nd Thursday.
- c) The VA IRB Coordinator is responsible for scheduling an alternate date and time for a convened meeting if quorum requirements cannot be met.
(See Section D, below)

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 or by teleconference policies and procedures (see VIII G, 8).

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 or designee 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 or designee 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 **initial review of new projects**, Primary, Secondary Reviewers (including Alternate Members selected as reviewers) and the IRB Chair will receive the following materials.
 - a) Full protocol or narrative containing the following information:
 - ☐ Rationale
 - ☐ Research Problems or Question
 - ☐ Specific Aims or Objectives
 - ☐ Background Information (Literature review, including significance of proposed research)
 - ☐ Preliminary data by Investigator (when applicable)
 - ☐ General Methods
 - ☐ Experimental Plan
 - ☐ Data analysis/interpretation
 - i.
 - b) Informed consent form or request of Waiver.
 - c) Investigator's brochure (if applicable).
 - d) Advertisements or subject recruitment information (if applicable).
 - e) Surveys or questionnaires (if applicable).
 - f) 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) More than half of the total number of voting members must be present (a quorum) in order to transact business. (If the IRB has 12 members, then at least 7 members present will constitute a quorum.)
 - b) At least one non-scientific member (laymember) must be present in order to transact business.
 - c) If the IRB roster includes a non-affiliated scientist member, this person must attend at least 6 of 12 meetings per year. The non-affiliated member does not have to be present at a specific meeting for the convened IRB to review and approve protocols or take actions requiring a vote.

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 1200.05]
 - (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.
 - (3) The IRB must review the data and safety-monitoring plan in the protocol developed by the investigator.
 - (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. (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.)

- 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 and Remote Participation

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 will chair the meetings. In his/her absence an experienced member (including an alternate member) will be designated by the ACOS/ Research to chair the meeting.
- 3) At least one non-scientist member must be present at convened meetings
- 4) At least one unaffiliated member must be present at convened meetings. The unaffiliated member must be included as part of any voting quorum. The IRB Minutes will document the specific attendance and participation of the unaffiliated member.
- 5) The VA IRB membership will include at least one member who represents the general perspective of

participants must be present at convened meetings. The general perspective member must be included as part of any voting quorum. The IRB Minutes will document the specific attendance and participation of the member representing the general perspective of participants.

- 6) The non-scientific member, the unaffiliated member, and the member representing the general perspective of participants may be the same person or may be represented by two or three persons.
- 7) A licensed physician member of the IRB must be present to review and approve research involving an FDA-regulated article. [VHA Handbook 1200.05, item 7 f (1)]
- 8) Votes are taken by counting raised hands (and by voice vote for remote participant). Greater than 50% of attending members are needed to approve or disapprove a study.
- 9) Only members with full voting rights may vote to approve or disapprove a study.
- 10) 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 all non-scientist members), the IRB may not take further actions or votes unless the quorum can be restored.
- 11) Remote participation by teleconference**
 - a) The remote participating IRB member must receive the same copies of all distributed documents (printed and/ or electronic) as received by members who are attending the convened meeting.
 - b) The remote participating IRB member must indicate they are able to hear all comments made by members who are attending the convened meeting.
 - c) The local attending IRB members must indicate they are able to hear all comments made by the remote participating IRB member.
 - d) When a vote is taken at the end of a project discussion, the remote participating IRB member must be made aware of the vote tally and the identity of any dissenting or abstaining IRB members who are attending the convened meeting.
 - e) The identity of the remote participating IRB member will be noted for each instance of their remote voting and for each instance of their abstention in a vote tally.
 - f) When there is a conflict of interest in the participation of the remote attending IRB member in the discussion and vote on a project review conducted by the local attending IRB members, the IRB Coordinator will insure that the teleconferencing equipment (i.e. speakerphone) is set to mute during the discussion at the local site meeting.
- 9) 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 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.
- 3) Continuing Review of Research
<http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm> (1/15/2007)
http://www.hhs.gov/ohrp/requests/200911guidance_rev.pdf (10/10/2009)
- 4) CALCULATION OF PROJECT EXPIRATION DATE:
- a) All approved studies will be subject to continuing review within at least every 365 days from the date of approval by the convened IRB (366 days in the case of a leap-year).
The expiration date is the last day on which the research may be conducted.
 - b) 30 Day Rule: When the IRB grants approval for one year at the time of continuing review, and the IRB performs continuing review and re-approves (with or without conditions) the research **within 30 days** before the IRB approval period expires, the IRB may **retain the anniversary of the expiration date** of the current IRB approval as the expiration date of the subsequent one year approval period.
- 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 3 weeks of the meeting date. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority. [VHA Handbook 1200.05]
 - 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. The R&D Committee waits until the final IRB minutes (approved by the IRB Chair) are provided before it approves new protocols.
 - 3) The VA IRB Minutes will be attached to the R&D Minutes for review by the Medical Center Director and the Chief of Staff.
 - 4) No institutional office or official of the VAAHS 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 VAAHS 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 serious adverse events and 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."
- 4) 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.]
- 5) 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 Serious Adverse Events and Unanticipated Problems that indicate increased risks to participants or others, 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.
- 6) 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.
- 7) 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.
- 8) The completion of the study is a change in activity and should be reported to the IRB.
- 9) 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)].
- i) The IRB may determine that any significant new findings that arise from the review process and that might relate to participants' willingness to continue participation are provided to participants.
- j) Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant must be promptly reported to the IRB and are reviewed by the IRB to determine whether each change was consistent with ensuring the participants' continued welfare.
- k) If the consent document is amended during the protocol approval period, the consent document will have the approval date of the amendment rather than the date of the approved protocol.

N. Review Reports of Serious Adverse Events and Unanticipated Problems

A complete description of definitions, investigator reporting responsibilities, IRB review procedures, and possible IRB actions is found in a separate VA IRB policy document

“VA IRB POLICY, ANALYSIS, AND REPORTING FORM FOR SERIOUS ADVERSE EVENTS, SERIOUS PROBLEMS, PROTOCOL DEVIATIONS, AND OTHER REPORTABLE EVENTS TO PARTICIPANTS AND OTHERS 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: VA patient status, gender, pregnancy status, minority status and decision-impaired status.
 - c) The Human Studies Research Application updated with all protocol changes. Upon request, the primary reviewer will be provided a copy of the full protocol.
 - 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). All members should receive copies of recruiting materials as well, and all HIPAA authorizations as a separate standalone document from the 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; Any newly proposed consent document, 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 collect 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 Research Compliance Officer will audit investigators files on an ongoing basis according to VHA Directive 2008-014.

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.
- 3) 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. The VA IRB must ensure that all the sites have FWAs (See VHA Handbook 1058.03).

- 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 (with appropriate consultation with the Chief of Staff) 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.

c) Administrative Hold: Actions initiated voluntarily by an appropriate facility official, research investigator, or sponsor for reasons that do not apply to the safety, rights, or welfare of human subjects, research investigators, research staff, or others. An administrative hold must not be used to avoid reporting deficiencies or circumstances otherwise covered by VHA Handbooks or other federal requirements governing research.

- 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.

V. Screening Reports of Research Non-Compliance

Apparent Serious or Continuing Noncompliance:

- 1) The IRB Coordinator will deliver a copy of the report to the VA IRB Chairperson (or a qualified, voting IRB member in the absence of the IRB Chairperson) within one business day of receipt.
- 2) The IRB Chairperson or (designated IRB member) will review the report within 5 days and determine if any interim action is needed to eliminate apparent immediate hazards to subjects. The IRB chair (or designated IRB member) may also initiate a further investigation into the apparent non-compliance if applicable.

The convened IRB will review the report at the earliest practicable opportunity, not to exceed 30 business days after the notification.

The information provided to Primary reviewers and to all other IRB members will include all discovered information and documents regarding the non-compliance, including: the

protocol (if applicable) and the consent document (if applicable).

- a) The convened IRB must determine and document whether or not serious or continuing noncompliance actually occurred.
- b) If the convened IRB determines that serious or continuing noncompliance has occurred:
 - i) the IRB must determine and document whether remedial actions are needed to ensure present and/or future compliance.
 - ii) the IRB must notify the VA facility Director, the ACOS/R&D within 5 days. If the apparent serious or continuing noncompliance was identified by an RCO audit, the IRB must notify the RCO within 5 business days after its determination, regardless of outcome. The IRB coordinator will transmit these notifications.
 - iii) the IRB must track the determinations above for use in the VA facility Director Certification. The IRB coordinator will establish and maintain an electronic system to do so.
 - iv) the IRB will review the remedial actions and determine if these are sufficient.
- c) The range of possible actions the IRB must consider include these required actions: Suspension of the research, Termination of the research, and Notification of current participants when such information may relate to participants' willingness to continue to take part in the research.
- d) If the IRB determines that there is no serious or continuing noncompliance, the IRB may determine whether any remedial action is required to prevent reoccurrence of similar problems. The IRB Chair and/ or IRB Coordinator may provide guidance to the investigators and may present a final report to the convened IRB if deemed appropriate.

Non-Compliance reports that may not require review by the convened VA IRB

- An event or problem is NOT RELATED to any research protocol approved at the VA Ann Arbor Healthcare System (VAAHS)
- An event or problem is a "minor" or administrative protocol deviation limited to a single subject which does not appear to affect the scientific soundness of the research or adversely affect the rights, safety, or welfare of human subjects and does not require remedial action by the VA IRB.
- An event or problem does not **reflect an apparent serious or** pervasive or persistent pattern of continuing noncompliance with VA IRB research requirements and does not require remedial action by the VA IRB.

W. Collaborative Research

Collaboration is encouraged when VA investigators have a substantive role in the design, conduct, and/or analysis of the research. VA may also serve as a Coordinating Center for collaborative studies. NOTE: Collaborative studies do not include studies conducted under a CRADA with pharmaceutical companies or other for-profit entities.

a. **IRB of Record Approval.** VAAHS IRB is responsible for safeguarding the rights and welfare of human subjects and providing oversight of the research activities conducted at this institution.

(1) Each collaborating institution engaged in human subjects research must obtain approval from its IRB of Record and hold a FWA or another assurance acceptable to VA, e.g. DoD assurance.

(2) VA investigators must submit a protocol or other documentation to their VA IRB of Record that delineates which research activities will be conducted by VA.

(3) Each institution engaged in the collaborative research must use the informed consent document and HIPAA authorization required by their respective institutional policies for subjects recruited from that institution, or procedures requiring participation of the subject at that institution. The informed consent document may contain information on the project as a whole as long as the document clearly describes which procedures will be performed at VA and which will be performed at other institutions.

(a) The VA informed consent document must clearly state when procedures mentioned at other institutions are part of the VA's portion of the study.

(b) The informed consent document and HIPAA authorization must be consistent and include information describing the following:

1. PHI to be collected and/or used by the VA research team;
2. PHI to be disclosed to the other institutions; and
3. Purpose for which the PHI may be used.

(c) **Waivers.** PHI obtained in research for which the IRB of Record has waived the requirements to obtain a HIPAA authorization and a signed informed consent document may not be disclosed outside VA unless the VA facility Privacy Officer ensures and documents VA's authority to disclose the PHI to another

institution. A waiver of HIPAA authorization is not sufficient to fulfill the requirements of other applicable privacy regulations such as the Privacy Act of 1974 (5 U.S.C. 552a).

b. **Research Data.** The protocol, addendum, and/or IRB of Record application must describe the data to be disclosed to collaborators, the entity(ies) to which the data are to be disclosed, and how the data are to be transmitted. This includes data from individual subjects as well as other data developed during the research such as the analytic data and the aggregate data.

(1) VAAAHS must retain a complete record of all data obtained during the VA portion of the research in accordance with privacy requirements, the Federal Records Act, and VHA Records Control Schedule 10-1.

(2) All disclosures and data transmission must meet privacy and security requirements per VA Directive 6500, VA Handbook 6500, and VHA Handbook 1605.1.

c. **Written agreements.** Collaborative research involving non-VA institutions may not be undertaken without a signed written agreement (e.g., a CRADA or a Data Use Agreement (DUA)) that addresses such issues as the responsibilities of each party, the ownership of the data, and the reuse of the data for other research. NOTE: Any reuse must be consistent with the protocol, the informed consent document, and the HIPAA authorization.

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 names of primary members for whom each alternate member can substitute

B. Written procedures and guidelines (including this document)

The VA IRB Standard Operating Procedures (this document), the VA Research Investigator Handbook, the VA IRB Application and all other applications and reporting forms and VA IRB Reviewer Checklists will serve to document and promote the written procedures and guidelines of the VA IRB.

C. Minutes of IRB Meetings.

- 1) The VA IRB 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 within three weeks of the meeting date.
- 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) If surrogate consent is to be used, findings as required by Handbook 1200.05
 - h) 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
 - i) Determination of the level of risk and the date of next scheduled continuing review of a project
 - j) When an alternate member replaced a primary member.
 - k) A written summary of the discussion of controverted issues and their resolution.
 - l) Justification of any deletion or substantive modification of information concerning risks or alternative

procedures contained in the DHHS-approved sample consent document.

- m) For initial and continuing review, the approval period.
- n) 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.
- o) Protocol-specific findings justifying determinations required by the regulations for waiver or alteration of the consent process, including documentation of CPRS flagging decisions (when appropriate).
- p) The rationale for significant risk/non-significant risk device determinations.
- q) 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.
- r) The determination of the level of risk.
- s) 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 VAAHHS, as mandated by federal regulatory agencies or by the VAAHHS 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 provided to subjects [see 38 CFR 16.115(a)(7)]
 - 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.
 - w) Other items, including audit reports, complaints, and documentation of remedial actions required by IRB.
- 3) VA IRB records are the property and the responsibility of the VA Research Office and are maintained and stored as required to protect the privacy and confidentiality of subjects.

F. Record Retention and Accessibility (Terminated Research Studies)

- 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 VA ORD Policies, VHA's Records Control Schedule (RCS 10-1), applicable FDA and DHHS regulations, or as required by outside sponsors. All other records are retained in

accordance with the record control schedule.

- a. Until RCS 10-1 is revised to include a policy for the destruction of local research records, the ACOS for Research must establish and maintain a secure, password-protected research computer data repository and a secure, double-locked research paper data repository for all completed and terminated research studies.
 - b. These repositories will be maintained to store any research data that contains personal identifying information (PII) and/or protected health information.
 - c. These repositories will be maintained until VA ORD issues new policies with specific guidance for appropriate archival storage or destruction of these materials.
- 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.
 - 7) Requirements Related To Research Information Protection [VHA Handbook 1200.12]
See IRB Policy Document 106, "Research Investigator Manual" (Sect. 12).

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

M. Requirements for Research Data Repositories (VHA Handbook 1200.12)

- 1) Sources of Data In Data Repositories
 - a. Data used for research purposes within VA may come from many different sources, and those sources may be internal or external to VA. Within VA, the data may come from individual research subjects during the conduct of a research protocol or may come from existing research or non-research data repositories. There are numerous external sources including registries, Medicare data, publicly available data, or private sources.
 - b. VA and VHA non-research data repositories are created to assist VA and VHA in its operations. These data repositories contain information gathered and used for a variety of non-research purposes, such as the ongoing treatment of Veterans, documentation of treatment provided, issues related to co-payments and collections from insurance companies, health care operations, personnel records, Veterans benefits, and statistical analyses to produce various management tracking tools, evaluations, or follow-up reports.
- 2) Determining If Data Are Identifiable (based on both the Common Rule [38 CFR Part 16] and the HIPAA Privacy Rule. (See VHA Handbook 1200.12)
 - (1) If either condition in following subparagraphs (a) or (b), is met, the data are identifiable.
 - (a) The identity of the subject is or may be readily ascertained by the investigator or research team member or others from the information contained within the data. The information is considered private information as defined in 38 CFR 16.102(f)(2) if it includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record or information about specific beliefs) or
 - (b) The subject is identifiable by HIPAA Privacy regulations because:
 - i. The data contain one or more of the eighteen types of identifiers listed in the HIPAA Privacy Rule in 45 CFR. 164.514(b) (2)
 - ii. The covered entity has actual knowledge that the information could be used alone or in combination with other information to identify an individual who is the subject of the information; (i.e., there are other data that when combined with the dataset will allow the identification of any individual) (45 CFR 164(b)(2)(ii)), or
 - iii. The data have not met the criteria for de-identification by statistical means as outlined in 45 CFR 164.514(b)(1).
 - (2) Social Security Numbers (SSNs), real or scrambled, are considered identifiers. NOTE: Scrambled SSNs are considered identifiers by the HIPAA Privacy Rule because they are unique to the individual and are derived from the SSN. In addition, this rule prohibits re-identification codes from being based on an identifier such as SSN (in whole or in part), name, or other direct identifier.
 - (a) Real SSNs may be obtained only when required to meet the specific aims of the research protocol and their collection and use is approved by the IRB and the R&D Committee. To obtain access to real SSNs, the procedures defined by the VHA Privacy Office must be followed.
 - (b) When a research protocol calls for use of scrambled SSNs, the SSNs cannot be unscrambled by research staff or other individuals without an amendment to the research protocol and approval by the appropriate review committees. All required approvals from VHA Privacy Officer must also be obtained.
- 3) Special Concerns for Use of Identifiable Data (See VHA Handbook 1200.12)
 - a. Human Subjects Protection. Research involving the use of identifiable data meeting the criteria for human subjects research must be in compliance with the Common Rule (38 CFR Part 16), all VHA policies related to protections of human subjects in research (e.g., VHA Handbook 1200.5), VHA Handbook 1605.1, and VA Handbook 6500.
 - b. Compliance with all Confidentiality Requirements. The collection, use, and release of PHI from a data repository must comply with all applicable confidentiality and information security provisions, including the Privacy Act of 1974, the HIPAA Privacy Rule, and 38 U.S.C. 7332 (confidentiality of medical records related to drug abuse, alcoholism, alcohol abuse,
 - c. Recruitment of Research Subjects. Identifiable information must not be used to recruit subjects for research protocols unless approved by the IRB(s) and the R&D Committee(s). In addition to the IRB's approval of the protocol, the IRB must include an approval of a waiver of HIPAA authorization in such instances. The initial contact with the potential human subject needs to be in person or by mail, **not by telephone**. [VHA Handbook 1200.12 §7.c.] Additionally, the contact must follow the most recent VA and VHA memoranda or guidance regarding this issue. NOTE: These may be found on the Office of Research and Development (ORD) website at: www.research.va.gov .

- d. Re-contacting Research Subjects. Identifiable information must not be used to re-contact individuals to obtain additional information unless approved by the IRB(s) and the R&D Committee(s). Re-contacting individuals without previous permission of the individual must meet the same requirements as those set forth by the IRB(s) and R&D Committee(s) for recruitment.
 - e. Decedent's Data. VHA must protect the individually identifiable health information about a deceased individual. A decedent's individually identifiable health information may be used for research purposes without obtaining HIPAA authorization from the decedent's personal representative and without IRB or Privacy Board (PB) approval. NOTE: For further requirements including the representations that must be made and information on the use of decedent's data see VHA Handbook 1605.1.
 - f. Use of Data that Contain Coded Private Information. Use of data that contains coded private information from data repositories requires IRB approval if the data are considered "identifiable" under the human subject protection regulations.
 - g. Use of Centers for Medicare and Medicaid (CMS) data. All requests for use, transmission, distribution, storage, and disposition of CMS data must follow all VA and VHA policies, as well as all CMS requirements and other applicable Federal regulations.
- 4) Privacy and Confidentiality (See VHA Handbook 1200.12)
- a. Privacy of research subjects and confidentiality of their data are critically important and must be addressed carefully to protect the rights of individual research participants, their families, and their communities. A number of laws, VA and other Federal regulations and policies control how a research subject's private information may be used and when that data can be shared with non-VA investigators or institutions. The laws, regulations, and policies also address use of individually identifiable information even when it does not contain any health data.
 - b. Privacy laws, regulations, and policies that are applicable to data repository research include, but are not limited to: HIPAA, (45 CFR Part 160 and Subparts A and E of Part 164); The Privacy Act (5 U.S.C. 552a) and implementing regulations at 38 CFR 1.575-1.584 and the associated Systems of Records; The VA Claims Confidentiality Statutes (38 U.S.C. 5701) and implementing regulations 38 CFR 1.500-1.527; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Human Immunodeficiency Virus (HIV) Infection, and Sickle Cell Anemia Medical Records (38 U.S.C. 7332), and implementing regulations at 38 CFR 1.460-1.496; Confidentiality of Healthcare Quality Assurance Review Records (38 U.S.C. 5705) and implementing regulations at 38 CFR 17.500-17.511; VHA Handbook 1605.1, Privacy and Release of Information.
 - c. Local Institutional Policies and Procedures. Each VA facility conducting research using data covered by the preceding regulations and requirements must develop policies and procedures that ensure compliance with all of the applicable privacy and security regulations and policies.
- 5) Storage and Security (See VHA Handbook 1200.12)
- a. All applicable Federal statutes and regulations and VA and VHA policies governing storage and security of data and information must be followed (see VA Handbook 6500). NOTE: Links to VA policies may be found at: www.va.gov/vhapublications.
 - b. All identifiable data used and maintained as part of a research protocol must be retained or stored for the period of time stated in the applicable Privacy Act System of Records notice, Records Control Schedule (RCS) 10-1, and VA policy. Identifiable information may not be destroyed except with appropriate destruction authority. **NOTE:** The current VA Records Control Schedule (RCS) 10-1 applies to all research records, including IRB-approved protocols with HIPAA authorizations or waivers of authorization. At this time, no research records may be destroyed. [July 2010]
- 6) Use of Data Repositories for Research Purposes (See VHA Handbook 1200.12)
- VA investigators may use VA and VHA data, including data from existing treatment, payment, operations, or research data repositories, to prepare a VA research protocol, conduct VA-approved research, or to create or maintain a VA research data repository.
- 7) Data in Research Data Repositories (See VHA Handbook 1200.12)
- A research data repository is created when data obtained from implementing a research protocol are placed in a data repository. The protocol may be a primary research project designed to prove or disprove a specific hypothesis, or it may be a protocol specifically designed to collect data that will be placed in a research data repository for future use. A research data repository can be created only after a research repository protocol is developed and approved by the IRB (if human research is involved) and the R&D Committee.
- 8) Responsibilities of VA Facilities Releasing Identifiable or De-Identified Information from Their Records to another VA Site for Research Purposes (See VHA Handbook 1200.12)
- VA facilities that release identifiable or de-identified information for use in a VA-approved research protocol to a VA investigator or to a VA research repository are not considered to be engaged in research if the releasing facilities do not have any other role in the research, i.e., the VA facility will not be considered

“engaged” in research solely on the basis of this transfer of data. The releasing VA facility does not need to hold a FWA, but if it does, the releasing VA facility’s IRB and R&D Committee is not responsible for reviewing specific individual research protocols, unless an investigator or other member of the protocol’s research team are at the same facility as the research data repository. Prior to the release of information the following steps must occur:

- 9) Administration of Research Data Repositories (See VHA Handbook 1200.12)
A VHA research data repository is a resource for VA investigators, and it must remain under the control of VA. The repository may contain either identifiable or de-identified data. The data may be released to non-VA personnel or non-VA entities only in accordance with VHA Handbook 1605.1. Data repositories must be maintained and operated in accordance with the requirements of this Handbook and all other applicable VA and VHA policies and regulations.
- 10) Role and Responsibilities of the IRB (See VHA Handbook 1200.12)
The IRB of record for the VA facility that houses the research data repository is the IRB responsible for the research data repository. This IRB is responsible for Complying with all requirements in VHA Handbook 1200.05 and all COI policies, especially those related to commercial ties of the investigator and conflict of role, as well as the suggested strategies to manage conflicts.
- 11) Role and Responsibilities of the R&D Committee (See VHA Handbook 1200.12)
The R&D Committee of record for the VA facility that houses the research data repository is responsible for oversight of the research data repository.
- 12) Responsibilities of the Investigators (See VHA Handbook 1200.12)
The investigator’s primary responsibilities for designing and conducting research involving the use of data repositories are similar to those for other types of studies. If the protocol involves human subjects then all policies related to human subjects research, including those in VHA Handbooks 1200.5 and 1605.1, are applicable.
- 13) Responsibilities of the Owner or Administrator of Non-research Data Repositories (VHA Handbook 1200.12)
The owner or administrator of each data repository or data warehouse must develop policies and procedures for responding to requests for data. Responsibilities of the owner or administrator of research data repositories are to be found in Paragraph 12 of this Handbook. NOTE: Although the term owner or administer is used within this Handbook, VA information is owned by the Administration, Staff Office, or other Agency component that generates or gathers the information to perform statutory responsibilities. The information system itself is owned by VA Office of Information and Technology.
- 14) Training (See VHA Handbook 1200.12)
Personnel to be trained. All research data repository personnel (including trainees, clerks, secretarial support, and oversight committee members), investigators and members of the research teams, research office staff, members of the IRB(s) and R&D Committee(s), and others who deal with issues related to a research data repository must complete the training required by ORD.
- 15) Research Data Repository for Terminated Research Studies
See Section IX, Part F in this document, “Record Retention and Accessibility (Terminated Research Studies)

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 VAAHS

- 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, including reports to FDA and study monitoring.
- 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 (if the research involves an investigational drug, and the FDA has issued an IND).
- 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 release the hospital or its agents from liability for negligence by signing the research consent form (see 38 CFR 17.85).
- 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 1200.05 10.b]
 - a) The plan may vary depending on the potential risks, complexity and nature of the study. [VHA Handbook 1200.05 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 1200.05 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 1200.05 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 1200.05 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 1200.05 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. Screening Reports of Serious Adverse Events and Unanticipated Problems

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.

[VAAHS Policy and Reporting Form for SAE and 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 (by the Research Compliance Officer) 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. The IRB can require remedial actions as well, without suspending or terminating.

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 VAAHS, 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 1200.05. 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 may 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.) In addition to the IRB Chair and/or an experienced voting member of the IRB, IRB administrators or IRB staff who have appropriate training

and experience are also allowed to make exempt determinations. For additional information on this topic, refer to ORD's guidance document on Exempt Research Determination.

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 must assume oversight and carry out continuing review of exempt protocols under Handbook 1200.01 § 10.c. 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 research activities in which the exemption determinations as required by laws, regulations, codes, and guidance 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.) If a research investigator will access identified data to extract the de-identified data set, then a HIPAA waiver should be obtained.

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) The research is conducted by or subject to the approval of state or local government officials. The research or demonstration protocol is 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. VHA does not conduct planned emergency research (see 21 CFR 50.24) or classified research involving human subjects. [VHA Handbook 1200.05 3.e (11/21/14)]

- 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.

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 (review by the VA 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 and VA 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. This does not apply to the VA. All VA research conducted under a DHHS Federal-wide Assurance is subject to the Common Rule
- 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 concurrence 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 complete description of definitions, investigator responsibilities, IRB review procedures, and possible IRB actions is found in a separate VA IRB Policy document

A. VA IRB POLICY AND CHECK LIST FOR EXPEDITED REVIEWS

(per VHA Handbook 1200.05, 38 CFR 16.110, and 63 FR 216)

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

Policies and procedures allow the IRB to waive the requirement for written documentation of the consent process by determining that the criteria for waivers are met.

B. 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.
 - i) must include information describing any photographs, video, and/or audio recordings to be taken or obtained for research purposes, how the photographs, video, and/or audio recordings will be used for the research, and whether the photographs, video, and/or audio recordings will be disclosed outside VA.

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)]

C. VA-specific Requirements.

- (1) The consent form must be the most recent IRB-approved consent form that includes all the required elements and, as appropriate, additional elements. The IRB approval must be documented on the consent form indicating the date of approval.
- (2) The informed consent document must be signed and dated by:
 - (a) The subject or the subject's LAR; and
 - (b) The person obtaining the informed consent. However, the IRB may waive this requirement for the signature of the person obtaining consent (even where the signature of the subject or the LAR continues to be required) where there is no physical contact with the subject (e.g., where the only contact with the subject is by telephone or mail).
 - (c) Consent may be obtained electronically so long as the informed consent process meets all requirements in paragraph 16 of this Handbook and VA requirements; and:
 - (1) Authentication controls on electronic consent provide reasonable assurance that such consent is rendered by the proper individual; and
 - (2) The subject dates the consent as is typical or that the software provides the current date when signed.

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

Policies and procedures have the IRB document its findings justifying the waiver or alteration. 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. The research is not FDA-regulated. OR,
- 4) The research involves no more than minimal risk to the participants. The waiver or alteration did not adversely affect the rights and welfare of the participants. The research cannot practicably be carried out without the waiver or alteration. When appropriate, the participants will be provided with additional pertinent information after participation. The research is not FDA-regulated.

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

To comply with Common Rule (VA Title 38, Section 16.116(d)) and the HIPAA Privacy Rule [45 CFR 160 and 45 CFR 164], the VA IRB may waive the requirement for obtaining informed consent and authorize access to PHI under the following circumstances:

- 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 waiver will not adversely affect the rights and welfare of the subjects.
- 3) Whenever appropriate, the subjects (including their physicians, as applicable) will be provided with additional pertinent information after participation.
- 4) The investigator must provide a specific description of all data categories with personal identifying information (PII) or personal health information (PHI) that will be collected on research subjects for the research study
- 5) 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.)

- 6) The investigator must explain why the research could not be practicably conducted without the waiver.
- 7) The investigator must explain why the research could not be practicably carried out without access to and use of the requested information.
- 8) The investigator must explain how long the data will be stored with personal identifiers and how the data will be de-identified (or destroyed) in accordance with the record retention policy of the VA ORD.

(See Section IX, Part F in this Policy.)

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 VAAHHS if the research will be conducted at the Ann Arbor VA site with direct contact with human research subjects.
- 2) An approved Consent Form from another research institution may be used to recruit research subjects **in addition to a VA Consent Form**, if the research study takes place at a non-VA institution with any combination of the following situations: VA funds will be used to support the research (e.g. MERIT or VERAM); VERAM will administer the project funds; VA paid time or other VA resources will be used to conduct the research. OR, a request for Waiver of Signed Informed Consent may be submitted (Form E).
- 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) A statement that in the event of a research-related injury the VA has to provide necessary medical treatment to a participant injured by participation. A statement that a veteran-participant does not have to pay for care received as a participant in a VA research project except in accordance with federal law and that certain veterans have to pay co-payments for medical care and services provided by VA.
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 a standalone document, separate from 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 and by the investigator obtaining the consent (except in cases where the written documentation of informed consent is waived by the IRB)
- 2) Witness Requirements:
 - a) A witness will not be required unless specifically approved by the VA IRB.
[VHA Handbook 1200.05, Sect. 33.c]
- 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 1200.05, 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.
 - b) The participant or the participant's legally authorized representative will sign and date the consent document on the Subjects Rights page. The subject should not begin participation in the study until the Consent Form is signed.
 - c) If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person needs to serve both capacities, a note to that effect is placed under the witness's signature line.
 - d) The person obtaining consent 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) In concordance with the most recent VHA handbook 1200.05 (November 12, 2014), the Ann Arbor VA IRB will not require routine scanning of informed consent documents into the health record or entering of a research study enrollment note into the health record except for research drug studies, investigational device studies, or any determined to be appropriate by the IRB. The Ann Arbor VA IRB will evaluate and determine, for each project, whether scanning of informed consent documents or entering a research study enrollment note will be required.

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.

I. Data Retention When Participants Withdraw From a Clinical Trial

- 1) When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.
- 2) A Researcher may ask a participant who is withdrawing whether the participant wishes to provide continued

follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

- 3) The Researcher must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document.
- 4) If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

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 VAAHS 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 VAAHS, all devices, regardless of whether they are investigational or marketed devices, will be inspected by the Bioengineering Service of the VAAHS. 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.

D. VA Information Security Officer and VA Privacy Officer

- 1) The ISO and PO who serve on the facility's IRB or R&D Committee thoroughly review each human subjects research protocol and document the review.
- 2) All human subjects research conducted at the facility is reviewed by the ISO and PO prior to the research being initiated by the VA R&D Committee.

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 Study Team Members.
- 1) The VA IRB educates IRB Members, Research Investigators and Study 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 bi-annual basis (within 3 years 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 names and completion dates 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. All persons involved in research must be credentialed and have a scope of practice (see VHA Directive 1200).
- 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. REQUIREMENTS FOR CONDUCTING VA-APPROVED INTERNATIONAL RESEARCH INVOLVING HUMAN SUBJECTS, HUMAN BIOLOGICAL SPECIMENS OR HUMAN DATA

It is VHA policy that permission must be obtained from the Facility Medical Center Director prior to initiating any VA-approved human subjects research conducted at international sites (not within the U.S., its territories, or Commonwealths) or to VA-approved research using either human biological specimens or human data originating from an international sites. This policy applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including agreements, Memoranda of Understanding (MOU), Cooperative Research and Development Agreements (CRADA), grants, or contracts.

- a. The VA Facility Medical Center Director is responsible for the review of, and action on, all requests for permission to conduct VA-approved research involving human subjects, or human biological specimens, or human data from international sites. NOTE: The Facility Director will not grant permission for an international research project involving prisoners as research subjects.
- b. Office of Research Oversight (ORO). ORO is responsible for the oversight of all on-going human subjects research conducted or supported by VA including research conducted at international sites.
- c. Facility Director. The facility Director is responsible for:
 - (1) Approving the request for permission to conduct international research.
 - (2) Providing an approval letter stating that he or she concurs that the part of the research proposed for the international site including the collection of human biological specimens and data could not be done within the VA or within the United States.
 - (3) Including a statement that they are aware of and approve the request for his/her facility to participate in the international research activity.
 - (4) If the international research activities are conducted by the VHA Cooperative Studies program, the CRADO must provide approval.

(5) VA Facility Director approval documentation must be in the Investigator's study files and in the R&D file of the Research Office.

XX. RESEARCH PARTICIPANT OUTREACH PROGRAM

VA Ann Arbor Healthcare System - Research Participant Outreach Program

Investigators are no longer required to perform subject outreach nor distribute the brochure, "Volunteering in Research - Here are Some Things You Need to Know" (deleted from VHA Handbook 1200.05 – 11/12/14).

XXI. REGULATORY & ADVISORY DOCUMENTS

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 1200.05, "Requirements for the Protection of Human Subjects in Research" (updated 11/12/14)
14. VHA Handbook 1058.01 " Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight" (06/15/15)
15. VHA Handbook 1058.03 "Assurance of Protection for Human Subjects in Research" (11/21/14)
16. VHA Handbook 1200.01 "Research and Development Committee Handbook" (6/16/09)
17. VHA Handbook 1200.12 "Use of Data and Data Repositories in Research" (3/09/09)
18. VHA Handbook 1605.1 "Privacy and Release of Information" (5/17/06)
19. VA Handbook 6500 "Information Security Program" (9/18/07)
20. VHA Handbook 1058.2 "Research Misconduct" (02/07/14)
21. VA Ann Arbor Healthcare System "Policy and Procedures for Dealing with Research Misconduct" (8/23/05)
22. VHA Directive 1200 "Veterans Health Administration Research and Development Program" (7/09/09)
24. VA IT Directive 06-2, "Safeguarding Confidential and Privacy Act-Protected Data at Alternative Work Locations" (6/06/06).