# Minneapolis VA Health Care System
# Minneapolis, Minnesota

## INSTITUTIONAL REVIEW BOARD

# STANDARD
# OPERATING
# PROCEDURES
# FOR THE PROTECTION OF
# HUMAN SUBJECTS IN RESEARCH

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# Standard Operating Procedures for the Protection of Human Subjects in Research

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# STANDARD OPERATING PROCEDURES

These Standard Operating Procedures for the protection of human subjects are the current policy and procedures for operation of the Institutional Review Board, also known as the Human Studies Subcommittee, of the Minneapolis Veterans Affairs Health Care System (MVAHCS). This document will be updated as regulations and policies change.

The Minneapolis VAHCS Institutional Review Board's authority includes research conducted at the St. Cloud VAHCS, St. Cloud, MN (see addendum A); Twin Ports VA Outpatient Clinic, Superior, WI; and the Community Based Outpatient Clinics (CBOCs) associated with the MVAHCS.

In this document, the abbreviation "IRB" is used to indicate the Institutional Review Board and "HSS" is used to indicate the Human Studies Subcommittees of the MVAHCS, Minneapolis, MN. It is also understood in this document that the MVAHCS includes the Twin Ports VA Outpatient Clinic and the CBOCs referenced above.

## 1. INSTITUTIONAL AUTHORITY UNDER WHICH THE IRB IS ESTABLISHED AND EMPOWERED

The IRB operates within the principles set forth by the Minneapolis VA Health Care System "Federalwide Assurance of Protection for Human Subjects" (FWA 00001480) enacted between the Minneapolis VA Health Care System (represented by the MVAHCS Medical Center Director), and United States Department of Health and Human Services (DHHS) represented by the Office for Human Research Protections (OHRP) of the National Institutes of Health (NIH), and the Department of Veterans Affairs represented by the Office of Research and Development (ORD) and the Office of Research Oversight (ORO).

VA is one of sixteen Federal departments and agencies that follow the Federal Policy for the Protection of Human Subjects, effective August 19, 1991, generally known as the "Common Rule". For the VA, this policy is incorporated in 38 CFR 16.

Under 38 CFR 16.102(f), an institution is engaged in human subject research whenever its employees or agents: intervene or interact with living individuals for research purposes; or obtain, release, or access individually-identifiable private information for research purposes. Agents in VA include study personnel with VA appointments, employees, IPA, and Without Compensation (WOC) appointments.

Each VA that conducts research involving human subjects is required to have an established or designated IRB. The Minneapolis VAHCS cannot use a commercial IRB for VA research. The MVAHCS IRB reports directly to and receives administrative support from the Research & Development (R&D) Committee of the Research Service and indirectly to the Medical Center Director of the Minneapolis VA Health Care System. The R&D Committee is responsible for all research activities conducted under the auspices of the MVAHCS and empowers the IRB to protect the rights and welfare of human research subjects.

The MVAHCS Medical Center Director is the Authorized Institutional Official for human studies research at the Minneapolis VA Health Care System. Oversight of the day-to-day operation of

the Human Subject Protection Program (HRPP) is delegated to the Associate Chief of Staff for Research (ACOS/R) by the Medical Center Director. The ACOS/R is also appointed as the Research Integrity Officer and is the point of contact for complaints, needs assessment and potential problems. The Research Compliance Officer (RCO) is responsible for monitoring compliance with regulations for the responsible conduct of research for the HSPP and reports to the Medical Center Director. The HRPP includes the IRB administrative staff, and the IRB and R&D Committees.

A Memorandum of Understanding exists between the VA Central IRB (CIRB) and Minneapolis VAHCS. The Medical Center Director is responsible for signing a MOU that delineates the respective roles, responsibilities, and authorities of the Minneapolis VA and the CIRB, including, but not limited to, the external organization's providing unredacted IRB minutes and other relevant documents to MVAHCS. When the VA Central IRB is the IRB of record, the Medical Center Director is responsible for delegating authority for commenting and responding to VA Central IRB review in response to initial review considerations, whether MVAHCS chooses or declines to participate in a study, and serving as liaison between as well as the Local Site Investigator (LSI) with VA Central IRB.

A Memorandum of Understanding between the St. Cloud VA Health Care System and the MVAHCS establishes the MVAHCS IRB as the IRB of record the St. Cloud VA Health Care System. All human research conducted under the oversight of the HRPP at the St. Cloud VAHCS is first reviewed by the MVAHCS IRB and R&D Committee. The St. Cloud Research and Development (R&D) Committee performs the final review of all St. Cloud research protocols. The Medical Center Director at the St. Cloud VA Health Care System is the Authorized Institutional Official for their HRPP, operating under FWA 00002102.

## 2. GOALS OF THE IRB

The primary goal of the IRB is to assure that, in research involving human subjects at the Minneapolis VA Health Care System (including Twin Ports VA Outpatient Clinic and CBOCs connected with the Minneapolis VAHCS), and the St. Cloud VA Health Care System (see Addendum 3), the rights and welfare of the human subjects are adequately protected.

Research is defined as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question. The Common Rule (38 CFR 16) defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge.

To achieve this goal, the IRB will:

- review all planned research involving human subjects prior to initiation of the research, including determining if the research design is sound and likely to yield the expected knowledge;
- approve research that meets established criteria for protection of human subjects;
- monitor approved research to ascertain that human subjects are indeed protected;
- educate potential research subjects as to their rights in regards to research participation and privacy;

- on request, assist the investigators in designing their research protocols in a manner to minimize potential harm to human subjects.

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

## 3. PRINCIPLES WHICH GOVERN THE IRB IN ASSURING THAT THE RIGHTS AND WELFARE OF SUBJECTS ARE PROTECTED (The Belmont Report)

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

(a) Respect for Persons: In consideration of respect for persons, investigators are required to seek voluntary, written informed consent from potential subjects. Voluntary informed consent means that subjects are given explicit assurances of the voluntary nature of their participation in terms that are easy to understand and when they are not under duress. The consent form also includes adequate information about the study that will assist subjects in intelligently deciding whether to participate in research. In addition, respect means honoring the privacy of individuals and maintaining their confidentiality. Respect for minors and mentally disabled persons requires taking extra precautions to protect those individuals who are immature or incapacitated, perhaps even to the extent of excluding them from the participation in certain research. There are also special rules which apply to prisoners.* The extent of the protection depends on the potential risks and benefits of the research to the participant.

**(*The MVAHCS IRB will not review or approve any research involving prisoners)**

(b) Beneficence: The principle of beneficence requires that researchers maximize the potential benefits to the subjects and minimize the potential risks of harm. The benefits should always outweigh risks. Finally, if there are any risks resulting from participation in the research, then there must be benefits, either to the subject, or to humanity or society in general.

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

## 4. GOVERNANCE OF HUMAN SUBJECT RESEARCH

All research involving human subjects including human biological specimens shall be reviewed by the IRB.

### 4.1 Region of Supervision of IRB

The following categories of research involving human subjects may be initiated only after review and approval by the IRB:

[1] Research conducted completely or partially on the premises of the Minneapolis VAHCS or Twin Port VA Outpatient Clinic or VA-staffed Community Based Outpatient Clinics (CBOCs) connected with the Minneapolis VAHCS or St. Cloud VAHCS, or conducted in approved off-site locations/facilities.

[2] Research conducted off the premises of the Minneapolis VAHCS or Twin Ports VA Outpatient Clinic or VA-staffed CBOCs or St. Cloud VAHCS, utilizing data collected on patients, research subjects, or staff of the same, including those data stored in any form.

[3] Research conducted by VA researchers while on VA official duty time

Classified research cannot be approved by a VA facility IRB or R&D Committee, or performed at a VA facility.

### 4.2 Responsibilities of IRB and R&D Committee in Overseeing Research Involving Human Subjects

(a) IRB is mandated to review and monitor any and all types of research in which human subjects are involved. Research meeting the criteria for exempt research may be ruled exempt.

The authority conveyed to the IRB includes the following:

[1] Review all research protocols involving human subjects, including all advertisements and subject recruitment efforts, questionnaires and any other research-related materials before the involvement of human subjects begins;

[2] Require, from investigators, revisions in research protocols and informed consent documents as a condition for initial or continuing approval;

[3] Approve new research protocols, and continuation of previously approved protocols, and determine which studies need to be reviewed more frequently than annually and which protocols need verification from sources other than the investigator that no material changes have occurred since the previous IRB review;

[4] Disapprove the initiation of a new research protocol;

[5] Monitor the activities in approved protocols, in any way deemed necessary, including regularly scheduled continuing review at least every twelve months, and verification of compliance with approved research protocols and informed consent procedures;

[6] Ensure prompt reporting to the IRB of any planned changes in approved protocols, and that no material changes occur without prior approval by the IRB, except where necessary to eliminate immediate hazard or danger to study participant;

[7] Ensure prompt reporting to the IRB of any adverse events occurring in approved protocols, or in other protocols related in context to the approved protocols;

[8] Suspend or terminate a previously approved protocol;

[9] Review and monitor the emergency use of test articles (investigational drugs, biological and devices) for the purpose of non-approved use in the treatment of serious or life-threatening illnesses;

[10] Ensure prompt reporting to the IRB, appropriate institutional officials, and the FDA (where appropriate) of:

- Unanticipated problems involving risks to subjects,
- Serious or continuing noncompliance with regulations,
- Suspension or termination of IRB approval; and

[11] Determine if investigational devices pose significant or non-significant risk and review investigator's plan for control of these devices.

(b) The IRB will employ a review process, which conforms to the "Federal Policy for Protection of Human Subjects," the regulatory codes 45 CFR 46 DHHS, 38 CFR 16 of the Department of Veterans Affairs, and 21 CFR 50, 56, 312, 600 & 8412 of the FDA, VHA Handbook 1200.05, and the current Federal-Wide Assurance, enacted between the Minneapolis VA Health Care System and the Health and Human Services and the Department of Veterans Affairs. The review process will be the same for all research involving human subjects, supported or otherwise subject to regulation by any Federal department or agency, sponsored by any other extramural entity, or initiated within the Minneapolis VAHCS.

(c) The IRB will notify the investigator of the protocol, and the Research and Development Committee of the Research Service of the Minneapolis VA Health Care System of its decisions to approve, require modifications to secure approval, defer, disapprove, suspend or terminate research protocols. In the case of disapproval, suspension or termination, the notification statement will include clearly defined reasons for the decision.

(d) The Research and Development Committee of the Minneapolis VA Health Care System delegates the assessment of scientific quality and appropriateness of all research involving human subjects and will have the authority to review the decisions. If the IRB has approved a research protocol, the Research and Development Committee may subsequently conclude that a protocol does not fully comply with policies or obligations of the Minneapolis VA Health Care System, the protocol may be disapproved, suspended or terminated on behalf of the institution. In the case of a decision by the IRB to disapprove, suspend or terminate a protocol, the decision may not be reversed by the Research and Development Committee or any other agency of the Minneapolis VA Health Care System, State Government, or Federal Government. The Institutional Official may not approve research that has not been approved by the IRB.

(e) When a protocol is disapproved by the IRB or Research and Development Committee, the investigator may submit a rebuttal to the Chair of the appropriate committee that disapproved the protocol. The committee will review the rebuttal and the investigator will notified of the resolution of the appeal.

(f) In the case of an approval decision of the IRB, the IRB Coordinator will act on behalf of the institution to notify the investigator of the protocol's compliance with the institutional Federal-Wide Assurance and on request from the investigator will inform the relevant Federal regulatory

agencies and sponsors of the research. The IRB approval letter issued to investigators informs Principal Investigators that studies may only be initiated after Research and Development Committee approval is obtained. In the case of disapproval, suspension or termination, the Research & Development Committee will notify the same organizations of the decision of the IRB.

(g) The Research and Development Committee will periodically, but not less than once every 2 years, review the qualifications of the IRB Administrator, IRB Chairs and Co-Chairs, and IRB members to determine that these individuals have the knowledge, skills, and abilities appropriate to their respective roles in overseeing research involving human subjects. Ongoing feedback is provided.

(h) The Research and Development Committee will annually review the HRPP resources, workload and budget. Resources include staff, consultants, equipment, finances, training and education, and space to securely store records, permit private communication, accommodate computers and office equipment, and accommodate meetings. Consideration will also be given to the volume and the types of human research reviewed, so that reviews are accomplished in a thorough and timely manner. Input will be requested from the IRB and R&D Committee members and HRPP components. The IRB Administrator will prepare a report to the R&D Committee, annually, summarizing information regarding the workload, budget and resource considerations listed above.

### 4.3 Responsibilities of Minneapolis IRB, the Minneapolis Research and Development Committee and St. Cloud VA Health Care System Research Committee in Overseeing Research Involving Human Subjects

For human studies research at the St. Cloud VA Health Care System, all IRB responsibilities and procedures outlined in 4.2 will be followed with the following additional procedures:

(a) The IRB staff will notify the Research Program Coordinator at the St. Cloud VAHCS of decisions by the IRB or the Minneapolis Research and Development Committee to approve, disapprove, suspend or terminate St. Cloud VA Health Care System research protocols. In the case of disapproval, suspension or termination, the notification statement will include clearly defined reasons for the decision. This information will in turn be communicated by the Research Program Coordinator to the Research and Development Committee at the St. Cloud VA Health Care System and to the investigator of the protocol. In the case of a decision by the IRB to disapprove, suspend or terminate a protocol, the decision may not be reversed by the St. Cloud Research and Development Committee or any other agency of the St. Cloud or Minneapolis VA Health Care Systems, State Government, or Federal Government.

(b) The Research and Development Committee of the St. Cloud VA Health Care System is responsible for the scientific quality and appropriateness of all research involving human subjects at their institution and will have the authority to review decisions of the IRB. If the IRB has approved a St. Cloud VA Health Care System research protocol, the St. Cloud Research and Development Committee may subsequently conclude that a protocol does not fully comply with policies or obligations of the St. Cloud VA Health Care System, and the protocol may be disapproved, suspended or terminated on behalf of the institution.

(c) The Minneapolis IRB will maintain records for each St. Cloud research protocol, including a copy of the IRB application, the protocol with all amendments, copies of IRB communications, the original consent form template, and continuing review forms in the file. The Research and Development Committee of the St. Cloud VA Health Care System and each investigator will maintain a duplicate file. The St. Cloud Research and Development Committee may request access to all IRB records pertaining to St. Cloud research protocols and will review all IRB minutes quarterly for meetings where St. Cloud research activities are reviewed by the IRB. The Coordinator of the IRB Committee reviewing St. Cloud research protocols will send copies of these IRB minutes to the St. Cloud Research Program Coordinator promptly after they are approved by the IRB.

### 4.4 Compliance with All Applicable State and Local Law

All human subject research conducted in the Minneapolis VAHCS or by the MVAHCS employees or agents or otherwise under the auspices of the VA will comply with applicable state and local laws. In general, Federal law supersedes when Federal and state laws are in conflict. However, if the state law provides added protections to the human research participant, it is followed. The VA Regional Counsel is available for consultation in all legal matters.

The age of majority in Minnesota is 18 years of age. VA policy and state law recognize as legally authorized representatives (1) persons appointed as health care agents under a Durable Powers of Attorney for Health Care; (2) court-appointed guardians*; (3) next of kin in the following order: spouse, adult child, parent, and adult sibling.
* A court-appointed guardian may only give consent as a surrogate if the court grants permission. (*Minn. Stat. §524.5-313(c)(4)*

## 5. IRB COMPOSITION

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

In the appointment of IRB members, equal consideration must be given to qualified persons of both genders. No appointment to the IRB will be made solely on the basis of gender. Every non-discriminatory effort will be made to ensure that the IRB membership does not consist entirely of men or entirely of women (38 CFR 16.107 (b)). The IRB may not consist entirely of members of one gender nor one profession (38 CFR 16.107(b)).

There will be two appropriately constituted IRBs that will conduct business with the participation of the following persons: Regular voting members, alternate voting members, non-voting members and *ad hoc* reviewers.

### 5.1 Regular Voting Members

As mandated by Federal regulations, the IRB will have at least five regular, voting members, including the Chairperson or Co-Chairperson. At least one IRB member will be a clinical scientist, one a non-scientist, and one a community representative. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members,

including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or community attitudes. The varying backgrounds of the IRB will promote complete and adequate review of research commonly conducted by the organization.

The IRB will ascertain that its membership possesses the professional competence necessary to review human subject research in all categories encountered at the Minneapolis VA Health Care 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. The membership will also be specifically regularly reviewed to determine that the IRB represents the interests of vulnerable populations, such as children, pregnant women, fetuses, neonates, adults who lack the ability to consent, employees, students, and homeless persons.

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 IRB may increase, above the Federally mandated minimum, the number of its members in any category. At its discretion, the IRB may also reduce its membership, as long as the membership conforms to the federally mandated minimum and composition. The IRB membership will determine the scope of expertise of its members, to assure appropriate review of the types of applications it receives.

Scientist Member

Scientist members of the IRB will have had experience in research involving human subjects, and will be recruited from among active or retired members of the staff of the Minneapolis VA Health Care System (38 CFR 16.107(c)).

Non-Scientist Member

Non-scientist members will have expertise in human rights issues and/or ethical or legal issues considered to be relevant to human subject research, and will be recruited from among active members of the staff of the Minneapolis VA Health Care System (38 CFR 16.107(d)).

Community Representative(s)

At least one community representative on each IRB Committee will be a non-scientist. The community representatives will not otherwise have been or currently be affiliated with the Minneapolis VA Health Care System or the University of Minnesota and will not be part of the immediate family of a person who is affiliated with either the Minneapolis VA Health Care System, or the University of Minnesota IRB (38 CFR 16.107(d)). Each IRB will have at least one member who represents the perspective of research subjects. (Note: the unaffiliated member, the member representing the general perspective of subjects, and the non-scientific member may be the same person or they may be represented by two or three different persons.) Examples of potential members of the Minneapolis/St. Paul community that would be considered for appointments as community representatives would be members of the clergy, teachers, attorneys, veterans, or representatives of legally recognized veteran's organizations.

Investigational Pharmacist
An Investigational Pharmacist will be a voting member of both IRB-A and IRB-B on protocols involving investigational drugs, if s/he is not named as an investigator or co-investigator for the protocol. [1]

Information Security Officer and Privacy Officer
The Information Security Officer and Privacy Officer at the Minneapolis VAHCS will serve as *ad hoc* consultants to the IRB. They will provide guidance to the IRB committees and IRB administration on data security and HIPAA/ privacy issues, as needed.

Appointment
Members will be appointed or re-appointed by the Medical Center Director for up to three-year terms, renewable for successive terms of up to three years at each renewal indefinitely, as long as a member continues to possess the desired qualifications.

As a routine, appointments or reappointments of voting members will occur once a year in December. Should a vacancy arise that would create a violation of the federally mandated composition of the membership, the search and appointment process may be activated at any time to fill that vacancy.

Duties
Regular voting members have the following duties:

[1] Understand and apply the basic ethical principles of the Belmont Report and regulatory requirements found in the Common Rule.

[2} Be familiar with the regulatory requirements for the approval of research.

[3] Provide substantive review of protocols and amendments submitted to the IRB;

[4] Maintain the integrity of the IRB review process.

[5] Be familiar with the requirements for protection of vulnerable subjects.

[6] Perform comprehensive review of IRB minutes.

[7] Complete all required courses as determined by Research Service.

[8] Notify the IRB chair or any member of the IRB Staff:

If they have suggestions for improvement of the program.

If they feel their opinion is not being heard or respected.

If they have concerns or problems related to the IRB.

If they believe a conflict of interest exists in their review of a protocol.

[1] The IRB reviewed this arrangement and did not identify a potential conflict of interest with having the Investigational Pharmacist as a voting member on the IRB committees.

[9] Notify the Institutional Official of any problems or concerns related to the IRB or management of the IRB that cannot be discussed or resolved with the IRB chair or the IRB Staff.

[10] Be prompt and regular in their attendance at IRB meetings.

[11] Notify the IRB Coordinator or IRB Administrator if they are unable to attend a meeting.

[12] Fulfill Primary Reviewer responsibilities as delegated.

[13] Participate fully and contribute in a meaningful way to the discussions.

New Member Orientation
New members will receive reference materials including the Institutional Review Board Guidebook, the 1998 FDA Information Sheets, the "Common Rule," (FDA) 21 CFR 50, 56, (DHHS) 45 CFR 46, VHA Handbook 1200.05 and the HRPP Standard Operating Procedures. New members will be oriented by the Chairperson and the IRB Administrator.

Continuing Education for Members
All members will be required to complete training at least once a year on the ethical principles and regulatory requirements associated with research involving human subjects, and good clinical practice.

Throughout the year, informational materials of interest or with special application to the studies to be reviewed will be included in the agenda. Subscriptions to IRB - A Review of Human Subjects Research will be provided to IRB members and the Research Office has instructional and training materials available for reference.

Compensation
The community representative may receive an honorarium for serving on the IRB. IRB members who are VA employees will serve on the IRB as part of their VA assignment and will not receive additional compensation.

Liability
IRB members will be officially carrying out the VA mission and will be protected from liability under the US Tort Claims Act. Non-VA employees will be registered as WOC (without VA compensation) employees with the Research Service. WOC employees will be officially carrying out the VA mission and will be protected from liability under the US Tort Claims Act.

Attendance
Regular voting members will attend at least 75% of the scheduled meetings each year.[2]

St. Cloud IRB Member on IRB-A Committee
At least 2 representatives will be designated by the St. Cloud Medical Center Director, with concurrence from the Minneapolis Medical Center Director, to be voting members of the IRB-A Committee (where St. Cloud research protocols are reviewed). At least one representative from

[2] David Yost, Acting Director, FDA Minneapolis District, FDA review recommendation, 4/2/01.

St. Cloud VAHCS must be present during an IRB meeting at which St. Cloud VAHCS research is being reviewed.

Protocols originating from investigators at the St. Cloud VAHCS will be assigned to the St. Cloud VAHCS member on the IRB-A Committee for primary review unless the IRB, IRB Administrator or IRB Coordinators deem that the protocol content requires additional reviewer expertise. The protocol will then be assigned to another member of the IRB-A or an *ad hoc* reviewer, in addition to the St. Cloud IRB-A member.

IRB Member on R&D Committee
At least one member of the IRB will be a member of the Minneapolis VAHCS Research and Development Committee.

Removal
Members may be removed by the Medical Center Director with the concurrence of the Research and Development Committee. Examples of reasons for removal include, but are not limited to: poor attendance at IRB meetings (attending <75% of the meetings). Recommendations for removal, along with a written justification, must be presented by the IRB Chair to the Medical Center Director and the Research and Development Committee for consideration and final decision (except in cases of absenteeism). Removal of members will generally be for cause but not, in any case, for purposes of retaliation or for unconstitutional reasons.

Reporting of Changes in IRB Membership to OHRP
Changes in IRB membership will be reported to OHRP through ORO by the IRB Administrator. The IRB rosters are updated electronically on the OHRP website by the IRB Administrator. Prior to final submission, the forms are saved, ORO Central Office must review and approve the update. The Midwestern ORO office is also notified of any updates.

Reporting Issues of Undue Influence
IRB members and staff should report any issues of undue influence to the Medical Center Director. The chair, or co-chairs, and members have direct access to the Medical Center Director for appeal if they experience undue influence or if they have concerns about the IRB.

### 5.2 Alternate Voting Members

The IRB, at its discretion, may recruit alternate members to substitute for certain regular classes of members of the IRB, whose input to the deliberations at IRB meetings have unique importance. The alternate member's qualifications will be comparable to those of the regular member's class to be replaced. Alternate members will be included in determining or establishing quorum with voting rights at IRB meetings when the respective members of the same class are absent, but not when they are present.

The procedure for appointment of an alternative member will be the same as that of a regular voting IRB member, except that the nomination will be made by the respective member class or the ACOS/Research.

### 5.3 *Ad Hoc* Non-Voting Consultants

For the review of some protocols, additional expertise may be needed for adequate review. With appropriate confidentiality safeguards, the Primary Reviewer, IRB staff, or IRB members may

request review by *ad hoc* consultants to provide supplemental information to the IRB for protocols under review. These individuals will be non-voting visiting consultants to the IRB and will complete an IRB Consultant Agreement to assure that they do not have a conflict of interest with the protocol to be reviewed.

### 5.4 IRB Chairperson and Co-Chairperson

Each IRB will have a Chairperson and a Co-Chairperson. The Chairperson and Co-Chairperson will be respected, active members of the medical or scientific staff of the Minneapolis VA Health Care System, who have the qualifications of a scientist member of the IRB, are concerned about human rights and ethical issues, and are well informed in regulations relevant to the use of human subjects in research.

Appointment
For the selection of a new IRB Chairperson or Co-Chairperson, the Associate Chief of Staff for Research will nominate a member of the IRB. The Research & Development Committee will approve the nominee. S/he will be appointed by the Medical Center Director, or designee, for a one-year term and may be reappointed indefinitely.

Duties
The Chairperson is responsible for:

[1] Chairing the IRB meeting;

[2] Reviewing requests for expedited review, and if approved, oversee assignment a reviewer or performing the review;

[3] Reviewing and acting on requests for exemption from IRB review; and

[4] Authorizing the signing of the final approval documents for protocols approved by the IRB. In the absence of the Chairperson, the IRB Administrator and IRB Coordinators have authority to sign the approval documents and IRB communications for the Chairperson.

Removal
The Chairperson or Co-Chairperson may be removed by the Medical Center Director with the concurrence of the Research and Development Committee. The potential reasons for removal will be the same as for all IRB members.

Duties of Co-Chairperson
Whenever the Chairperson is not available, the Co-Chairperson will assume the responsibilities of the Chairperson during the period of his/her absence. The Co-Chairperson will also conduct the meeting when the Chairperson is presenting a protocol to the IRB Committee as the primary reviewer.

Acting Chair in the Absence of Chairperson and Co-Chairperson
If the Chair and Co-Chair are unavailable to attend the IRB meeting, the Chair may designate another voting IRB member with experience to conduct the meeting in his/her absence.

### 5.5 Other Non-voting IRB Members

Officials in Research Service, including, but limited to the ACOS/R&D, Administrative Officer for Research (AO), IRB Administrator, and IRB Staff, may be non-voting members of the IRB.

## 6. IRB MEETINGS

### 6.1 IRB Meeting Agenda and Meeting Materials

The IRB will have an agenda for each of its meetings. The agenda will include IRB number, title, and name of investigator for all research protocol applications awaiting action by the IRB. The agenda and materials for review will be made available to the members of the IRB, at least 7 days in advance of the scheduled meeting date. Included with the agenda are instructions to the IRB members with electronic access to the VA network to review items which were approved by expedited procedures since the previous meeting. IRB members who do not have electronic access will receive these items in printed format with the other meeting materials.

### 6.2 IRB Meeting Procedures

Each IRB Committee will meet once a month to fulfill its mandate to oversee research involving human subjects at the Minneapolis VA Health Care System. These meetings will usually be convened on the first or third Monday of the month, to process the research protocol applications submitted for approval.

An emergency meeting of the IRB may be called as necessary.

With the exception of applications eligible for expedited review (Section 12), the IRB membership will determine the outcome of its review of research protocol applications at meetings, where quorum has been established.

A quorum requires the presence of at least a majority of the voting members of the IRB. If quorum is lost during a meeting, the IRB cannot take votes until the quorum is restored. A VA IRB member is present during all reviews of research.

The approval of a protocol requires the vote of the majority of the members present at the meeting. The Chairperson, the Co-Chairperson or, in their absence, an experienced voting member of the IRB will chair the meetings.

At least one physician will be present when reviewing studies involving FDA-regulated articles.

At least one member whose primary concern is in a non-scientific area will be part of the quorum at each meeting. At least one unaffiliated member (Community Representative) will be part of the quorum at each meeting. At least one member who represents the general perspective of subjects will be part of the quorum at each meeting. (The unaffiliated member, the member representing the general perspective of subjects, and the non-scientific member may be the same person or they may be represented by two or three different persons.)

Review by Primary Reviewer
One or more primary reviewer(s) will be assigned to review the complete study documentation, report to the IRB and lead the discussion.

Primary reviewer assignments will be dictated by protocol content and the primary reviewers' research, clinical and IRB expertise, and will be assigned by the IRB Administrator or IRB Coordinators.

If there is a question regarding the expertise of the potential reviewer in regards to the protocol to be reviewed, the IRB staff will contact the potential reviewer to determine if the assignment is appropriate.

- The primary reviewer will receive the information packet for review at least 7 days prior to the convened IRB meeting. The packet will include: IRB Application, the full protocol or complete grant application (if applicable); consent and authorization forms or request for waiver of consent and authorization; waiver of authorization for screening and recruiting, if applicable; narrative summary; all recruitment materials; Investigational Drug Brochure (if applicable); all tests, surveys, and questionnaires; and the DHHS-approved sample consent document (when one exists); the complete DHHS-approved protocol (when one exists).

IRB Packets for IRB Members Who are Not Primary Reviewers

Other members will receive the information packet for review at least 7 days prior to the convened IRB meeting. Their summary protocol information packets will include the same elements as the packet of the Primary Reviewer, except the protocol and Investigator Brochure (if applicable). The protocol will be electronically available in a limited access shared folder on a Minneapolis VAHCS server. IRB members will also have access to complete study documentation on request.

Primary Reviewer for St. Cloud VAHCS Protocols

Protocols originating from investigators at the St. Cloud VAHCS will be assigned to the St. Cloud VAHCS member on the IRB-A Committee for primary review, unless the IRB, IRB Administrator or IRB Coordinators deem that the protocol content requires additional reviewer expertise. The protocol will then be assigned to another member of the IRB-A or an *ad hoc* reviewer, in addition to the St. Cloud IRB-A member.

Consultants and Ad Hoc Reviewers

The IRB, IRB Administrator or IRB Coordinators may invite scientists or non-scientists from within or outside the Minneapolis VA Health Care System, who are not members of the IRB, and have special expertise to function as consultants or *ad hoc* reviewers of a protocol application, to assist the IRB in its review process.

This will be done at the discretion of the IRB or IRB staff, when it is determined on preliminary review of the protocol, that there is not sufficient expertise among the IRB membership to provide adequate review of the protocol.

The *ad hoc* reviewer will be chosen based on the reviewers' clinical and/or research expertise and his/her willingness to perform the review. If there is a question regarding the expertise of the potential reviewer in regards to the protocol to be reviewed, the IRB staff will contact the potential reviewer to determine if the assignment is appropriate.

The *ad hoc* reviewer will have access to all documents submitted to the IRB relevant to the specific protocol under review, may participate at the deliberations, make recommendations on the protocol and be required to provide documentation of his/her review as required of primary reviewers, but may not vote with the IRB (38 CFR 16.107(f)).

The *ad hoc* reviewer will be required to complete the reviewers' section of the IRB Application form and to submit his/her comments in writing.

Proxy votes
Members must be present at convened meetings to vote. **Proxy votes, in writing or via telephone, will not be allowed.**

IRB Member and Consultant Reviewer Conflict of Interest
The Minneapolis VA Health Care System Conflict of Interest in Research Policy #08-001 will be followed for all research activities by the HRPP program. All IRB members and consultant reviewers will consider potential conflict of interest for all protocols that they review. Potential conflicts of interest will be indicated to the IRB staff when these individuals are asked to review a research project proposal. IRB members and consultant reviewers may not review a research protocol with which he/she has a conflict of interest. The research project will be reassigned and reviewed by an IRB member who does not have a conflict of interest with the research to be reviewed. This includes all review events including initial and continuing review, full committee and expedited review procedures, adverse events, amendments, etc.

Whenever an item is being reviewed by the IRB, in which a member of the IRB, including non-voting members, & consultant reviewers may have a conflict of interest, that member may remain in the room at the discretion of the IRB to provide information requested by the IRB, but will not participate in the deliberations, and will not vote on the item (the IRB member will recuse themselves from the deliberation and the vote).

Deferring Protocol Review to Next Convened Meeting Due to Expertise Needed
When the IRB reviews research involving participants likely to be vulnerable to coercion or undue influence, the IRB Chair, or his/her designee, will evaluate each protocol to ensure that at least one IRB member knowledgeable about or experienced in working with such participants is present at the meeting. Otherwise, review of the protocol will be deferred to the next meeting when such an individual will be present.

The IRB Chair, or his/her designee, will defer review and discussion of a protocol to the next meeting until at least one person on the IRB with appropriate scientific expertise to conduct an in-depth review of the protocol is present.

### 6.3 IRB Meeting Minutes

The IRB Administrator or IRB Coordinators will prepare minutes of each meeting of the IRB. The minutes will be in sufficient detail, and will include the following:

[1] Attendance – names of members present and absent; staff, alternative member(s), and guests present;

[2] Presence of a quorum, including the presence of one member whose primary concern is in a non-scientific area;

[3] When an alternate member replaced a primary member;

[4] Approval of prior meeting minutes;

[5] New business items presented to the IRB Committee;

[6] Decisions reached on each new research protocol and continuing review application reviewed and actions taken by the IRB at the meeting including interval of continuing review at initial and continuing reviews, as related to the degree of risk;

[7] The basis for requiring changes in research;

[8] The basis for disapproving research;

[9] Unless documented in the IRB records, protocol-specific findings justifying required regulatory determinations for waiver or alteration of the consent process;

[10] The approval of research contingent on specific minor conditions by the chair or designee, in the minutes of the first IRB meeting that took place after the date of the approval;

[11] The determination of the level of risk;

[12] Attendance of members or alternate members who participated through videoconference or teleconference, and documentation that those members received all pertinent material before the meeting and were able to actively and equally participate in all discussions.

[13] Separate deliberations for each action.

[14] Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.

[15] The rationale for significant risk/non-significant risk device determinations.

[16] Distribution of membership votes on the decisions, documenting the number of votes for, against, abstaining, recused, and excused;

[17] The names of IRB members who left the meeting because of a conflicting interest along with the fact that a conflicting interest was the reason for the absence.

[18] Risk level for each reviewed protocol;

[19] A list of items/documents reviewed for each protocol;

[20] Rationale, assessment of study design and the likelihood the design will yield the expected knowledge, risks and provisions to reduce risks, special concerns, questions regarding IRB application for each initial review;

[21] A note indicating that when a member has a conflict of interest relative to the proposal under consideration, the member (named in the minutes) did not participate in discussions (except to answer questions from the IRB), was not present during the deliberations, abstained/recused from the vote on the proposal and a quorum was maintained.

[22] Whether an electronic flag posting, study entry and progress notes are required

[23] Reasons for requiring changes in a protocol, or disapproving, suspending or terminating a protocol;

[24] If vulnerable groups of subjects were included in the research, the justification for their inclusion, and adequacy of special precautions taken to minimize risks;

[25] Summary of the discussion of controverted issues (an issue is controverted if it has raised a lot of questions and dialog); a summary of the controverted issues must be documented) and their resolution

[26] A description for the justification for all waivers.

[27] A description of considerations for use of surrogate consent.

[28] Date of next scheduled continuing review of a protocol, and the perceived level of risk on which the time of next review was based;

[29] Summary of Administrative Approvals and Notifications, including expedited amendments, expedited initial reviews, expedited continuing reviews, expedited study closures, expedited off-site SAE reports from sponsor, expedited on-site VA SAE reports, and expedited notifications granted since the last meeting;

[30] Notification of status of protocols approved with stipulations at previous meeting.

[31] A summary of the justification for including non-veterans as subjects, if applicable.

[32] A summary of the discussion when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used in the study. The summary needs to include the security measures that are in place to protect the SSN instances embedded in the study. ***NOTE:*** *This does not apply if the only use of SSNs is on the informed consent form or the HIPAA authorization.*

Proceedings must be written and available for review within 3 weeks of the meeting date. The minutes will be made available for review and approval by the IRB members at the subsequent meeting and will be submitted for approval to the next scheduled Research and Development Committee of the Research Service. 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).

See also **Section 21- IRB Documentation and Records**

### 6.4 IRB Notification of Meeting Decisions

All IRB actions will be communicated in writing. Upon completion of the review of a research protocol application, the IRB Administrator or IRB Coordinators will prepare a notification document, to inform the applicant Principal Investigator of the outcome of the review. This document will include the following information:

The outcome of the review by the IRB, and the date the decision was reached;

For protocols that require consent or minor protocol changes before final approval, the required changes will be communicated as expeditiously as possible to the investigator;

For approved protocols, the date of the next scheduled continuation review, and the reporting requirements for the Principal Investigator;

For disapproved, deferred, suspended or terminated protocols, the reasons for these decisions, the rights of the investigators for rebuttal of the decision, and to whom the

appeal should be addressed. In the event of an appeal the investigator will be notified of how the appeal is resolved.

Notifications Regarding St. Cloud VA Health Care System Human Research
Written notification of the results of the Minneapolis IRB and Research and Development Committee review of St. Cloud VA Health Care System research will be promptly forwarded to the St. Cloud Research Program Coordinator for dissemination to the St. Cloud Research and Development Committee. The Research Program Coordinator will promptly send written notification to the Principal Investigator and the Minneapolis IRB of all decisions of the Research Committee at the St. Cloud VA Health Care System.

Notifications to Sponsor
Unless specifically required by the sponsor or the IRB, no written notification of IRB decisions will be provided to the sponsor. The Principal Investigator usually serves as the communication link between the IRB and the sponsor. For FDA-regulated test articles, such linkage is agreed to by the sponsor and the Principal Investigator when they sign Form 1572.

Notification of R&D Committee and Other Organizational Components
Information about IRB actions and decisions is conveyed to the R&D Committee in the form of IRB minutes, memos, and other notifications placed on the agenda. The Director, COS, Information Security Officer, Privacy Officer, IRB Administrator, and RCO are non-voting ex-officio members of the R&D Committee, therefore, they are aware of IRB decisions. The Investigational Pharmacist is a voting member of the R&D Committee. The Chair of the R&D Committee is a voting member on both IRB Committees and functions as liaison between the IRB and R&D Committees.

## 7. HUMAN SUBJECTS OF RESEARCH

The focus of activities of the IRB will be living human subjects who are involved in research.

### 7.1 Definitions of Human Research

The IRB will use the Human Research Determination worksheet to assist with evaluating protocols to see if they are human research and should therefore be reviewed by the IRB.

According to DHHS regulations an activity involves research when both of the following are true:

1) The activity is a systematic investigation, including research development, testing and evaluation
    a. Systematic - designed to answer a question or test a hypothesis that addresses a research intent by an organized method.

2) The activity is designed to develop or contribute to generalizable knowledge.
    b. Generalizable – knowledge that may be applied to populations or settings different from the ones used in the investigation

Also, per DHHS regulations, the both of the following must also be true. The activity involves human participants because:
1) The investigator will obtain data about living individuals

2) Either or both of the following are true:
   1) The investigator will obtain that that data through intervention (physical procedures by which data are gathered and manipulations of the participant or the participant's environment for research purposes) or interaction (communication or interpersonal contact between investigator and participant) with those individuals
   2) The information obtained is both private and identifiable. Private is defined as information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place OR the individual has provided the information for specific purposes and can reasonably expect that the information will not be made public (for example, a medical record).

To determine whether an activity if "human research" according to FDA regulations, we must first determine if the involves an FDA regulated test article. For this to be true, one or more of the following are true:
1) The activity involves the use of a drug[3], other than the use of a marketed drug in the course of medical practice:
2) The activity involves the use of a device[4] to evaluate safety or effectiveness of that device;
3) Data from the activity will be submitted to, or held for inspection by, the FDA in support of a marketing or research application for an FDA-regulated product[5].

By FDA regulations, once it is established that an FDA regulated test article is part of the activity, then one or more of the following must be true to be considered "human research":

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[3] The term "drug" means
   (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
   (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
   (C) articles (other than food) intended to affect the structure of any function of the body of a man or other animals; and
   (D) articles intended for use as a component of any article specified in clause (A), (B), (C). A food or dietary supplement for which a claim, subject to sections 403(r) (1)(B) and 403(r) (3) of this title or sections 403 (r) (1) (B) and 403 (r) (5) (D) of this title, is made in accordance with the requirements of section 403 (r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403 (r) (6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

[4] The term "device" means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is-
   (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
   (2) intended for use in the diagnosis of disease of other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
   (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purpose through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

[5] Includes foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

1) The test article will be used on one or more humans.
2) Data obtained from controls will be submitted to, or held for inspection by , the FDA in support of a marketing or research application for an FDA-regulated product[5].
3) Data obtained from use of a device[4] on tissue specimens will be submitted to, or held for inspection by, the FDA in support of a marketing or research application for an FDA-regulated product[5].

Each research protocol will be reviewed by the IRB or the IRB staff to determine if it is human research. In addition to the FDA and DHHS regulations, the IRB considers research involving human biological specimens (e.g., urine, blood, tissue or other bodily fluids) that include protected health information (PHI) and research involving identifiable data about living or dead individuals to be human subject research. The researcher will be notified in writing by the IRB of the determination of whether an activity is defined as research.

### 7.1a FDA Definition of Clinical Investigation

FDA regulations define a clinical investigation as any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA, or is not subject to requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

### 7.2 Vulnerable Populations

Vulnerable Groups
The IRB will consider certain groups of human subjects to be particularly vulnerable to coercion or undue influence in a research setting. These include but are not limited to:

[1] Children

[2] Pregnant women and fetuses

[3] Mentally disabled and those with impaired decision-making capacity

[4] Persons with a serious, persistent mental illness

[5] Economically or educationally disadvantaged persons

[6] Employees

[7] Students

[8] Prisoners- **The IRB will not review or approve any research focused on prisoners.**

In reviewing research protocols, the IRB will scrutinize those involving these vulnerable groups, to ascertain that their use is adequately justified, and additional safeguards to protect the rights and welfare are implemented to minimize risks unique to each group, as described in the research protocol and the IRB Application. Examples of additional safeguards, include:

- Ensuring subjects' understanding by requiring prospective subjects to take a test or to independently write or dictate their understanding of the research and its risks
- Obtaining an independent assessment by a physician not involved in the study
- Employing a consent monitor to independently verify that informed consent has taken place
- Providing prospective subjects with an advocate during the consent process
- Providing additional opportunities for prospective subjects to decline to participate or to end their participation in the study
- Constructing an assent mechanism for subjects with limited autonomy
- Requiring a ceiling for level of risk of non-therapeutic procedures
- Requiring that research be limited to the medical conditions affecting the subjects
- Requiring that research not be performed on subjects who are unable to provide consent for themselves
- Obtaining new consent from subjects who previously had impaired-decision making capacity and were enrolled via proxy consent, who become competent during the time of the study

Where relevant, the IRB will document why it considers an individual or population to be vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of subjects who are likely to be vulnerable. Individuals or populations that may be temporarily or permanently vulnerable include, but are not limited to, those who:

[1] Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).
[2] Lack comprehension of the research and its potential risks (e.g., educationally disadvantaged, dementia, schizophrenia, depression).
[3] Have increased susceptibility to harm from the procedures of the specific study under review (e.g., individuals who would have to answer study survey questions about their sexual assault).
[4] Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status).

<u>Conditions for Approval</u>
The IRB will consider for approval research protocols involving vulnerable persons, if **all** of the following conditions are met:

[1] The vulnerable population comprises the only appropriate subject population and the research question focuses on an issue unique to subjects in this population;

[2] The research does not involve more than minimal risk to the subject or the research is likely to benefit the subject directly, even if the risks are considered to be more than minimal.

[3] Participation is voluntary;

[4] Procedures have been devised to assure that the participants' representatives are well informed regarding their roles and obligations to protect vulnerable subjects.

### 7.2a Mentally Disabled Persons or Those Persons with Impaired Decision Making Capacity as a Vulnerable Population in Research

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

IRB composition

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

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

Temporary or Fluctuating Lack of Decision-Making Capacity
Individuals, who because of a known condition, are at high risk for temporary (e.g., head trauma) or fluctuating (e.g., schizophrenia) lack of decision-making capacity must be evaluated by a qualified practitioner (who may be a member of the research team), to determine the individual's ability to provide informed consent. This evaluation must be performed as described in the IRB-approved protocol. If the individual is deemed to lack decision-making capacity at the time of their participation in the study, a LAR must provide informed consent. If the subject regains decision-making capacity, the investigator or designee must repeat the informed consent process with the subject, and obtain the subject's permission to continue with the study.

The IRB must make a determination in writing of each of the criteria listed in this section. The IRB minutes include descriptions regarding how each of the conditions, as described below are met. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research protocols on the basis of informed consent from authorized representatives as defined in the Surrogate Consent section of this document. Before incompetent persons may be involved in any VA research, the IRB must find and document in writing that the proposed research meets all of the following conditions: (Consultation may be sought from the Chief of Service (COS). Consultation should also be obtained from psychiatry, if based on a diagnosis of mental illness.)

[1] Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.

[2] Favorable Risk/ Benefit Ratio. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

[3] Voluntary Participation. Participants do not resist participating. Under no circumstances may participants be forced or coerced into participating. Participants may not be forced to participate even if the surrogate consent is obtained. An assent document will be administered to the subject who is incompetent or with impaired decision making capacity, when feasible, and the need for consent and HIPAA authorization has not been waived.

Well-Informed Representatives. 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, must be given descriptions of both proposed research studies and the obligations of 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. **In the State of Minnesota, a court appointed Legal Guardian may not give consent for their ward to participate in research without court permission.** (*Minn. Stat. §524.5-313(c)(4)*

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

b. 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.

c. The IRB has approved the use of an instrument, referred to as the Modified Dysken Tool, to assess capacity. This is to be employed when decision-making capacity of a potential research subject, to provide informed consent to participate in a research study, is questioned. This is located on the IRB SharePoint site under FORMS and on the shared VA server.

d. See also section 9.6-Surrogate Consent.

**7.2b Children as a Vulnerable Population**

VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans. **Therefore, research involving children must not be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer (CRADO).** If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D 46.401 – 46.409, Additional Protections for Children Involved as Subjects in Research). **NOTE:** For requirements to request a waiver contact 202-254-0183. In Minnesota, the age of majority is 18 years.

After a waiver has been granted by the CRADO, the IRB will consider three main issues when reviewing research involving children:

[1] Risk-benefit analyses
VA policy stipulates that research involving children must not present greater than minimal risk of harm.

[2] Parental permission
At least one parent will sign informed consent. The IRB will stipulate the necessary consent document(s).

[3] Assent of the child
Provision will be made to obtain the child's assent when the IRB has determined that the child is capable of giving assent. The IRB will consider the age, maturity and psychological state of the child involved. If it is deemed appropriate that the child's assent should be solicited, the IRB will ensure that the assent form is tailored for the child, with respect to his or her level of understanding. For young children, especially, the assent form will be a one-page document, with simple, age-appropriate language and presented in a manner understandable to the child. The research may not proceed without initial and continuing agreement to participate on the part of the child, regardless of parental consent.

<u>VA Headquarters waiver to conduct research involving children</u>

Prior to requesting a waiver, the following conditions must be met:

[1] The IRB must determine that the study represents no greater than minimal risk.

[2] The study must meet all the requirements in 45 CFR 46, Subpart D, “Additional DHHS Protections for Children Involved as Subjects in Research.”

[3] The IRB must have appropriate expertise to protect the rights of welfare of children enrolled in the research.

[4] The IRB must have specific policies and procedures regarding children in research.

[5] The Medical Center Director must certify that the facility is prepared to respond to pediatric emergencies.

[6] If a contractor and/or a non-VA employee conducts the research, the facility must assure that the individual, or entity performing the research, has procured appropriate liability insurance.

To request a waiver, the following information must be submitted to the Chief Research and Development Officer (CRADO):

[1] A cover letter signed by the Medical Center Director containing the following:

[1a] Certification that the facility is able to respond to pediatric emergencies

[1b] Any additional safeguards that have been incorporated into the clinical site where children will be studied

[1c] Information on the study's funding source

[1d] Information on whether the research will be conducted by a contractor and/or by non-VA employees and, if so, the liability coverage for the study

[1e] Certification that the IRB has determined the study to be of no greater than minimal risk and has approved the study

[1f] A statement that the required elements have been met

[1g] A description of the relevance of both the study and the inclusion of children in the study to veterans' health

[2] A copy of the study protocol, the informed consent form, and the assent document

[3] Minutes of the IRB and R&D Committee meetings approved the study. The IRB minutes should reflect the discussion regarding level of risk, the consent and assent forms, the investigators' qualifications to conduct research involving children, and any additional safeguards incorporated into the protocol.

### 7.2c Pregnant Women and Fetuses as Vulnerable Populations

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

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

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

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

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

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

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

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

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

d. General limitations

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

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

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

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

Any decision as to the timing, method and procedures used to terminate the pregnancy;

OR

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

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

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

The risk to the fetus is minimal.

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:

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

His identity or whereabouts cannot reasonably be ascertained,

He is not reasonably available,

OR

The pregnancy resulted from rape.

**7.2d Minneapolis VA Employees and Students as Healthy Subjects of Research**

Whenever employees or students of the Minneapolis VA Health Care System are to be used as "healthy subject pools" in research, the 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.

For some research protocols, Human Resources or local union representatives may need to be consulted prior to approval of the research. Any surveys given to professional staff at the Minneapolis VAHCS need to be anonymous and voluntary. A copy of the survey, stating that it is "anonymous and voluntary" on the first page, must be submitted to the AFGE 3669 union office with an explanatory memo requesting approval or sent electronically via Outlook to VHAMIN AFGE Local 3669 Official Time, with a request for approval. Investigators will submit a copy of the approval by the union to the IRB prior to granting of final approval for the protocol.

The following language will be included in the informed consent template to inform VA employees of possible coercion or undue influence resulting from decision to participate as a research subject:

If you are a VA employee you are considered a special class of research subject who deserves special protections: 1) Your decision to participate in this study should be free from pressure or coercion to participate. 2) The VA research team will work to secure your information according to VA data security and privacy policies and every effort will be made to keep your information from your supervisor and co-workers. However, accidental disclosure or release of your private information could occur during the conduct of this study.

### 7.2e Participation of Non-Veterans as Research Subjects

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

All regulations pertaining to the participation of veterans as research subjects including requirements for indemnification in case of research-related injury pertain to non-veteran subjects enrolled in VA-approved research.

A VA medical record must normally be created for all subjects for whom a consent waiver has not been granted. All requirements that govern the documentation of consent and research procedures in CPRS notes that apply to veterans are also applicable for non-veterans. The IRB may waive the requirement for CPRS documentation for studies that involve minimal risk if the very existence of such documentation represents the primary risk to the subjects. Such waivers must be specifically requested by the study investigator and must be approved by the IRB.

### 7.2f Special Review of Studies Focused on Subjects with Post Traumatic Stress Disorder (PTSD)

The IRB applies special consideration to all VHA research studies involving individuals with PTSD. The purpose of this review is to ensure appropriate:

a) sensitivity to the PTSD study population;

b) consideration of relevant FDA or sponsor advisories, alerts, and warnings;

c) subject notification regarding such advisories, alerts, and warnings; and

d) review of risks associated with medications likely to be used in the PTSD study population.

A form entitled “IRB Review of Human Studies Focusing on Individuals with Post-Traumatic Stress Disorder (PTSD)” is available to the IRB primary reviewer for reference at initial review of applicable protocols.

### 7.3 Independent Contacts for Research Participants

Current, prospective, or past research participants or their designated representatives may contact either the Patient Representative or the Research Service office, if they have any questions about the rights of a research subject, or would like to discuss problems or concerns, or have questions about a study or offer input regarding a research study and would like to speak to an individual who is not part of the research team of this study. This information is included in the Informed Consent templates.

### 7.4 International Research

***NOTE:*** *Research conducted at U.S. military bases, ships, or embassies is not considered international research.*

VA international research is defined as any VA-approved research conducted at international sites (not within the U.S., its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research that entails sending such specimens or data out of the U.S. ***NOTE:*** *This includes sending such*

*specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA investigator on sabbatical at an international site). It also includes a VA's serving as a coordinating center for an international research project.*

All individuals who participate as subjects in research at international sites must be provided appropriate protections that are in accord with those given to research subjects within the U.S., as well as protections considered appropriate by local authority and custom at the international site (38 CFR 16.101(g)).

**7.5 Multi-Site Studies**

If conducting human research studies involving more than one engaged institution, each institution is responsible for safeguarding the rights and welfare of human subjects entered at its site, and for complying with all applicable local, VA, and other Federal requirements.

Investigator Responsibilities

In addition to relevant regulations and local SOPs:

(1) The PI of the overall study in a VA multi-site study must submit a protocol to the IRB of record for the PI's facility that includes the following:

(a) A method for ensuring that all engaged participating sites have the most current version of the protocol, the most current version of the informed consent form, and the most current version of the HIPAA authorization.

(b) A method for ensuring that all required approvals have been obtained at each engaged participating site (including approval by the site's IRB of record) before the study is implemented at that site.

(c) A method for notifying the Director of any facility deemed by the PI's IRB of record not to be engaged in the research, but on whose premises research activities will take place, before initiating the study (e.g., the PI conducts a survey of employees at a facility that is not engaged in the research).The facility Director has the authority to disapprove the conduct of these research activities on that facility's premises.

(d) A method for confirming that all amendments and modifications to the protocol, the informed consent form, and the HIPAA authorization have been communicated to engaged participating sites, and that all required local facility approvals (including approval by the local facility's IRB of record) have been obtained before the amendment or modification is implemented.

(e) A method for assuring that all engaged participating sites will safeguard VA data as required by VA information security policies.

(f) A method for communicating to engaged participating sites SAEs that have the potential to affect implementation of the study.

(g) A method of communicating regularly with engaged participating sites about study events and interim results (if appropriate).

(h) A method for ensuring all Local Site Investigators (LSIs) conduct the study appropriately.

(i) A method to ensure all non-compliance with the study protocol or applicable requirements is reported in accordance with VHA Handbook 1058.01.

(j) A method for notifying local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).

(2) When the investigator is a LSI for a multi-site study (whether the LSI is also a PI or solely a Local Site Investigator), the LSI must:

(a) Conduct the study according to the most recently approved version of the protocol, the most recently approved version of the informed consent form, the most recently approved version of the HIPAA authorization, and all applicable local, VA and other Federal requirements;

(b) Ensure that all amendments and modifications to the protocol and the informed consent form are submitted to and approved by the local IRB of record prior to initiating any changes;

(c) Report any unanticipated internal or local SAEs, whether related or unrelated to the research, in accordance with VHA Handbook 1058.01;

(d) Report study events and interim results (if available) to the local IRB of record as required by local IRB policies; and

(e) Oversee all aspects of the study at their local site.

**Local VA Facility's IRB of Record's Responsibilities for Multi-Site Research When the VA Facility's Investigator is the Multi-Site Study PI for All Participating Facilities and the VA Central IRB is Not Being Used**

When the VA facility's investigator is the multi-site study PI or study sponsor for all participating facilities, and VA Central IRB is not being used, the PI's or study sponsor's local VA facility's IRB of record is responsible for:

(1) When a participating site is added to the study, determining:

(a) Whether or not that site will be engaged in human subjects research.

(b) If the site will be engaged in research, then reviewing and confirming that it:

1. Has an active FWA, and
2. Has provided documentation of all relevant approvals, including approval of its IRB of record.

(2) Approving the study-wide protocol and sample informed consent document to be provided to each LSI at engaged facilities.

(3) Ensuring the study-wide protocol contains a mechanism for ensuring that any differences in the protocol or informed consent at engaged local participating sites are justified by the LSI, and that they are approved by the PI before being implemented.

(4) Ensuring there are clear AE reporting requirements, a data monitoring committee if applicable (or other reliable monitoring mechanism) with clear procedures and requirements, and a clearly defined feedback loop to the PI's or study sponsor's IRB.

(5) Reviewing the PI's plan for communicating appropriate critical information (e.g., reports of data and safety monitoring) to engaged participating sites.

(6) Ensuring, when relevant, confidentiality and information security requirements are met for information storage at and transmission to statistical or coordinating centers.

(7) Reviewing reports from applicable DSMBs/DMCs.

c. **Local VA Facility's Responsibilities When Using the VA Central IRB as an IRB of Record.**

The facility Director, when using the VA Central IRB as an IRB of Record, is responsible for:

(1) Entering into an MOU with the VHA Central Office that stipulates the respective authorities, roles, and responsibilities of the VHA Central Office, the VA Central IRB, and the local VA facility when the local VA facility elects to use the VA Central IRB as an IRB of record.

***NOTE:*** *A new MOU must be executed when there is a change in the FWA signing official (e.g., when there is a new facility Director or acting facility Director).*

(2) Modifying its FWA to list the VA Central IRB as an IRB of record.

(3) Maintaining SOPs for using the VA Central IRB as an IRB of record.

(4) Retaining responsibility for oversight of its local HRPP.

## 8. INITIAL REVIEW BY IRB OF HUMAN SUBJECT RESEARCH

An investigator, who intends to initiate a research protocol involving human subjects, shall be responsible for submitting an application to the IRB for review and approval of the protocol before the protocol begins. If the investigator is unsure whether IRB review is required, the research plan will be submitted to the IRB and a determination requested. No aspect of use of human subjects in research may begin until IRB and R&D Committees have granted the approval.

### 8.1 Documents Required for Initial Review

To apply for initial review and approval of a new protocol, the Principal Investigator shall complete the "Request to Review Research Protocol" and the application template form issued by the IRB ("IRB Application", previously called the "Request for Approval by the Institutional Review Board").

The study protocol application will include but is not limited to:

- the title of the study;
- identification of Principal Investigator (PI) and signed PI assurance;
- identification of contact person for study, other co-investigators, and other study personnel;
- study sponsor (if any);
- description of data and safety monitoring plan;
- an assessment of potential conflict of interest;
- summary of activities for study, including research question, significance, and study type;
- inclusion and exclusion criteria of subjects;
- a description of study subject characteristics, recruitment methods and materials;
- waivers of consent, authorization, or documentation, identification of vulnerable or incompetent subject categories and justification for their use;
- description of informed consent process;

- whether surrogate consent will be used;
- compensation to subjects for their participation;
- disclosure of risks and benefits;
- data security, confidentiality and privacy protections; assessment of research personnel safety;
- use of radiation or radioactive substances;
- use of audiotaping or videotaping;
- use of biological samples or specimens;
- use of investigational drugs or biological products;
- use of investigational devices;
- request for exempt/expedited review;
- copies of all written instrument/tools/surveys;
- provisions for managing adverse reactions; any compensation for injured research subjects;
- and extra costs to subjects for their participation in the study.

When a study involves "usual care," in the protocol or a separate document in the IRB application the researcher must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject's health care provider) responsible for relevant aspects of both the research and the usual care.

Each application shall be accompanied by all documents necessary for an orderly review of the protocol, particularly those aspects involving human subjects. The application shall be accompanied by copies of:

[1] IRB Application

[2] Abstract (limited to 500 words, for entry into the VA Research and Development Information System, RDIS)

[3] Request to Review Research Proposal signed by the investigator; Investigator Data form (if first submission by Principal Investigator)

[4] Research protocol (prepared by the investigator for investigator-initiated protocols, or by the sponsor of the study) or grant application

[5] Investigator's brochure for investigational drugs or devices (if applicable)

[6] Application to Radioactive Drug Research Committee (RDRC) if study involves ingested or injected radioactivity for research purposes only and approval documentation from RDRC if available at submission deadline.

[7] Texts of advertisements for subject recruitment (if applicable)

[8] Copy of all questionnaires, surveys, tests, etc.

[9] Original, signed copy of VA Form 10-9012, if the study involves an investigational drug

[10] Copy of FDA Form 1572 (if applicable)

[11] Informed consent documents (may be substituted by the explanatory statement, if IRB is being requested to waive the documentation of the consent or waive informed consent

[12] PHI authorization documents (may be substituted by a waiver of authorization if IRB is being requested to waive the documentation of authorization or waive authorization)

[13] PHI waiver of authorization documents for screening and recruiting, if the IRB is not being requested to waive authorization for the conduct of the study

[14] Minneapolis VAHCS PHI and Sensitive Information Use Statement for Initial Review Submissions.

[15] The DHHS-approved sample consent document (when one exists).

[16] The complete DHHS-approved protocol (when one exists).

[17] Any relevant grant applications.

[18] Any other supporting document that would facilitate a meaningful review.

## 8.2 IRB Criteria for Approval of New Research

In consideration of approval of a new research protocol involving human subjects, the IRB will review the application to determine if all of the following criteria are met:

[1] Human subjects' protection training and good clinical practice training, and credentialing for the investigator(s) and study coordinator(s) that are connected with this study and physically conducting research at the Minneapolis VAHCS documented in the Research Office.

[2] Study design and study rationale are scientifically sound and justify the potential risks.

[3] Risks to subjects are minimized to the extent possible.

[4] Risks to subjects are reasonable in relation to anticipated benefits, all known risks are included in the consent form, and sponsors and Principal Investigators have not used language that inappropriately minimizes risks and exaggerates potential benefits. The IRB should only consider those risks and benefits that may result from the research.

[5] Selection of subjects is equitable.

[6] Exclusion of classes of persons who might benefit from the research has scientific and ethical justification.

[7] Appropriate informed consent will be sought from prospective subjects or their legal representatives - a significant part of the initial review process focuses on the consent form.

[8] The research will be conducted in an appropriate setting. Consent will be sought only under circumstances that provide the subject (or the legally authorized representative) sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

[9] Informed consent will be appropriately documented.

[10] An adequate data and safety monitoring plan is in place for monitoring and reporting data collected to ensure the safety of subjects and others (when appropriate).

[11] There are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data; Research data will be used, disclosed, transferred or transmitted, stored and/or destroyed in compliance with all policies and procedures for research as outlined in Human Subject Protections for Veterans, including the protection of confidentiality and privacy, found in 38 CFR Part 16, VHA Handbook 1200.05, VA Directive 6504, and the HIPAA privacy rule for research (45 CFR Parts 160 and 164).

[12] Whenever subjects are considered to be vulnerable to coercion or undue influence (such as children, pregnant women and fetuses, prisoners*, mentally disabled persons, persons with impaired decision-making capacity, persons with a serious and persistent mental illness, economically or educationally disadvantaged persons, employees and students), their use is adequately justified, and additional safeguards have been included in the study to protect the rights and welfare of these subjects.

**(*The IRB will not review or approve any research focused on prisoners.)**

[13] Certain studies may require special attention including:

[13a] Withdrawal of therapy, whether or not it is replaced by experimental treatment, when there is significant risk of morbidity or mortality;

[13b] Any invasive surgical procedure, even if the experimental procedure replaces a standard surgical procedure that is thought to involve higher risk;

[13c] Significant risk of serious impairment;

[13d] Risks when there is no potential clinical benefit to the subject (e.g., Phase I studies).

[14] For protocols where the Principal Investigator is the lead investigator of a multi-center study or where the Institution is the lead site of a multi-center trial, the IRB will evaluate whether the management of information obtained in multi-center research that might be relevant to participant protections is adequate.

[15] The research study will have the resources necessary to protect subjects, including availability of medical or psychosocial resources that subjects may need as a consequence of the research.

## 8.3 IRB Process of Initial Review

Primary Reviewer

Upon receipt of the documents for an initial review, the IRB Administrator or IRB Coordinators will identify one of the regular members of the IRB, who has expertise in the relevant field of research, to function as the "primary reviewer." A complete set of documents will be forwarded to the primary reviewer.

To facilitate the review, the IRB Application form requires the reviewer to approve or disapprove each element, to ensure that inadvertent omissions do not occur in considering the conformity of the application to all criteria for approval of research and that a proposed continuation date and special monitoring requirements are identified.

Prior to the IRB meeting, the primary reviewer will have the authority to request from the applicant investigator, either directly or via the IRB staff, revisions or additional information, including documents, and to discuss the protocol with the applicant investigator. Upon completing his/her review, the primary reviewer will present the protocol at a meeting of the IRB. At his/her discretion, the primary reviewer may invite the investigator or his/her designee to the IRB meeting to answer the IRB committee's questions prior to deliberations and voting.

Consideration of Risk/Benefit

The IRB will consider the overall level of risk to subjects in evaluating proposed research and distinguish research that is greater than minimal risk from research that is not greater than minimal risk. ("Minimal risk" means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.) Special consideration and protections will be required when vulnerable subjects are enrolled in research that is greater than minimal risk. To approve the research, the IRB will determine that risks are minimized by using procedures that are consistent with sound research design and that subjects are not exposed to unnecessary risks. The IRB will examine the research plan, including research design and methodology, to determine that there are no obvious flaws that would place subjects at unnecessary risk.

Risk in studies also includes the risk that the research is so poorly designed that meaningful results cannot be obtained. To approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any). In addition, the IRB assesses the importance of the knowledge that may be reasonably expected to be obtained. The IRB will determine the interval for continuing review based on the level of risk, and this will be documented in the IRB minutes. The interval for continuing review will be at most one year. However, if the protocol is deemed high-risk or has a high risk/potential benefit ratio the continuing review interval may be required to be less than a year, based on the judgment of the primary reviewer and the IRB.

Data and Safety Monitoring Plans

All research studies that are greater than minimal risk should have a data and safety monitoring plan. Provisions for safety monitoring must be documented in the protocol and IRB Application form. Data and Safety Monitoring Plans (DSMP) are meant to assure that each clinical investigation has a system for appropriate oversight and monitoring of the conduct of the clinical

investigation. This oversight ensures the safety of the participants and the validity and integrity of the data. A DSMP is commensurate with the risks involved with the investigation. The DSMP can be as simple as the investigator annually submitting his/her safety and AE information to the IRB or as complex as having a Data and Safety Monitoring Board. The IRB will review the Data and Safety Monitoring Plan of each greater than minimal risk protocol to determine:

- If reporting mechanisms and frequency of the monitoring are appropriate
- If the entity conducting the monitoring is appropriate for the protocol
- What data will be monitored, and adequacy of the procedures for analysis and interpretation of the data
- What actions will be taken upon specific events or end points
- Procedures for communication from the data monitor to the IRB and sites.

Protocols Involving Investigational or Unlicensed Test Articles

Under FDA regulations 21 CFR §312.2 all clinical investigations that involve drugs (any use of a drug other than the use of a marketed drug in the course of medical practice [21 CFR §312.3(b)]) must have and IND, unless the drug meets one of the five exemptions from the requirements for and IND in 21 CFR §312.2(b). These categories are:

There are four (4) criteria for exemption from IND and they are:

1. Investigation of a drug product that is lawfully marketed in the United States may be exempt if (*all must be true)*:
    i. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, or is not intended to be used to support any other significant change in the labeling for the drug.
    ii. The drug being used in the investigation is lawfully marketed as a prescription drug product and the investigation is not intended to support a significant change in the advertising of the drug.
    iii. The investigation does not involve a route of administration, dosage level, use in a new patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the drug.
    iv. The investigation is being conducted in compliance with IRB review (21CFR56) and the requirements for informed consent (21CFR50).
    v. The investigation is being conducted in compliance with 21CFR312.7 which means that the sponsor or investigator are not promoting the drug being studied, as safe or effective.
    vi. The investigation does not involve an exception for informed consent (21CFR50.24).
2. Clinical investigations of an in-vitro diagnostic biological product (e.g. blood grouping serum, reagent red blood cells and anti-human globulin) may be exempt if (*all must be true)*:
    i. The biological product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
    ii. The biological product is shipped in accordance with 312.160.

iii. The investigation does not provide for exception for informed consent (21CFR50.24).

3. The investigational study is utilizing a drug intended solely for in-vitro tests or in laboratory research animals and is shipped in accordance with 312.160 and the investigation does not involve an exception for informed consent (21CFR50.24).
4. The investigation involves only the use of a placebo and the investigation does not involve an exception for informed consent (21CFR50.24).

Under FDA regulations 21 CFR §812.2 (a) all clinical investigations that determine safety or efficacy of a medical device must have an IND, unless the device meets one of the exemptions from the requirement for an IDE in 21 CFR §812.2 (b).

There are two ways that a medical device can have an IDE:

1) FDA issues an IDE.
2) The device meets the requirements for an abbreviated IDE.

Research that falls into the following category is considered to have an abbreviated IDE and does not need an FDA-issued IND: [21 CFR §812.2 (b)]:

Abbreviated IND: (*All must be true*):

1) The device is not a significant risk device, defined as:

i. Device is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
ii. Device 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. Devise 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. Device otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

2) The device is not a banned device.
3) The sponsor labels the device in accordance with 21 CFR §812.5.
4) The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
5) The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under §56.109(c).
6) The sponsor complies with the requirements of §812.46 with respect to monitoring investigations;
7) The sponsor maintains the records required under §812.140(b) (4) and(5) and makes the reports required under §812.150(b) (1) through (3) and (5) through (10).;

8) The sponsor ensures that participating investigators maintain the records required by §812.140(a)(3)(i) and make the reports required under §812.150(a) (1), (2), and (7); and 5.9. The sponsor complies with the prohibitions in §812.7 against promotion and other practices.

There are seven categories where research involving a medical device is exempt from the requirement for an IND [21 CFR 812.2(b)]

Exemption #1: A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

Exemption #2: A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart # or 21 CFR §807 in determining substantial equivalence (i.e. "FDA-approved device).

Exemption #3 (*all must be true*):

1) A device is a diagnostic device.
2) The sponsor complies with applicable requirements in 21 CFR §809.10 (c).
3) The testing is noninvasive.
4) The testing does not require an invasive sampling procedure that presents significant risk.
5) The testing does not by design or intention introduce energy into a subject.
6) The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Exemption #4: A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

Exemption #5: A device intended solely for veterinary use.

Exemption #6: A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR §812.5 (c).

Exemption #7: A custom device as defined in 21 CFR §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

The PI will provide the IND information to the IRB in Appendix G (for IND) of the IRB Application form. The IRB staff will confirm that the drug has an IND or meets one of the FDA exemptions from the requirement to have an IND.

The PI will provide the IDE information to the IRB in Appendix H (IDE) of the IRB Application form. When research is conducted to determine safety or effectiveness of a device, the IRB staff will confirm that the device fulfills the requirements for an abbreviated IDE, or that the device fulfills one of the IDE exemption categories.

Validation of the IND or IDE number will be done by the IRB staff prior to IRB review of the clinical investigation. This will be done by reviewing information provided on Appendix G or

Appendix H of the IRB application form and evaluating the IND or IDE number on one of the following materials supplied by the investigator:

(a) sponsor protocol

(b) sponsor correspondence

(c) FDA correspondence

(d) contract research organization correspondence.

Research approval involving and FDA-regulated investigational drug, biologic, or investigational device will only occur after the IRB:

[1] Has received documentation that the research will be conducted under and applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) or

[2] Has formally determined that satisfactory justification has been provided by the investigator why an IND or IDE is not required.

[3] Has determined that the investigator's plan for control of investigational devices is acceptable. (An example of an acceptable plan would be for the investigator to keep the test articles in a locked space and keep an inventory log, which he/she will submit to the IRB at continuing review.)

Electronic Flags

The IRB will determine for each protocol if an electronic flag posting (e.g., Research Participant Note) or other non-flagging note (i.e., a CPRS note title containing the word "research") is required. The purpose of these items is to protect the subject's safety, communicate study participation with health care providers, and to provide a source of more information about the study. The participant's medical record must be flagged if participation involves:

1. Any invasive procedure;
2. Interventions that will be used in the medical care of the participant, or that could interfere with other care the participant is receiving or could receive;
3. Clinical services that will be used in the medical care of the participant, or that could interfere with other care the participant is receiving or could receive; or
4. The use of a survey or questionnaire that may provoke undue stress or anxiety unless the IRB determines that mandatory flagging is not in the best interest of the participant;
5. In other situations in which the IRB determines flagging is necessary.

The IRB may waive these requirements for a particular protocol if:

[1] The subjects' participation in the study involves:

(a) Only one encounter,

(b) Only the use of a questionnaire, or

(c) The use of previously collected biological specimens or data.

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

If the IRB determines and documents that the participants' health record must be flagged in CPRS as participating in research, the record must identify the researcher and include contact information for a member of the research team who would be available at all times, and contain information about the research study or identify where this information is available. This flag is to be removed by the researcher once the subject is no longer participating in the research study by placing an addendum on the enrollment CPRS note documenting that the subject is no longer participating. In the case of trials for which a Research Participant note was required (therefore creating a Crisis Notes, Warning Notes, Allergies and Directives (CWAD) alert), a message must be sent in VistA to the address **g.error** requesting the removal of the clinical flag. The subject line of this message cannot contain PHI/PII, however the body of the message should indicate the subject name, the full SSN, the study's IRB number, and the date of the initial CPRS research note.

Master List of Subjects Who Have Signed Consent

The investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not the IRB granted a waiver of documentation of informed consent.

Investigators must not add a subject's name to the master list of all subjects until after:

(a) Informed consent has been obtained from that subject, and

(b) When appropriate, informed consent has been documented using an IRB-approved informed consent form.

The IRB may waive the requirement for the investigator to maintain a master list for a given study if both of the following conditions are met:

(a) There is a waiver of documentation of informed consent, and

(b) The IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.

If the IRB waives the requirement to maintain such a master list, the IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.

The investigator must secure the master list appropriately in compliance with all VA confidentiality and information security requirements in the investigator's file for each study.

Action of the IRB

After sufficient discussion, the IRB members will vote on the application, either to approve, require modifications in order to approve or disapprove it. The IRB may defer a decision until revisions are implemented, additional information is provided, or further expert review is obtained (including invitation of *ad hoc* reviewers). The members will set the frequency of the continuing review based on the nature of the study, the degree of risk involved, the vulnerability of the study subject population, likely medical condition of the proposed subjects, overall qualifications and research experience of the Principal Investigator and other members of the research team, nature and frequency of adverse events observed in similar research, and other factors that the IRB deems relevant. The decisions will be based on the votes of the majority of the voting members present.

Notification to Investigators
IRB decisions will be conveyed in writing to the Principal Investigator. Communications regarding modifications required to secure approval will describe necessary changes. Communications regarding disapprovals will include the reasons for disapproval and may suggest changes needed before review will be reconsidered.

Modifications Required to Secure Approval
The IRB may approve a protocol if no changes or only minor revisions are necessary. Minor stipulations are defined as editing changes to the protocol or submitted materials because of grammatical/formatting errors, or substitution of a phrase or section in the protocol or submitted materials, as specified by the IRB. If stipulations are of a substantive nature, or if open-ended questions must be asked of the PI, the protocol must be deferred and re-reviewed by the full IRB Committee.

If minor revisions or requirements are required, the Chairperson or a designated IRB member may subsequently review and approve the study on behalf of the IRB, upon completion of these tasks. The approval date for these studies will be the date of the convened IRB meeting at which the minor changes were stipulated. Work on protocols approved by the IRB may not commence until approval from the Research and Development Committee is obtained.

Date of Expiration of Approval
The initial date of approval for protocols is the date of the convened meeting at which the IRBs approved the protocol, or when the IRB determined modifications were required in order to secure approval. When protocols are approved for 12 months, the approval period will be no longer than one year. (For example, a protocol approved on 10/01/2011 would expire on 09/30/2012). Continuing review or approval must occur on or before the date when the IRB approval expires.

When the IRB designates a continuing review period less than 12 months, the date of expiration of approval will be the calculated by number of months of approval. For example, a protocol approved on 1/1/07 for a 6 month review period, would expire on 6/30/07. **The expiration date is the last date on which the research may be conducted for a given protocol.**

Rebuttal of Decision
In case of disagreement between the IRB and the investigators of a protocol under review in regards to requested revisions or a decision to disapprove the protocol, the IRB will provide the opportunity of rebuttal for the investigators, either in writing, or by appearing at a meeting of the IRB, to defend their positions.

IRB Fees

The sponsor will be charged for the review of all industry-sponsored protocols reviewed by the Minneapolis VAHCS IRB.

## 8.4 Subject Privacy and Confidentiality including HIPAA Requirements

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a federal privacy law that went into effect on April 14, 2003. The obtaining, creating, using and/or disclosing of

individually identifiable health information when conducting research are regulated under this law.

HIPAA defines Protected Health Information (PHI) as health information that has any one of the following 18 identifiers of the individual or of relatives, employers, or household members of the individual attached to it:

- Names
- Geographic subdivisions smaller than a state, including street address, city, county, precinct, and zip code if, according to the current policy available from the Bureau of the Census
  - The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people; AND
  - The initial 3 digits of the zip code for all geographic units containing 20,000 or fewer people is changed to 000.
- Dates, except the year, directly related to an individual such as date of birth, discharge date, date of death) and all ages over 89 and all elements of dates including the year indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
- Telephone numbers
- Fax numbers
- Electronic mail addresses
- Social Security numbers
- Medical Record numbers
- Health plan beneficiary numbers
- Account number
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web Universal Resource Locators (URLs)
- Internet Protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- Any other unique identifying number, characteristic, or code.

To approve research, the IRB must determine that there are adequate provisions to protect the privacy of subjects and the confidentiality of data. In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information within and outside the research. It will evaluate the effectiveness of proposed de-identifying techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections as stated in the research application document, IRB Application or the research protocol.

Privacy: Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, economically or intellectually) with others.

Confidentiality: Treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure without permission.

Identifying potential subjects for research

It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent and authorization of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations and circumstances in which the IRB may approve a waiver of documentation of informed consent and authorization requirements. **Waivers of consent and authorization may not be used for FDA-regulated studies, except as provided for in 21 CFR 50 §50.23 and 50.24.**

### 8.5 Protected Health Information (PHI) Waiver of Authorization

If the investigator or their assigned research staff are initiating contact with the potential research subjects a waiver of authorization must be granted by the IRB prior to screening and recruiting of potential research subjects or if the investigator is requesting a waiver of authorization for conducting the research. The waiver of authorization documentation must include all of the following:

a. Confirmation that the study is not FDA-regulated

b. Identification of the IRB

c. Date of IRB approval of the waiver of authorization

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

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

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

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

   a. An adequate plan to protect the identifiers from improper use and disclosure;

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

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

(2) The screening and recruiting of potential research subjects or the research could not practicably be conducted without the waiver or alteration;

(3) The screening and recruiting of potential research subjects or the research could not practicably be conducted without access to and use of the requested information;

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

IRB approval for data access
IRB approval for the study of data, documents, records, or pathological specimens where the subjects are identified, without documentation of informed consent and authorization, will require that the subject's interests are adequately protected and the importance of the research justifies the invasion of privacy. (Refer to section 8.5 for circumstances under which the IRB may approve a waiver or alteration of consent elements.)

Federal regulation exempts from review all research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if the sources are publicly available or if the information is recorded by the investigator in a manner that does not allow subjects to be identified, either directly or through identifiers that are linked to them.

The VHA, considered a covered entity under HIPAA, may always use or disclose for research purposes health information that has been de-identified, in accordance with 45 CFR 164.502(d) and 164.514(a)-(c) of the Rule.

Research on Protected Health Information of Decedents – Representations from the researcher, in writing that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought will be submitted to the IRB for review. See 45 CFR 164.512(i)(1)(iii).

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

Persons not employed by the VA can only access medical and other VA records within the restriction of the Federal Privacy Act and other statutes. Requests for such documents must be submitted to the Chief Officer, Office of Research Development in VA Central Office at least 60 days before access is desired.

Confidentiality of research data
The need for confidentiality exists in virtually all research in which data are collected about identified subjects. In most research, assuring confidentiality is only a matter of following some routine practices: substituting codes for identifiers, removing face sheets (containing names and addressees) from survey instruments containing data, properly disposing of computer sheets and other papers, limiting access to identified data, impressing on the research staff the importance of confidentiality, and storing research records in locked cabinets or in password controlled computer databases.

Additional safeguards may be necessary when data are collected on sensitive matters such as mental health issues, sexual behavior or criminal activity. In studies where keeping the identity of the subject confidential may be as or more important than keeping the data obtained about the participants confidential, having subjects sign consent and authorization forms may increase the risk of a breach of confidentiality. The consent and authorization forms constitute a record identifying the subject as a member of the group studied. For studies that are not FDA-regulated, Federal policy allows for waiver of the requirement for obtaining signed consent where it will be the only record linking subjects to the research and where a breach of confidentiality presents the principal risk of harm that may result from the research.

Where data are being collected about sensitive issues (such as illegal behavior, alcohol or drug use, or sexual practices or preferences) protection of confidentiality consists of more than preventing accidental disclosures. There have been instances where the identities of subjects or research data about particular subjects have been sought by law enforcement agencies. Under federal law, researchers can obtain a Certificate of Confidentiality that will provide protection even against a subpoena for research data. More information on Certificates of Confidentiality may be obtained at: http://grants.nih.gov/grants/policy/coc/ index.htm.

Disclosure to participants about confidentiality
During the process of informed consent using the HIPAA authorization form, subjects will be told what PHI will be used and/or disclosed, the purpose of the use and/or disclosure of their PHI, to whom the PHI will be shared with during the course of the research, and the limits, legal or other, to the researchers' ability to safeguard confidentiality and of the consequences that could result from breaches of confidentiality.

### 8.6 Protected Health Information (PHI) Authorization
A valid authorization must be written in plain language and contain at least the following elements:

a. A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion including drug abuse, alcoholism or alcohol use, testing for or infection with Human Immunodeficiency Virus (HIV), and/or sickle cell anemia, if applicable.
b. The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure.
c. The name or other specific identification of the person(s), or class of persons, to whom the covered entity (VHA) may make the requested use or disclosure.
d. A description of each purpose of the requested use or disclosure.

e. Signature of the subject and date. If the authorization is signed by a personal representative of the subject a description of such representative's authority to act for the individual must also be provided.
f. A statement giving the subject the right to revoke the authorization in writing.
g. The subjects' status with the VA will not be adversely affected by the subject refusal to sign the authorization.
h. The consequences to the subject for refusal to sign the authorization.
i. The potential for information disclosed pursuant to the authorization to be subject to re-disclosure by the recipient and no longer being protected by the VA.
j. An authorization for research purposes may state that the authorization does not expire, however, if there is an established end date for the study this date should be used.
k. The Paperwork Reduction Act of 1995 and release of information templates required by VHA.

<u>If appropriate, the following additional element(s) may be necessary</u>:

Tissue banking information, and request for storing of specimens and/or data on the PHI Authorization

Information regarding the conditions allowing the subject to request his/her PHI that is created or obtained during the course of the study.

An authorization template, utilizing the elements listed above, is located on the shared VA server.

<u>Disposition of Authorizations</u>

The signed authorization document should be attached to the consent document and distributed and handled in the same manner as the consent document, see section 9.2.

<u>Accounting of Disclosures</u>

An Accounting of Disclosure must be maintained on all research subjects' PHI disclosed **outside of VHA.**
An accounting of disclosure must be maintained for the following:

a. An accounting of disclosure must be maintained even if a signed authorization form is obtained from the research subject.
b. Anytime PHI is disclosed when a waiver of authorization is approved for the conducting of the study.
c. Disclosures required by law and for public health purposes.

An Accounting of Disclosure does not need to be maintained when the data used has been stripped of the 18 identifiers designated by HIPAA, i.e., de-identified data.

The templates (single disclosure form and multiple disclosure form) for the accounting of disclosures are located on the shared VA server. **The completed accounting form must be attached to the authorization form or to the waiver of authorization form, and placed in**

**the subjects' medical chart.** The accounting may be done at one time for multiple disclosures, i.e., at the end of the study.

HIPAA Transition Provisions
Under HIPAA guidelines, a covered entity such as the VHA may use and disclose PHI that was created or received for research, either before or after 4/14/03, if the covered entity obtained any one of the following prior to 4/14/03:

a. An authorization or other express legal permission from an individual to use or disclose PHI for research; or
b. The informed consent of the subject to participate in the research; or
c. A waiver of informed consent by an IRB in accordance with the Common Rule or an exception under FDA's human subject protection regulations at 21 CFR 50.24.

HIPAA allows covered entities to rely on such express legal permission, informed consent, or IRB-approved waiver of informed consent, which they created or received before 4/14/03, to use and disclose PHI for specific research studies, as well as for future unspecified research that may be included in such permission.

Business Associate Agreements will be completed in conjunction with MVAHCS Regional Counsel and the medical center contracting service, as needed.

Reporting of Disclosures or Violations of Information Security
Any and all unauthorized use, loss, or disclosure of individually identifiable patient information as defined by VHA Handbook 1200.05 will be reported to the Minneapolis VA Health Care System Privacy Officer. Violations of information security requirements will be reported to the appropriate Minneapolis VA Health Care System Security Officer.

## 8.7 Payment of Subjects

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

1. *There is no direct patient benefit.* When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this situation.
2. *Others being paid.* In multi-institutional studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.
3. *Comparable situations.* In other comparable situations, in which the opinion of the IRB, payment of patient volunteers is appropriate.
4. *Transportation expenses.* When transportation expenses are incurred by the subjects that would not be incurred in the normal course of receiving treatment and that are not reimbursed by any other mechanism.

Investigators who wish to pay research subjects must indicate the justification for the payment in their proposal. The payment must be fair and appropriate and not constitute (or appear to constitute) undue pressure on the subject to volunteer for the research study. Compensation should be pro-rated for subjects not completing the entire research protocol. The amount and terms of the compensation should be described in the consent form. The form of payment must be included in the consent form, i.e., cash, check, gift card or voucher, and when the payment will be received, i.e., two months after the study visit is completed.

### 8.8 Recruitment/Advertisement

Recruitment procedures will be designed to reach diverse populations, inform potential subjects of a research activity, and offer them an opportunity to contact the researcher. All recruiting materials will be approved by the IRB before use, usually under expedited review procedures. The following mandatory elements must be included:

[1] Investigator's name

[2] Purpose of research

[3] Criteria for eligibility

[4] Brief list of benefits, if any

[5] Time or other commitment required of subject

[6] Location of research

[7] Contact person and means of contact

Advertising that is intended to be seen or heard by prospective subjects is an acceptable recruitment practice and does not require a waiver of informed consent or authorization. All recruiting materials must be pre-approved by the IRB.

The advertisement may indicate whether subjects will be paid for their participation. However, dollar signs or the remuneration in large font cannot be the central focus of the advertisement.

The IRB will also review:
[1] The mode of communication for the advertisements.
[2] The final copy of printed advertisements.
[3] The final version of audio/video taped advertisements.

An advertisement may not:
[1] State or imply a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol.
[2] Include exculpatory language.
[3] Promise "free treatment" when the intent was only to say participants would not be charged for taking part in the investigation.

For FDA-regulated research, an advertisement may not:
[1] Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that were inconsistent with FDA labeling.

[2] Use terms, such as “new treatment,” “new medication” or “new drug” without explaining that the test article was investigational.
[3] Include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it had been approved for marketing.

The medical center director is responsible for ensuring that recruiting documents, flyers, and advertisements for non-VA research are not posted within or on the premises of a VA facility. General guidance may be posted within VA indicating that veterans may speak with their health care providers if they wish to participate in research and that information on clinical trials is available at: http://clinicaltrials.gov.

The Minneapolis VAHCS maintains a Research Kiosk in a public area of the facility for posting IRB-approved recruitment materials (posters and flyers). Medical Media prepares posters in compliance with Minneapolis VAHCS requirements for posting informational materials. Flyers may not be inserted into the panels of the kiosk, but may be placed in the slots below the poster section.

Recruitment material content cannot be altered once it is IRB-approved. If changes are necessary, the revised materials must be submitted for IRB review through the amendment process. For this reason it is recommended that researchers who intend to have brochures, flyers, posters, or other materials printed by MVAHCS Medical Media for posting in or distribution by MVAHCS submit their advertising/recruitment text/concepts to Medical Media *prior* to submitting for IRB review. Medical Media will ensure the required elements for VA-printed documents (e.g., VA logo, permissioned graphics) are in place and may offer additional suggestions for improving the readability of the document, however these suggestions are not binding.

**Recruitment materials cannot be posted for studies not approved by the Minneapolis VAHCS IRB.**

### 8.9 Compensation for Identifying Subjects

The Minneapolis VAHCS prohibits payments to professionals in exchange for referrals of potential participants (“finder’s fees”) and/or payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”).

### 8.10 Gene Transfer Research

Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the National Institutes of Health (NIH) Office of Biotechnology Activities.

- FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.
- DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) approval has been obtained, local IRB

approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).

- While the RAC is advisory to the Director of the NIH, compliance with its guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

### 8.11 Genetic Research

Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks warrant careful IRB review and discussion.

Detailed guidance for investigators and IRB members is contained in Appendix 4. In brief, IRB review of genetic research will address, at a minimum, these specific issues:

- Possible psychological and social risks to subjects and family members;
- Protection of subjects from disclosure of their medical or other personal information to family members;
- Protection of the confidentiality of the personal information of family members ("secondary subjects") and the limits of those protections;
- Provisions for re-contact of subjects or family members;
- Any planned future use of data or samples;
- Counseling to subjects before or after the study;
- Confidentiality measures and extent of possible disclosure to third parties.

## 9. INFORMED CONSENT OF HUMAN SUBJECTS OF RESEARCH

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them; the informed consent process is the instrument to provide this opportunity. The IRB will ascertain that the investigators of a research protocol will obtain from human subjects, or their legally authorized representatives, a legally valid informed consent. The only persons eligible to conduct the consent process are the investigator(s) and other persons who have human research protection training and good clinical practice training, and credential verification documented with the Research Office. They must also have a thorough knowledge of all aspects of the protocol.

Informed consent shall be obtained prior to entering the subject into the study and the conduct of any procedures required by the protocol, unless consent is waived by the IRB. The IRB has the authority to observe the consent process. In obtaining informed consent, the investigators shall:

[1] Give the subject (or representative) sufficient information about the study and how the study may affect the subject, so the nature and anticipated consequences of the study are sufficiently clear;

[2] Deliver the information in a comprehensible manner, using a language readily understandable by the subject;

[3] Assure voluntariness of the participation, by providing sufficient opportunity to consider whether or not to participate, and minimizing the possibility of coercion, undue influence, or harassment.

The process of obtaining informed consent has two 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, and obtaining the consent to participate in the research as a subject, and

[2] Documentation that informed consent has been obtained. The basic rule of human subject research is that both components of the informed consent process shall be completed. However, in accordance with Federal guidelines, under certain circumstances, the IRB has the authority to waive the requirement for obtaining informed consent, or for documenting that informed consent has been obtained.

## 9.1 Elements of Informed Consent

VA Form 10-1086 will be used to document informed consent. The content shall be easily understandable by a layperson with modest education, and if the subject or their authorized representative does not speak English, a validated and approved translation of the consent form must be used.

The consent form must be approved by the IRB and signed by the subject or the subject's legally authorized representative, except in cases where the documentation of informed consent is waived by the IRB. The consent form template prepared by the IRB (available on the IRB SharePoint under FORMS and on the shared VA server) must be used or the consent will not be reviewed. The consent form content includes the appropriate basic and additional elements as set forth in VA and other Federal regulations, and applicable state law. The basic elements of informed consent are as follows:

[1] Title of the study

[2] Name of the Principal Investigator (PI)

[3] Statement that the study involves research

[4] Explanation of the purposes of the research and the expected duration of the subject's participation

[5] Description of the procedures to be followed and identification of those being done for research purposes

[6] Identification of any experimental procedures

[7] Description of any reasonably foreseeable risks or discomforts to the subject including for example, privacy risks (legal, employment and social)

[8] Description of any benefits to subject or others, which may reasonably be expected from the research

[9] Disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject

[10] Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. If appropriate, a statement that Federal agencies such as the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP) and the Government Accounting Office (GAO) may have access to the records. If an FDA-regulated test article is involved, the FDA requires a statement that the FDA may choose to inspect research records that include the subjects' individual medical records.

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

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

(b) The regulation at 38 CFR 17.85 does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances must be included in the consent form. **NOTE**: VHA Handbook 1200.05, strongly suggests the investigator make provisions for coverage of such cost in research awards and contracts.

[12] Explanation of whom to contact for answers to pertinent questions about research and research subject's rights, and whom to contact in the event of a research-related injury to the subject. At least one contact's name and phone number must be other than the investigators or study personnel.

[13] Statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; (In obtaining informed consent, the investigator or person obtaining informed consent may not

request from the subject any exculpatory statements to suggest that any legal rights are being waived, or the investigator, sponsor, or the Minneapolis VA Health Care System is being released from liability for negligence.)

[14] Statement that a veteran-subject will not be required to pay for treatment received as a subject in a VA research protocol except as follows:

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

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

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

Statement of additional information for employees as research subjects.

**Additional Elements of Informed Consent**. Depending on the nature of the research, additional types of information must be given to the subject as a part of the informed consent process, when appropriate (See also Appendix 1):

[15] If applicable, the financial or other arrangements with a sponsor or institution that may pose a conflict of interest.

[16] Payment to subject, including amount and schedule for prorating the payment;

[17] 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;

[18] Anticipated circumstances under which the subject's participation may be terminated by the investigator, without regard to the subject's consent;

[19] Additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment and with the provisions of 38 CFR 102 described above.

[20] The consequences of a subject's decision to withdraw from the research, and procedures for orderly termination of participation by the subject.

[21] Statement that any 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.

[22] Approximate number of subjects involved in the study.

[23] If human biologic specimens obtained could be part of or lead to the development of a commercially valuable product or if the specimens will be retained after the end of the study, current VA policy and Veterans Health Administration (VHA) regulations must be followed. If genetic testing is to be done, VA requirements pertaining to genetic testing must also be met. **[See Appendix 2- VA Policy on Storage and Reuse of Specimens]**

**The following types of studies require additional elements of informed consent:**

Any study that involves currently unforeseeable risks to the subject (or to an embryo or fetus, if the subject is or may become pregnant) should include information about these risks in the informed consent document stating these risks. This is especially true with studies conducted under an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE).

Any study in which the protocol outlines circumstances under which the subject's participation may be terminated by the investigator, without regard to the subject's consent, requires a statement identifying these anticipated circumstances under which the investigator may terminate the subject's participation. An unexplained statement that the investigator and/or the sponsor may withdraw subjects at any time does not adequately inform the subject of anticipated circumstances of withdrawal.

If subjects may incur additional costs because they are participating in research, the costs should be explained. Some insurance and/or other reimbursement mechanisms may not fund care that is delivered in a research context.

When withdrawal from a research study may have deleterious effects on the subject's health or welfare, the informed consent must explain any withdrawal procedures necessary for the subject's safety and state why they are important to the subject's welfare.

Any study in which the subject's participation is expected to continue over a period of time during which new findings may become available requires a statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subjects.

If the IRB determines that the number of subjects in a study is material to the subject's decision to participate, the informed consent document must state the approximate number subjects involved in the study. This is particularly true in studies involving small numbers of subjects, as in Phase 1 and 2 studies.

When following FDA regulations:
With regard to data retention when subjects withdraw from a clinical trial, policies and procedures have the IRBs:

- When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- A researcher may ask a participant who is withdrawing whether the subject 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 subject distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
- The researcher must obtain the subject's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
- If a subject 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 subject's medical record or other
- confidential records requiring the subject's consent. However, a researcher may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

**Research Involving Collection of Data From Voice, Video, or Photographs Made for Research Purposes**

Informed consent for research must be obtained from each research subject before taking photographs or making voice or video recordings that will be used for research purposes.

1. Unless IRB grants a waiver of documentation of informed consent for research, the informed consent form for research (i.e., VA Form 10-1086) must include a discussion of why photographs, or voice or video recordings are being taken for the research, who will have access to them, and what their disposition will be after the research is completed
2. VA Form 10-3203, Consent for Use of Picture and/or Voice documents permission for pictures, video, and voice recordings to be made or taken. In the conduct of research, VA Form 10-3203 must be used in accordance with applicable VA and VHA policy.
3. When the research subject is a patient (either an inpatient or outpatient), the subject must sign VA Form 10-3203 to permit photographs or video and voice recordings that will be used for research purposes even if the IRB has waived the requirement for documentation of informed consent for research. Photography or recordings cannot occur prior to the patient's granting such permission.
4. When the research subject is a patient, the subject's signed and dated VA Form 10-3203 must be placed into the medical record along with, if applicable, the signed and dated research informed consent form. The signed VA Form 10-3203 must be obtained and placed in the subject's medical record, even if the IRB has waived documentation of informed consent for research.
5. VA Form 10-5345, Request for and Authorization to Release Medical Records or Health Information: VA Form 10-5345 documents permission for the disclosure of medical records or health information, including pictures, video, and voice recordings to another

individual. In the conduct of research, VA Form 10-5345 must be used in accordance with applicable VA and VHA policy.

Research Subject's Rights Section of the Consent
In most instances, in addition to the information given to the subject or the subject's legally authorized representative, the written document shall contain a section to document that informed consent has been obtained. In rare instances, the documentation section may be deleted from the written informational document, if the IRB has waived that requirement.

(See sections 9.4 and 9.5 in this document for information regarding the HIPAA waiver of authorization and authorization.)

Appendix 1 contains examples of suggested special language that to be included in the informed consent document:
For certain Risks and/or Discomforts if:

a) Blood draws are used
b) The study medication may affect an embryo, fetus or nursing infant
c) Radiation is used in the research

2. If tissue is used to develop something that has potential for profit
3. If biological tissues or specimens will be stored for future research
4. If MRI scans will be used

## 9.2 Documentation of Informed Consent Process

The IRB requires that the information necessary to give informed consent by the person being recruited as a research subject is given to that person or the person's legally authorized representative in writing.

Informed consent must be obtained prior to entering a subject into a study or the conduct of any procedures required by the protocol including taking photographs or making voice or video recordings that will be used for research purposes, unless consent is waived by the IRB. VA Form 10-1086 (either paper or electronic version), must be used as the consent form and must embody the elements required in VHA Handbook 1200.05 and 38 CFR 16.116. In addition, it must contain any additional elements as required by the IRB. A valid consent form has been reviewed and approved by the IRB and contains the approval date, expiration date and signature of the IRB Chairperson or designee. This form may be read to the subject or the subject's legal representative. The investigator must ensure that the subject (or representative) is given an adequate opportunity to read the form and ask questions before signing it. Informed consent shall be documented by the IRB-approved form and signed by:

[1] Subject or the subject's legally authorized representative

[2] Witness to the subject's legally authorized signature, if the IRB determines a witness is required such as in studies involving invasive intervention or an investigational drug or device). A witness is always required when a short form consent is employed.

a) The witness is required to witness only the subject's or subject's legally authorized representative's signature, not the informed consent process, unless the sponsor or IRB requires the witness to witness the informed consent process.

b) The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member. EXCEPTION: **If the protocol is a VA Cooperative Study the witness may NOT be associated with the research**.

c) If the sponsor or IRB requires a witness to the consenting process, **in addition to witnessing to the participant's signature, and if the same person needs to serve both capacities**, a note to that effect will be placed under the witness's signature line.

[3] Person obtaining the consent.

[4] Some study sponsors may also require the signature of the Principal Investigator.

Incompetent subjects

In the case of incompetent subjects, the legal representative for the subject; the witness; the investigator; and the person obtaining the consent, if other than the investigator should sign the surrogate consent.

Child's assent

In the case of children being recruited as subjects of research, an assenting document will be prepared at the reading level of the minor subjects. Several versions of the child's assent may be necessary, e.g. one for subjects 8-13 years of age and one for 14-18 year olds. An assenting signature of the subject of an age sufficient to comprehend the nature, risks and benefits of the study, should be obtained on the written consent documents, in addition to the signature of the legally authorized representative, witness, investigator, and person obtaining consent, if other than the investigator.

Disposition of consents

[1] The original, signed consent document(s) should be filed in the subject's case history kept by the investigator;

[2] Copy sent to the Research Office (consent forms will be reviewed for accuracy by research office staff) to be scanned into the subject's VA Health Care System electronic medical record, if required by VA policy;

[3] Copy of the consent given to the subject or subject's legal guardian; and

[4] Copy sent to the Investigational Pharmacist (if study drugs need to be administered within a short period of time after consenting).

Progress Note

If informed consent is not waived by the IRB, a progress note documenting the informed consent process must be placed in the subject's medical record.

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

(a) The name of the study,

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

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

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

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

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

Electronic Posting of Research Participation in the Subject's Medical Record.

Electronic flag posting and progress note entries are required in the subject's medical record for most human research protocols to protect the subject's safety, communicate study participation with health care providers, and to provide a source of more information on the study. The IRB will determine whether this is required for each approved research protocol.

The electronic flag posting is accomplished by the PI or his/her designee by completing the "Research Participant" template in the Computerized Patient Record System (CPRS), which will create a CWAD (Crisis Notes, Warning Notes, Allergies and Directives) or clinical "flag", for each subject. After the subject has completed the protocol or the protocol has ended, an addendum will be added to the posting to communicate this information to health care providers.

A Research Progress Note should be completed for the initial visit/consent process and all subsequent protocol events. The IRB will specifically notify the PI at the time of initial approval if the requirement for electronic posting and progress note entry has been waived for a particular protocol.

A CPRS record should be created for all research subjects (both veteran and non-veteran) if any of these situations apply. (For additional information, see VHA Handbook 1200.05 and VHA Handbook 1907.01):

(1) Research subject is admitted as an inpatient as part of the research.

(2) Research subject is treated as an outpatient as part of the research.

(3) When research procedures or interventions are used in medical care of a research subject

(4) If any clinical resources such as radiology, cardiology, clinical laboratory, or pharmacy are used as part of the research

(5) If intervention may lead to physical or psychological adverse events

The research subject's health record must contain:

(1) A copy of signed VA form 10-1086

(2) A copy of signed HIPAA authorization form

(3) Enrollment progress note and other applicable progress notes

(4) Information on possible drug interactions and/or toxicity of pharmaceutical agents that are being administered to research subjects because of research

(5) Form 10-9012

(6) A copy of any research results used for medical care

(7) Information on all research and experimental interventions including potential risks, indications and applicable progress notes

Except as indicated above, research records should not be stored in the patient's health record: specifically, IRB and R&D Committee records, records of all research observations, other data pertinent to the investigator, progress notes, research study forms, surveys, questionnaires, or other study documents.

### 9.3 Consent "Short Form"

Federal regulations also recognize a "short form," a shortened written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there will be a witness to the oral presentation. Both oral presentation and written short form must be in a language understandable by the subject or the subject's representative. **This consenting procedure is rarely recommended and approved by the MVAHCS IRB.** The following is a summary of the method:

[1] The IRB shall approve a written summary of what is to be said to the subject or the subject's legally-authorized representative and the "short form" consent document.
[2] The short form is to be signed by the subject or the subject's legally authorized representative.
[3] There will be a witness present for the entire consent procedure who will sign both the short form and the summary of the oral presentation. For participants who do not speak English, the witness will be conversant in both English and the language of the participant.
[4] The person obtaining the consent shall sign the summary. The original short form and summary shall be filed in the investigator's documentation.
[5] A copy of the signed summary of the information and of the signed short form documenting the consent must be given to the subject or the subject's representative.

### 9.4 Waiver of Requirement for Written Informed Consent

**If an FDA-regulated test article is being used, IRB waiver of informed consent or documentation of informed consent is not allowed.**

Waived documentation of informed consent
The IRB may waive the requirement for documentation of the informed consent (a signed informed consent document), even though informed consent of the subject may be required, if it finds either:

[1] The principal research risk is potential harm resulting from a breach of confidentiality, and the only record linking the subject and the research is the consent document. Each subject will be asked if the subject wants documentation linking the subject to the research and the subject's wishes will govern;

***OR***

[2] The research presents no more than minimal risk of harm to subjects, and does not include any procedure for which written consent would be required outside of the research context (45 CFR 46.117(c)(2)). 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.

In cases where the IRB waives the requirement for documentation of informed consent, the IRB will require the investigator to provide the subjects with a written statement regarding the nature and scope of research, the text of which shall be reviewed and approved by the IRB. The IRB will document its justification for granting a waiver of requirement of informed consent.

The IRB may waive the requirement for the investigator to maintain a master list for a study if both of the following conditions are met:

(a) There is a waiver of documentation of informed consent, and
(b) The IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.

If the IRB waives the requirement to maintain such a master list, the IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.

### 9.5 Waived or Altered Informed Consent

**VHA policy does not allow waivers for planned emergency research. In addition, consent may not be waived for FDA-regulated research, except as provided in 21 CFR 50 §50.23 and 50.24.**

In other settings, the IRB may approve a consent procedure that alters some of the elements of informed consent, or waives the requirements to obtain informed consent, if the regulatory requirements for waiver are met.

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

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

***OR***

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

(a) The research or demonstration protocol is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

1. Public benefit or service programs;
2. Procedures for obtaining benefits or services under those programs;
3. Possible changes in or alternatives to those programs or procedures; or
4. Possible changes in methods or levels of payment for benefits or services under those programs.

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

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

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

***OR***

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

[a] The research involves no more than minimal risk to the subjects;

[b] The research cannot practicably be carried out without the waiver or alteration of consent;

[c] The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

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

[f] The informed consent requirements stated are not intended to pre-empt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

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

- That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- That research presents no more than minimal risk of harm to subjects and involves no procedures for which a written consent is normally required outside of the research context. In cases which the documentation requirement is waived, the IRB may

require the investigator to provide subjects with a written statement regarding the research.

The IRB will document its findings justifying waivers or alterations of consent.

**9.6 Surrogate Consent**

The use of a surrogate consent procedure may be necessary when the prospective research participant is incompetent or has an impaired decision-making capacity. Surrogate consent procedures are designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity (e.g., a study of treatment options for comatose persons can only be done with incompetent subjects).

Consent from the legally authorized representative (LAR) may be obtained not only from a health care agent appointed by the patient in a Durable Power of Attorney for Health Care (DPAHC) or similar document, court-appointed guardian of the person* but also from next-of-kin in the following order of priority:

[1] Spouse

[2] Adult child (18 years or older)

[3] Parent

[4] Adult sibling (18 years or older)

[5] Grandparent

[6] Adult grandchild (18 years of age or older)

* A court-appointed guardian may only give consent as a surrogate if the court grants permission. (*Minn. Stat. §524.5-313(c)(4)*)

**NOTE:** The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes.

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

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

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

(c) Disclosures required by VHA Handbook 1200.05 to be made to the subject by the investigator must be made to the subject's surrogate.

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

Investigators must:

[1] Provide the IRB with a description of the procedures to ensure that subjects' LARs are well informed regarding their roles and obligations to protect persons who lack decision-making capacity.

[2] Provide information (i.e., informed consent process and HIPAA authorization) to the subjects' LARs that would ordinarily be required to be made to the subjects themselves if they had decision-making capacity.

(See also Section 7.2a) Templates for Surrogate Consent and Assent are located on the IRB SharePoint site and the shared VA server.

### 9.7 Observation of Informed Consent Process

Per 45 CFR 46(s), the IRB has the authority to observe or have a third party observe the consent process and, when necessary, the IRB may require such observation as part of the consent process. The observation may be done by an IRB member, IRB staff, the RCO, or other individuals as delegated by the IRB.

IRB observation of consent may be required in situations in which the competence of the subject to provide informed consent in questionable, e.g., research subjects with diminished capacity. Other situations where observation of informed consent may be requested include:

- Concerns raised during the initial review due to the sensitive nature of the study (e.g., if the investigator described safeguards to assure the protection of research subjects, verification that safeguards are in place)
- High risk projects (e.g. Phase I trials)
- Clinical investigations where the investigator is also the sponsor
- Previous noncompliance
- If there have been complaints
- Other situations as the IRB sees fit

<u>Procedures for Observation of the Consenting Process</u>
When the IRB determines that a protocol can be approved, but needs observation of the consenting process, its rationale for that decision is described in the minutes of the convened meeting (e.g. risk of study). The IRB will also decide the number of observations to be done, ranging from observing the first or a specified number of participants, to including the entire sample, based on their judgment of risk. The RCO or IRB Administrator or their designee will conduct the observation.

The IRB Administrator or the IRB staff will contact the study coordinator and the study Principal Investigator (PI) about the need for observing consenting of study participants. They will work out mutually agreeable dates and times for the observer to observe consenting.

Just prior to observing consenting, the observer will: 1) introduce himself/herself to the potential study subject, 2) explain the reason for the observer's presence, and 3) obtain the participant's verbal permission for observing consent.

The observer will document his/her observations on the Consent Observation Checklist. During consenting, should any issues or questions arise that the consenter is unable to address and that the observer is qualified to discuss or answer, the observer may offer appropriate explanations or information.

After consenting has been completed, the observer may meet with the person who administered consent to discuss the findings about the consenting that has just taken place. Often, the consenter does not have an opportunity to sit down with the observer immediately after a participant has been consented, because the staff member must stay with the participant to initiate study screening.

In all cases, the observer will prepare a written report, which is conveyed to the consenter. If either the observer or the consenter wishes to discuss the findings face-to-face, they will arrange an informal meeting. Occasionally, the observer may schedule a second consent observation with the study staff member, to determine if some observed "deficiencies" have been corrected.

Because the informed consent observations are done for both educational and monitoring purposes, the written reports are first shared with the consenter who is being evaluated. Then, with that person's response in mind (and possible corrective actions planned), the observer would share his/her findings with the RCO, the IRB Chair, and the IRB Administrator. If repeated serious deficiencies be noted by the observer, the policies on non-compliance would be followed.

## 10. INVESTIGATIONAL MEDICAL DEVICES

Additional information regarding IRB approval with regard to abbreviated IDE and IDE exemptions may be found in Section 8.3, under the heading, Protocols Involving Investigational or Unlicensed Test Articles .

### 10.1 Procedures for Determining whether a Device is Significant Risk (SR) or Non-Significant Risk (NSR)

A medical device is defined, in part, as any health care product that does not achieve its primary intended purpose by chemical action or by being metabolized. An investigational medical device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21CFR part 812]. Certain clinical investigations of medical devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations. Unless exempt

from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or “non-significant risk” (NSR).

**The judgment whether a device study poses a Significant Risk or Non-Significant Risk will be based solely upon the seriousness of the harm that may result from the use of the device, and not the device alone (even if the sponsor considers the device to be NSR), and the rationale for the IRB’s determination will be documented in the IRB minutes**. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered Significant Risk. Also, if the subject must undergo a procedure as part of the investigational study (e.g., a surgical procedure) the IRB will consider the potential harm that could be caused by the procedure in additional to the potential harm caused by the device. To determine whether a device study is significant risk or non-significant risk, the IRB will:

[1] Review the risk assessments and rationale used by the sponsor and/or the investigator (including any FDA IDE Approval Letter), description of the device, reports of prior investigations, subject selection criteria, monitoring procedures, and nature of the harm that might result from use of the device. Risk determination is based on proposed use of a device and not on the device alone.

[2] Review examples of Significant Risk Devices and Non-Significant Risk Devices in the FDA Information Sheet 1998, web site www.FDA.gov;

[3] Discuss questions and concerns about whether a device is deemed “significant risk” or “non-significant risk” with the FDA at (301) 594-1190;

[4] Request additional information, if needed, to help determine risk

[5] If necessary, verify an IDE exists by requesting a copy of the sponsor’s letter from the FDA

[6] SR device studies must be conducted in accordance with the full IDE requirements (21 CFR Part 812). Pursuant to these regulations, an investigation may begin 30 days after FDA receives the application (unless FDA provides notification that the investigation may not begin), or after the FDA approves, by order, an IDE for the investigation (21 CFR 812.30). In addition, the investigator must have approvals from the IRB and R&D Committee. The FDA considers all SR studies to be greater than minimal risk. *NOTE: The IRB needs to verify the existence of the IDE when applicable*.

[7] NSR device studies do not require submission of an IDE application, but must be conducted in accordance with the “abbreviated requirements” of the IDE regulations (21 CFR 812.2(b)). Unless otherwise notified by the FDA, a NSR study is considered to have an approved IDE if all abbreviated requirements are fulfilled. *NOTE: NSR devices may represent greater than minimal risk depending upon the research study.*

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

[9] The Principal Investigator conducting the research is responsible for compliance with all applicable FDA regulations.

[10] Emergency use of unapproved devices must follow FDA guidance.

If the IRB disagrees with the sponsor or Principal Investigator regarding risk designation, written notification will be provided. The sponsor or investigator may provide additional information or attend an IRB meeting to discuss concerns pertaining to the protocol.

If the IRB decides the study is Significant Risk, the sponsor and investigator will be notified in writing and the initial review by under full IRB procedures will not proceed until the IDE is obtained by the sponsor.

### 10.2 Storage, Security, Inventory and Dispensing of Investigational Devices

The Principal Investigator will be responsible for receipt, storage, inventory, and dispensing of investigational medical devices.

Receipt

Investigational devices will be delivered to the Principal Investigator or designated study coordinator for receipt, storage and distribution.

Storage and Inventory

All investigational devices will be stored separately from like devices. The storage area will be locked.

An inventory of the investigational devices will be maintained:

[1] Name of device
[2] Manufacturer of device
[3] Date of receipt of the device
[4] Expiration date of the device
[5] Serial number and lot of the device
[6] Subject identifier
[7] Date device was used
[8] Name of Principal Investigator (PI)
[9] Protocol number
[10] Date and reason for return of unused devices

Defective or unused, but opened, devices will be returned to the sponsor and recorded on the inventory.

A copy of the inventory will be requested at each continuing review of the protocol.

Dispensing
Access to the device will be limited to authorized study personnel who will dispense the device as described in the protocol.

**10.3 Humanitarian Use Devices (HUD)**
As defined in 21 CFR 814.3(n), a HUD is a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year."

The FDA may grant marketing approval for certain devices that may benefit persons who have rare diseases. The use of a HUD does not in itself constitute research, although IRB approval is required.

IRB Review of HUDs
The IRB is responsible for both initial and continuing reviews of the use of HUDs. Full board review is required for initial approval. The IRB may grant approval for a protocol or on a case by case basis, but should be cognizant that the device should not exceed the scope of the FDA approved indication. The IRB does not need to review individual uses of a HUD, but must conduct a continuing review. For a continuing review, the IRB may utilize an expedited review process unless it determines that a full review is appropriate.

Waiver of Consent (HUDs)
The FDA does not require the administration of informed consent. The IRB may still require informed consent if it determines that this is appropriate.

Off-Label Use of HUDs
a) Emergency Use. A HUD may be used to save the life, or to protect the physical well-being of a patient. However, the following conditions apply:

- Prior approval of the IRB Chair should be obtained if at all possible.
- Informed consent should be obtained.
- A separate determination should be obtained from an uninvolved physician.
- After emergency use, a follow-up report on the patient's condition and information concerning patient protection measures must be submitted to the HDE holder.

b) Compassionate Use. A HUD may be used for compassionate use. However, the same conditions apply as are outlined for emergency use. In addition, the following also apply:

- Prior approval from the FDA must be obtained.
- The follow-up report must also include a discussion of why alternative therapies are unsatisfactory.

The treating physician must also devise an appropriate schedule for monitoring the patient, taking into consideration the limited information that is available regarding the potential risks and benefits of the device and the specific needs of the patient.

The healthcare provider is responsible for obtaining IRB approval before he or she uses a HUD to treat or diagnose patients. In accordance with Section 520(m)(4) of the act and section 21 CFR 814.124(a), IRB approval is required before a HUD is used in a facility, except in emergencies where the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient.

The IRB is responsible for initial as well as continuing review of the HUD. For initial review of a HUD, the IRB is required to perform a full board review. For continuing review, however, the IRB may use the expedited review procedures (21 CFR 56.110) unless the IRB determines that full board review should be performed.

The IRB is not required to review and approve individual uses of a HUD, although it may do so. The IRB may use its discretion to determine how to approve use of the HUD. The IRB may approve use of the HUD, for instance, without any further restrictions, under a protocol, or on a case-by-case basis. In reviewing the use of a HUD, the IRB should be cognizant that the FDA recommends that the use of the device not exceed the scope of the indication approved in the Humanitarian Device Exemption (HDE).

Neither the act nor the regulations require informed consent for use of a HUD. Because a Humanitarian Device Exemption (HDE) provides for marketing approval, use of the HUD does not constitute research or an investigation, which would normally require informed consent.

Although informed consent is not required, there is nothing in the statute or regulation that preempts a state or institution from requiring prospective informed consent.

Most HDE holders, however, develop patient labeling that incorporates information to assist a patient in making an informed decision about the use of the HUD. That is, the patient labeling generally contains a discussion of the potential risks and benefits of the HUD and any procedures associated with its use. Patient labeling also should state that the device is a humanitarian use device and effectiveness for the labeled indication has not been demonstrated.

## 11. IRB MONITORING OF HUMAN SUBJECT RESEARCH IN PROGRESS- CONTINUING REVIEW PROCESS

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

Regular monitoring of all previously approved protocols will be in the form of continuing reviews, scheduled at the time of the most recent IRB approval of the protocol. The frequency of the scheduled continuing reviews will be appropriate to the degree of risk, but not less than once per year. In addition, the IRB will ensure that the investigators of active research protocols carry out the following, as needed, as a condition of approval of their protocol:

[1] Report to the IRB any planned change in the study, and do not implement any change without receiving prior approval, except to eliminate immediate hazard;

[2] Report to the IRB any deviations or non-compliance from the approved protocol or other regulations and policies;

[3] Report to the IRB any adverse events or unanticipated problems involving risks to subjects or others (serious adverse events from investigators and Med Watch reports, etc. from sponsors); and

[4] Submit to the IRB updated Investigator Brochures, if applicable and have not previously been submitted for review;

[5] Report to the IRB any new information on the protocol that changes and/or adversely influences the risk/benefit ratio, and whether risks have been minimized.

[6] Report to the IRB the current status of data security and privacy using the Minneapolis VAHCS PHI and Sensitive Information Use Statement.

[7] A qualified clinician is designated to be responsible for all study-related healthcare decisions

The investigators will be informed and reminded of these conditions of approval in letters of notification of initial and continuing approval of the protocol.

If the risk/benefit ratio of the study changes, the IRB may require changes to the protocol or consent form or change the interval for continuing review or suspend/ terminate the study.

### 11.1 Regular, Scheduled Continuing Review

The IRB will conduct substantive and meaningful continuing review based on regulatory criteria of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB reserves the right to change the approval period at any time for any reason. At the time of initial review or the most recent scheduled continuing review, the IRB will establish the interval until the next continuing review ("Expiration Date" of IRB approval), by taking into consideration the presumed degree of research risks; the higher the risk, the sooner will the continuing review be scheduled. The IRB approval period for research may not extend more than 365 days from the time that the convened IRB voted on approval, or approval pending minor stipulations, or the date of approval resulting from the expedited review process, if expedited review was performed.

Investigators are notified in writing of the approval date and the expiration date at the time of final initial IRB and R&D approval. The IRB continuing review date is set approximately 1-2 months prior to the expiration of IRB approval.

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

The Principal Investigator of an active research protocol shall be responsible for submitting to the IRB office an application for continued review and approval of the protocol, well in advance of the expiration date of the current period of approval. Investigators will receive a reminder notice and continuing review paperwork two to four months in advance of the date of expiration of the approval period.

To apply for continuing review and approval, the Principal Investigator shall complete the protocol renewal application form, "Continuing Review of Approved Human Studies Protocol" and the “Minneapolis VAHCS PHI and Sensitive Information Use Statement”.

The information to be provided by the investigator in the application form shall include the following:

[1] Project status

[2] Summary of disposition of the original and copies of the consent and authorization forms, if applicable

[3] Number of subjects enrolled since last approval, the total number of subjects enrolled to date and the total number of subjects approved for the study

[4] Gender and ethnicity of research subjects (unless exempt from this element, i.e., the investigator is conducting a retrospective chart review and is not recording gender and ethnicity). The investigator will also provide the number of research subjects enrolled in each gender and ethnicity category.

[5] Number of subjects considered as members of specific vulnerable populations;

[6] Provide an accounting of research subjects of those who were randomized, withdrew from the study and experienced a Serious Adverse Event. Names and social security numbers of research subjects should not be included in the materials supplied to the IRB for continuing review.

[7] Status Report, including:

[7a] The investigator's current risk-potential benefit assessment based on study results.
[7b] Number of participants considered as members of specific vulnerable populations.
[7c] Any adverse events or unanticipated problems involving risks to subjects or others, if any, and an assurance that all serious or unexpected adverse events had been reported as required.
[7d] Any withdrawal of subjects from the research
[7e] Complaints about the research
[7f] Protocol violations and/or deviations

[8] Description of proposed changes to the protocol

[9] Summary of any recent literature and/or findings obtained thus far

[10] Summary of any amendments or modifications to the research since last review

[10a] Research protocols that the IRB judges the requirement for verification from sources other than the investigators, that no material changes have occurred since previous IRB review, is necessary, include, but are not limited to: randomly selected protocols; complex protocols involving unusual levels or types of risk to subjects; protocols conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determination of the IRB; and protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.

[11] Summary of any reports on multi-center trials and any other relevant information, especially information about risks associated with the research

[12] A clean (not stamped) copy of the current IRB-approved informed consent and HIPAA Authorization documents; if revisions are needed in the text of these documents, the investigator will provide a copy highlighting the changes, and a clean copy for IRB stamping (submitted only if the study is still recruiting subjects).

[13] Copy of the current protocol.

[14] An updated Minneapolis VAHCS PHI and Sensitive Information Use Statement.

[15] Copy of investigator's log of investigational medical devices, if applicable.

The review process for application for continuing approval of a research protocol will be similar to that for initial approval of a new research protocol. Primary reviewer procedures will be followed for the review. The Primary Reviewer will review the entire record of the study since the last review. All IRB members will be provided and will review:

[1] An abstract with all relevant information
[2] Current consent and HIPAA Authorization documents (if study is still recruiting subjects)
[3] Continuing Review Application
[4] Status Report
[5] Copy of investigator's log of investigational medical devices, if applicable.
[6] Conflict of Interest forms for all investigators and collaborators

As a result of the continuing review, the IRB will decide by voting to re-approve with or without requirements for modifications, suspend, or terminate the research and the date of the next continuing review. The IRB's decision will be reported in writing to the designated authorities within the MVAHCS and to the investigator. Once IRB approval at continuing review is achieved, the study is considered approved to continue.

### 11.2 Lapse of Approval, Administrative Holds, Protocol Suspension and Protocol Termination

Lapse of Approval

The Federal regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol, continuing review must occur no later than one year after the date the protocol was reviewed. These conditions must be approved before the anniversary date. If the IRB **has not reviewed and approved** a research study by the continuing review date the IRB has specified, the research must stop. Enrollment of new subjects cannot occur after the expiration of IRB approval. A lapse of approval does not need to be reported to federal agencies as a suspension of IRB approval.

**Once notified of the lapse of approval, the Principal Investigator (PI) conducting the research must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm. Already enrolled subjects may only continue research activities** if **the IRB or IRB Chair, in consultation with the Chief of Staff**

**(with copies of all correspondence sent to the ACOS/Research), finds an over-riding safety concern or ethical issue involved such that it is in the best interest of individual subjects to continue participation. (OHRP Guidance on Continuing Review, 7/11/02; FDA 1998 Information Sheets Update).**

**Suspension:** A directive of a convened IRB or IRB designee either to temporarily or permanently stop some or all previously approved research activities, short of stopping permanently all previously approved research activities.

**Termination:** A directive of the convened IRB or IRB designee to stop permanently all activities in a previously approved research protocol.

Regulations require that the IRB have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants or others.

Examples of the circumstances that would result in suspension or termination of IRB approval, include:

- Conduct of the research that is not in accordance with the IRB's requirements
- Research that has been associated with unexpected serious harm to participants

Suspension and termination do not include:

- Interruptions in research resulting solely from the expiration of a project approval period.
- "Administrative holds" or other actions initiated voluntarily by an appropriate facility official, research investigator, or sponsor for reasons other than concerns regarding the safety, rights or welfare of human research participants, research investigators, research staff, or others.

***Note***: An administrative hold cannot be used to avoid reporting deficiencies or circumstances that otherwise require reporting to federal agencies.

If the investigator does not fulfill the continuing review requirements, the IRB, IRB Chair or their designee may terminate or suspend a previously approved protocol. All terminations or suspensions should be promptly reported to and reviewed by the IRB. When a protocol is terminated by the IRB, the subjects rights and welfare and procedures for safe participant withdrawal will be considered by anyone suspending or terminating a research protocol, including:

- Transfer of participants to another investigator
- Arrangements for clinical care outside of the research protocol
- Continuation of some research activities under the supervision of a monitor
- Requiring follow-up of participants to determine long-term safety
- Reporting adverse events or outcomes that resulted from the suspension or termination to the IRB

This is especially important in research involving subjects with an implantable device, research involving investigational drugs providing a potential benefit.

The IRB Chair or their designee shall:

- Notify the Investigator in writing of it the IRB decision to suspend or terminate its approval along with a statement of the reasons for the IRB action and any terms and conditions of any suspension.
- Report the decision to suspend or terminate to the RCO, the Medical Center Director, the Chief of Staff, the VA Office of Research Oversight and all federal agencies, as applicable. (See Section 13.8 for reporting requirements and procedures)
- Determine the methods to be used to inform current research participants of the termination or suspension.
- Determine if any adverse events or outcomes will be reported to the IRB after the suspension or termination of the research

The Investigator shall be provided with an opportunity to respond in person or in writing to the IRB on a suspension or termination.

If the IRB action in relation to the suspension or termination involves the withdrawal or modification of participation of current participants from the research, the IRB shall direct the Investigator to contact the participants to:

- Make such notification with an explanation, after its review and approval by the IRB
- Describe any monitoring and follow-up for safety reasons that will be conducted
- Provide contact information for the investigator and the IRB where the participant may report any adverse events or unanticipated problems.

- If the study is FDA-regulated, the COS and IRB Chair must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.

- The Principal Investigator has the responsibility to inform the sponsoring agency of a lapse of approval.

### 11.3 Amendments/Revisions Prior to Scheduled Continuing Review

Investigators of a previously approved protocol may request approval from the IRB to make amendments/revisions in various aspects of the protocol, before the protocol's next regularly scheduled continuing review. No amendment/revision may be implemented without the approval of the IRB, except to eliminate immediate hazard. The date of approval of an amendment/revision will not change the date by which the regularly scheduled continuing review of the protocol will be completed.

An amendment/revision may be in the content or the form of documentation. Examples of amendments or revisions include the following:

[1] Amendment/change to the study protocol

[2] Amendment/change to the investigator's brochure describing a test article

[3] Amendment/change to the informed consent document

[4] Change in the identity of the investigator or study staff or change their role in the study

[5] Modification or addition of tests, questionnaires, surveys

[6] A change in approved research that has been initiated without IRB approval to eliminate apparent immediate hazards to the participant

[7] Premature completion of a study

Different types of amendments/revisions may be requested individually or in combination. Particularly, a change in the study protocol or investigator's brochure may require a change in the informed consent document.

The IRB, under full board review primary reviewer procedures, will review 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 Full Committee Amendment Reviewer form will be completed to assist in the determination that all regulatory criteria for approval have been met. For modifications to previously approved research by a convened IRB, all IRB members will receive a copy of the amendment and all supporting documentation. A copy of the current or revised informed consent document shall accompany the amendment application, if applicable.

If an amendment changes the risk with respect to biosafety or radiation safety, approval of those subcommittees is required prior to final approval of the amendment. The IRB Coordinator or other IRB staff will coordinate communication between the IRB and the subcommittees to accomplish this goal.

If a change in approved research has been initiated without IRB approval to eliminate apparent immediate hazards to the participant this change must be submitted to a fully Convened IRB to determine if the change was consistent with ensuring the participant's continued welfare.

If there are any significant new findings that arise from the review process and that might have related to participants' willingness to continue participation in the study, the IRB will require the investigator to provide these findings to participants.

All amendments/revisions involving changes in the Principal Investigator or Co-Principal Investigator; substantive changes to the informed consent (other than minor editorial changes); all substantive changes to the HIPAA authorization form; and protocol changes must be processed under full IRB board review.

As a result of the review, the IRB will decide by voting to approve with or without modifications required to secure approval, defer, or disapprove the amendments/revisions.

Closure of a study

When a study is completed before the next continuing review date, the investigator will submit a final abstract and a completed and signed "Request for Closure of Approved Human Study Protocol." The requirement that investigator inform the Chief, Pharmacy Service when a study involving investigational drugs has been terminated is accomplished by having the Investigational Pharmacist as a member of both the IRB and R&D Committees. The Investigational Pharmacist communicates this information to the Chief, Pharmacy Service.

## 11.4 Reporting of Serious Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

Definitions (from VHA Handbook 1200.05):

**Adverse event (AE).** An adverse event is defined as any untoward physical or psychological occurrence in a human subject participating in research. An adverse event can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. An adverse event does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.

**Serious Adverse Event (SAE).** A SAE is defined as death; a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly or birth defect; or an event that requires medical, surgical, behavioral, social or other intervention to prevent one of the preceding outcomes.

**Unexpected (or Unanticipated) Adverse Event (UAE)**. An UAE is an event which is new or greater than previously known in terms of nature, severity or frequency of occurrence as documented in the protocol or other materials approved by the IRB (e.g., clinical investigator's brochure, product labeling, consent form, etc) and the characteristics of the study population.

NOTE: The unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance.

**Unanticipated Problem Involving Risks to Subjects or Others (UP)**: Those events that (a) are not expected (in terms of nature, severity or frequency)[6], given the nature of the research procedures and the subject population being studied **and (b) related** [7] to or possibly related to participation in research **and** (c) suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, social, or legal harm) than was previously known or recognized.

Reporting Requirements for AE, SAE, and UP

All AE, SAE, and UP that cause harm or risk of harm to human subjects or groups, as required by VHA Handbook 1200.05, will be reported to Minneapolis VAHCS officials, including the Chief of Staff and Medical Center Director. In addition, the ORO, FDA, DHHS, OHRP reporting requirements will be followed.

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[7] **Related:** Based on the investigators' judgment, there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

**Possibly Related**: The adverse event may have been caused by the drug, device intervention, however there is insufficient information for the investigator to determine if the event is definitively related to the research.

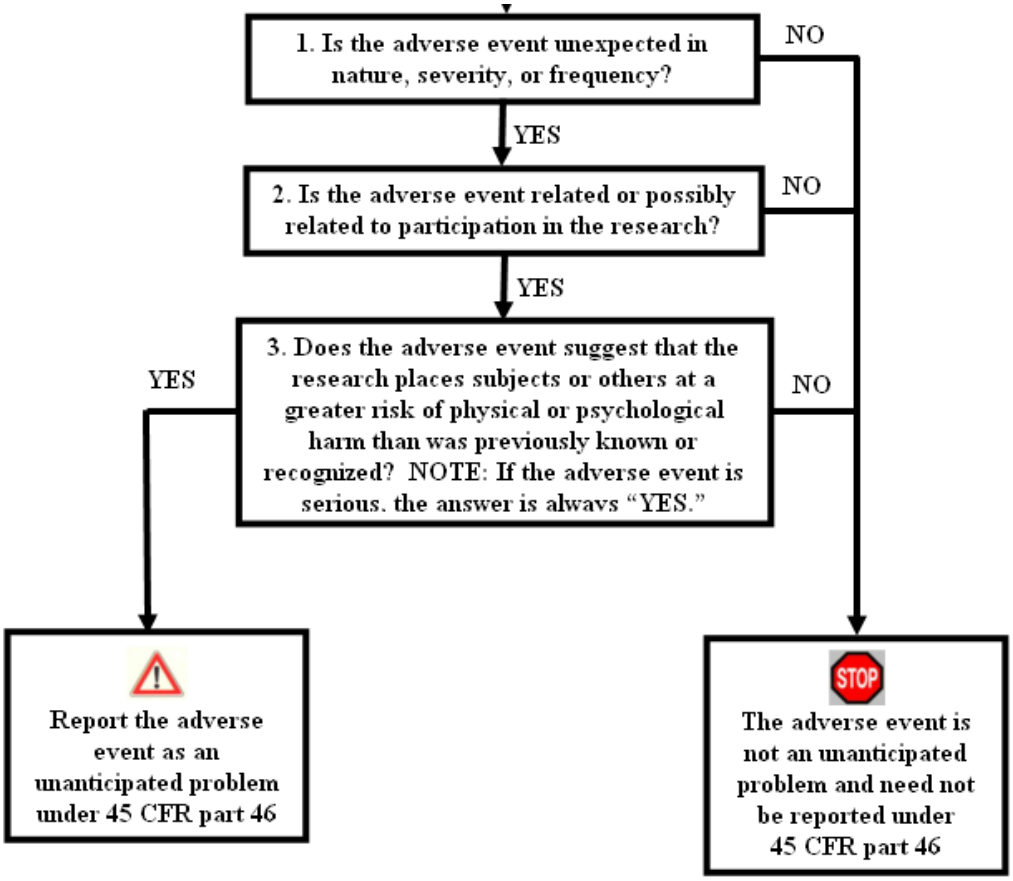
**11.4a IRB Reporting Guidelines**

VA Office of Research Oversight requires that "any research-related problems involving risks that are not anticipated in terms of nature, severity, or frequency of occurrence….must be reported promptly to the IRB." [§5(a)] *Reporting Unanticipated Problems and Adverse Events to the IRB, ORO Memorandum, Dec. 6, 2006*

**Examples of events that should be reported to the IRB for review and subsequent determination may include (but are not limited to):**

- Adverse events (see OHRP decision tree at the end of this section)
- Unresolved complaints or violent or illegal behavior
- Loss of research data
- A breach of privacy or confidentiality
- Reports of injury or death involving subject or others
- A research subject becomes unexpectedly pregnant
- Pharmacy or lab errors
- Scientific reports
- Interim data analysis
- DSMB findings
- Inability to conduct specified safety assessments
- Loss or disclosure of individually identifiable protected health information (PHI)
- Findings of scientific or ethical misconduct
- Sponsor monitor reports
- Compliance reports
- Events that require prompt reporting to sponsor, institutional or oversight officials
- Equipment problems – ex. The investigator or staff finds that a piece of equipment is not calibrated properly
- Discovery of lapse in licensure of study personnel
- Incarceration of a participant
- Unanticipated problems with study facilities – ex. Unanticipated reassignment of space, temperature problems
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant
- Sponsor imposed suspension for risk.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- Protocol violation/deviation (meaning a change or alteration in a procedure or procedures as outlined in the IRB approved protocol, health care system or IRB policies and standard operating procedures)

OHRP decision tree for determining whether an AE is reportable to the IRB




In FDA clinical trials, adverse events that are serious, unexpected, and reasonably related to the study treatment or intervention and that are expected to result in a change to the protocol or consent documents and/or dissemination of new information to subjects. In FDA clinical trials, any unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

**Please note: different forms are used to report Adverse Events and Unanticipated Problems; see sections 11.4b and 11.4c below.**

### 11.4b Reporting and Review of Unanticipated Problems

UP Submission Procedures

For events reported by the PI
UP involving risks to subjects or others must be reported to the Minneapolis VA HCS IRB within 5 working days after the investigator becomes aware of the problem on the **Unanticipated Problem Report** form. If the PI recognizes that the event/problem involves risk to subjects or

others and a modification to the IRB consent and/or protocol is required, he/she will also submit a revised consent form and/or protocol, as well as an Amendment form.

Serious unanticipated problems involving risks to subjects or others include:

(1) Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

(2) Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death.

(3) Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects.

(4) Any DMC, DSMB, or DSMC report describing a safety problem.

(5) Any sponsor analysis describing a safety problem for which action at the facility level may be warranted. ***NOTE:*** *Sponsor AE reports lacking meaningful analysis do not constitute "problems" under this paragraph of VHA Handbook 1058.01.*

(6) Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;

(7) Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs.

Unanticipated Problem Report Form

This form is used to report unanticipated problems (including protocol deviations) which have occurred during the conduct of a research study. The Investigator is required to submit the signed, completed form to the IRB no later than 5 working days after the investigator first learns of the event. This form can be found on the IRB SharePoint under FORMS and on the shared VA server. On the form, the Investigator will be asked to describe:

- the UP which occurred
- provide an explanation of why the UP occurred
- characterize the impact of the UP on the research subject or others
- the potential effect on subject burden
- the impact on scientific validity of the study
- the steps which have been taken to resolve the UP
- the plan implemented to avoid or prevent future occurrences
- whether the current enrolled subjects need to be informed about this UP
- whether the UP has been reported to someone other than the IRB (e.g. sponsor, FDA, etc.)whether the UP requires modification of the currently approved protocol and/or consent form

Any supporting documentation should be attached to the form.

Events reported by other persons, committees, organizations, etc.

Reporting requirements apply to all human subjects' research which is part of the HRPP of the Minneapolis VAHCS IRB. All investigators, IRB members and staff, R&D members and staff, and institutional officials are required to report these unanticipated problems involving risks to

subjects or others to the IRB, unless an exception has been previously granted by the IRB[8]. Others who may report possible unanticipated problems include subjects, subjects' family members, the VA patient relations offices, sponsors and other auditors, and others not involved with the research project, but having information about a possible unanticipated problem.

IRB Review Procedures

The IRB Chairperson, Co-Chair, or a qualified member of the IRB designated by the Chair will review all such reports. The reviewer must make a determination whether a reported event meets the definition of an unanticipated problem involving risks to subjects or others and if the UP represents apparent non-compliance. Apparent non-compliance is addressed in Section 13 of this document.

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

If the event meets the definition of an unanticipated problem involving more than minimal risks to participants or others, the report, along with the reviewer's recommendations, is forwarded to all IRB members for review at the next convened meeting.
During the convened meeting review, the IRB may require one or more of the following actions:

- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to current subjects (this must be done whenever the information may relate to the subject's willingness to continue participation) and identifying who should provide that information
- Providing additional information to past subjects and determining who should provide that information
- Requiring current subjects to re-consent to participation
- Requesting a for-cause internal audit
- Coordinating corrective action with other services in the medical center (lab, pharmacy, nursing service, medical service, surgical service, etc.) to resolve the problem
- Referring the problem to other organizational entities (e.g. legal counsel, risk management, institutional official, RCO, etc.), especially in cases of serious or continuing non-compliance
- Alteration of the frequency of continuing review
- Observation of the research or the consent process
- Requiring additional training of the investigator and/or the research staff
- Notification of investigators at other sites
- Reporting the event to institutional officials and/or regulatory agencies
- Suspension or termination of the research
- Obtaining additional information

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

- Revise policies and procedures
- Taking no action

The IRB's decision will be documented in the meeting minutes and the Investigator will be notified of the findings of the IRB.

If the reviewer has immediate concerns about the safety and welfare of research subjects that cannot wait until the next fully convened IRB meeting, the reviewer will immediately notify the Institutional Official, the Chief of Staff, or the ACOS/Research or his/her designee in his/her absence, who has the authority to take immediate actions (e.g. call for an emergency meeting of the convened board, suspend study procedures, etc, as appropriate, as long as the justification for such actions is documented. The Investigator will immediately be notified of the immediate actions to be implemented and will cooperate with the HRPP to protect the welfare of the affected research subjects. A report of the action will be reviewed at the next convened IRB meeting, or a specially convened IRB meeting. The IRB will review the report, with the reviewer's recommendations at the next meeting and make a determination as described above.

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

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

**11.4c Reporting Adverse Events (AE) to the IRB**

Reporting **EXTERNAL** Adverse Events and Deaths
An External Adverse event is defined by **both** of the following criteria:

- AE has not occurred at the Minneapolis VAHCS; CBOCs connected with the Minneapolis VAHCS; Twin Ports VA Outpatient Clinic and/or the St. Cloud VAHCS

- The subject is not enrolled in the research study at the Minneapolis VAHCS; CBOCs connected with the Minneapolis VAHCS; Twin Ports VA Outpatient Clinic; and/or the St. Cloud VAHCS

Reporting Requirements for **EXTERNAL DEATHS:**
Report only if the death is unexpected, related or possibly related to the research and occurs during the study or 30 days after termination from the protocol. Reports must be submitted to the IRB as soon as possible, but not later than 5 working days after the investigator learns of the event. *For reportable external deaths the* ***External Adverse Event*** ***form*** *located on the IRB SharePoint under FORMS or on the shared VA server.*

Reporting Requirements for **Non-Fatal External Adverse Events:**
**A non-fatal external adverse event must be reported only if the event meets all 3 conditions listed below:**

- The adverse event is expected or unexpected.
- The adverse event is related or possibly related to the research.
- The adverse event serious or more prevalent than expected (as stated in protocol and/or informed consent).

The Investigator is responsible for reviewing all adverse event reports received from the study sponsor. If the adverse event represents a change in the risk/benefit ratio of the study or if risk to subjects or others is increased, the Investigator must notify the IRB within 5 business days after he/she learns of the event. The External Adverse Event form located on the IRB SharePoint under FORMS or on the shared VA server is used for this purpose. *If AE is a death, see section above entitled "Reporting External Study Deaths".*

Other Reporting as Required by Sponsor *Study Sponsors may require investigators to report all External Adverse Events to the IRB, on an individual case basis.* ***Investigators are responsible for checking their study protocols for these requirements. When an IRB review of External Adverse events is required by the Study Sponsor, the Investigator will review the events and complete an External Adverse Event form*** located on the IRB SharePoint under FORMS or on the shared VA server.

*For Study Sponsors that are willing to waive the requirement for reporting External Adverse Events to the IRB, a memorandum stating the Minneapolis VAHCS policy regarding reporting External Adverse Events is* located on the IRB SharePoint under FORMS or on the shared VA server.

Reporting **INTERNAL** Adverse Events
An Internal Adverse event is defined by the following criteria:

- AE occurs at the Minneapolis VAHCS; VA-staffed CBOCs connected with the Minneapolis VAHCS; Twin Ports VA Outpatient Clinic; and/or the St. Cloud VAHCS

and

- The subject is enrolled in the research study at the Minneapolis VAHCS; VA-staffed CBOCs connected with the Minneapolis VAHCS; Twin Ports VA Outpatient Clinic and/or the St. Cloud VAHCS

Adverse events are collected as specified by the individual protocol (e.g., through a given time point, but not for the duration of the entire trial). AEs that are not recorded per protocol are not required to be reported to the IRB.

An internal adverse event must be reported on an individual case basis **only** if the event meets all 3 conditions listed below:

- The adverse event is unexpected.
- The adverse event is related or possibly related to the research.
- The adverse event serious or more prevalent than expected. *If AE is a death, see section below entitled "Reporting Internal Study Deaths".*

The unexpected, related or possibly related and serious or more prevalent than expected adverse event must be reported to the IRB no later than 5 working days after the investigator first learns of the event. *An Internal Adverse Event form,* located on the IRB SharePoint under FORMS or on the shared VA server*, must be completed and submitted to the IRB for each internal adverse event.*

An adverse event is **not immediately reportable** if:

- **The adverse event is unrelated** to the research regardless of seriousness. **However all internal deaths must be reported.****
- The adverse event is not serious in nature.

Reporting Internal Study **Deaths**

****For all research studies, all internal study deaths occurring during the study or 30 days post termination from the protocol are required to be reported as adverse events even if they are unrelated**. All internal deaths must be reported to the IRB as soon as possible, but no later than 5 working days after the investigator learns of the event. *An Internal Adverse Event form,* located on the IRB SharePoint under FORMS or on the shared VA server*, must be completed and submitted to the IRB for each internal adverse event.*

Continuing Review- Aggregate Reporting Internal Related Non-Serious Adverse Events

Investigators/ study coordinators will maintain a log of all Internal Related Non-Serious adverse events for each protocol. At continuing review, all internal related non-serious adverse events occurring since the last continuing review, must be submitted to the IRB in aggregate form, using the excel spreadsheet form entitled “Continuing Review Internal Related Non-Serious AE form” located on the IRB SharePoint under FORMS or on the shared VA server.

**NOTE**: All data safety monitoring and other safety reports should be submitted to the IRB for review as they become available.

### 11.4d Reporting of AE and UP to Minneapolis VAHCS Officials and Regulatory Agencies

AE and UP involving risks to subjects or others will be reported to MVAHCS Officials and the appropriate regulatory agencies by the RCO.

DHHS requires that the IRB promptly report any unanticipated problems involving risks to subjects or others. The report should include: project identification, description of the problem, and an action plan. [45 CFR 46.103 (b) (5) Policy and guidance for incident reporting to OHRP can be found at www.hhs.gov/ohrp.

Office of Research Oversight (ORO) Reporting Requirements

(VHA Handbook 1058.1)

A. The MVAHCS will report, using VA form 10-0420, to the Midwestern Region Office of the ORO all AEs in research and imminent threats of AEs in research conducted on site that result in either:

[1] An IRB taking substantive action[9] (s) as defined in the definitions section. A written report of the AE in research (or an imminent threat[10] thereof), and the IRB action(s) to be taken, must be submitted to the Midwestern Region Office of ORO within **10 working days** of the IRB's determination to take such action(s).

OR

**B.** [2] An unexpected death[11] of a research subject, regardless of IRB action. Such death must be reported to the Midwest Office of ORO **within 24 hours** after the IRB determines that the death was unexpected, see the definition section. If the IRB is unable to determine whether a research subject's death was unexpected after 10 working days of being informed of the death, the death must then be reported to the Midwestern Region Office of ORO. When a final determination is made as to whether or not the death was unexpected, a follow up report must be made to the Midwestern Region Office of ORO.

**C. Written Report**

The institutional official (VHA facility Director), or designee, must:

[1] Prepare a separate report, for each AE in research (or imminent threat thereof) required to be reported by this Handbook, following the format indicated in the ORO reporting **Form 10-0420.**

[2] Initial the completed report and facilitate its submission to the Director of the Midwestern Region ORO, using express mail (e.g., Fed Ex) <u>and</u> either e-mail or fax. A copy of all IRB minutes from meetings in which the AE in research and subsequent actions were discussed, ratified, or summarized needs to accompany the report to ORO, or be sent when the IRB minutes become available, but in no case no later than 4 weeks after the IRB meeting.

[3] The IRB must determine if the adverse event requires reporting to the Office for Human Research Protections (OHRP) based on the risks to human subjects. (See OHRP section in subsequent reporting instructions.) If the IRB judges the adverse event to be an "unanticipated problem" posing risks to subjects the adverse event must be reported to OHRP.

[4] All written reports sent to ORO and OHRP will be sent to the MVAHCS Medical Center Director and the Chief of Staff. In compliance with VHA Handbook 1050.1, the Medical

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

[10] **Imminent Threat of an AE in Research:** Any situation in which an AE in research has not yet occurred but is likely to occur, as determined by an IRB, research, or clinical team member, without preventive measures.

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

Center Director and Chief of Staff are responsible for the implementation of Health Care System procedures for the Disclosure of Unanticipated Outcomes (Policy #RI-17).

FDA reporting requirements

For studies involving investigational drugs or devices, IRBs are responsible for ensuring that reports of unanticipated problems involving risks to human subjects or others are reported to the FDA. Usually, this reporting is accomplished through the normal reporting channel, i.e., the investigator to the sponsor to FDA.

FDA IND regulations (for both drugs and biologics) have requirements related to the reporting of adverse events.

(1) **Investigator Reports to Sponsor:** FDA IND regulations require that the investigator report promptly to the sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)).

(2) **Sponsor Reports to FDA and Investigators:** FDA IND regulations require that the sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of the drug or biologic that is **both** serious **and** unexpected as soon as possible but **in no event later than 15 calendar days after the sponsor determines it to be reportable.**

The FDA should be notified by telephone, facsimile, or in writing as soon as possible but **in no event later than 7 calendar days of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience.**

"Serious adverse drug experience" is defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect" (21 CFR 312.32(a)).

FDA IDE (device) reporting requirements are similar, but not exactly the same as for drugs and biologics.

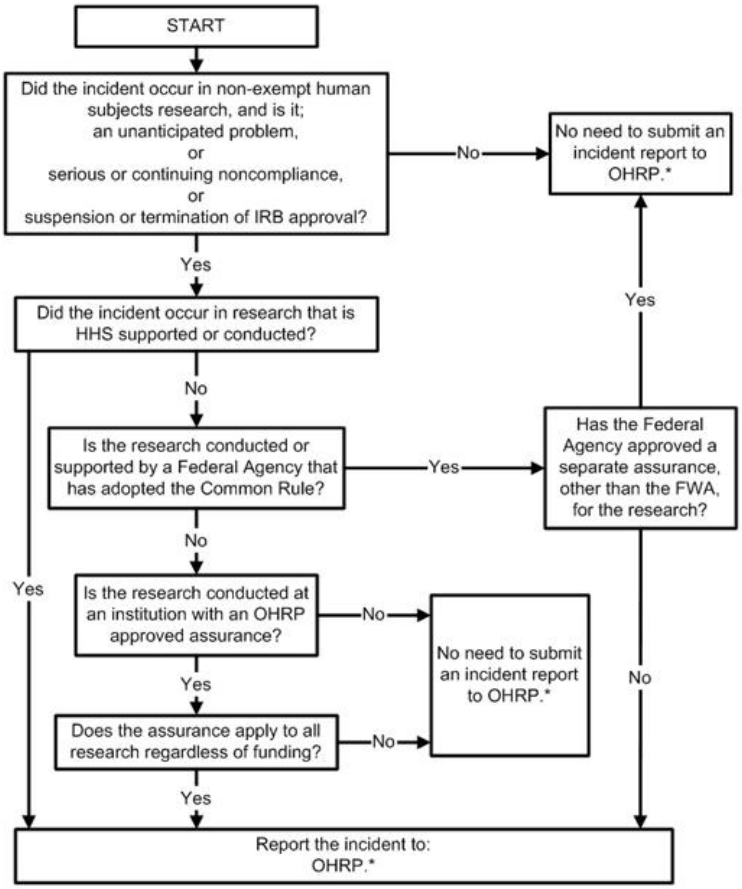
(1) **Investigator to Sponsor**: FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect **within 10 days of discovery.**

(2) **Sponsor to FDA, Investigator, and IRB.** The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all reviewing IRBs **within 10 working days of the sponsor's receipt of the information.**

Any AE information submitted to the sponsor by the investigator should also be submitted to the IRB. In addition to providing **prompt** written notification to relevant federal agencies, including ORO, FDA, and OHRP, of any unanticipated problems involving risks to subjects or others, the IRB should also report the resolution of those problems.

*OHRP reporting requirements*- OHRP requires prompt reporting of any unanticipated problems involving risks to subjects or others. The decision tree provided by OHRP should be used by the IRB to help determine which UP should be reported. The report should include:

- Project identification
- Description of problem
- Action plan




## 11.5 RCO and IRB-Initiated Audits

The IRB can accept audits conducted by the RCO to fulfill auditing requirements. (See Research Compliance Program SOP and Reporting Research Events for Members of the Research Community and Research Compliance Officers SOP.)

## 11.6 Additional Measures of IRB to Monitor Active Research Projects

Additional monitoring of approved protocols may occur at the discretion of the IRB (e.g., in the event of evidence of investigator non-compliance, complaints from subjects or employees) in the form of targeted:

[1] Requests for progress reports from investigators;

[2] Examinations of research records;

[3] Contacts with research subjects;

[4] Dispatch of observers to the sites, where research involving the human subjects is being conducted;

[5] Verification from sources other than investigators that no material changes in the study have occurred. In targeting research protocols to be subjected to these additional monitoring activities, the IRB will consider the level of risks of harm, the frequency and nature of adverse events, the vulnerability of the subjects of research, and any complaints received from the subjects.

If the information gained during its monitoring process indicates that human subjects of a research protocol are exposed to unexpected serious harm, or the requirements of the IRB are not being met, the IRB will suspend or terminate the research. In such instances, the IRB will provide the opportunity of rebuttal for the investigators, either in writing, or by appearing at a meeting of the IRB to defend their positions.

**11.6a Complaints**
Every effort will be made to address and resolve complaints made regarding the research by the individual who is the point of contact (i.e., the investigator, research staff, etc.). All complaints, regardless of initial point of contact, will be reported to the Patient Advocate per Patient & Family Center policy. Complaints will be addressed per the procedures of the Research Compliance Program and the Minneapolis VAHCS.

**11.7 Reporting of All Study Site-Monitoring Visit Results**

Notification of ACOS/Research
Upon learning of an upcoming external monitor visit the investigator or study coordinator will notify the Research Office either by e-mail at IRBMN@VA.gov or by sending a memo containing the information listed below. If the visit is unscheduled, the Research Office must be notified as soon as the study personnel become aware of the visit. The information required by the Research Office is as follows:

- MVAHCS Protocol number and name of the study;
- Principal Investigator and study coordinator and their telephone numbers
- Sponsor
- Monitor and his/her contact information
- Date and time of the monitoring visit

Visitor Sign-In
All study monitors and visitors to Research Service must sign in and sign out as a visitor in the Research Office (3M-112) each day of their visit. A visitor badge will be issued at the initiation of the visit and must be returned to the Research Service office at the end of each day. The receipt of the visit badge back from the monitor will be noted in the log by Research Office staff.

Investigator Responsibilities for Study Monitor Visits
All potential or actual serious findings must be conveyed to the investigator and the ACOS/Research or in the absence of the ACOS/Research, the Administrative Officer/Research

or his/her designee during an exit interview. Findings that require an exit interview include but are not limited to:

- Any suspicions or concerns that serious non-compliance may exist, and
- All findings of serious non-compliance with the study protocol, Institutional Review Board (IRB) requirements or applicable regulations and policies (examples: failure to consent subjects, entering subjects who do not meet entrance criteria into protocols, and failure to report serious or unexpected adverse events).

The monitors' written report is to be sent to the IRB regardless of the findings. It is the responsibility of the investigator or research study coordinator to submit a copy of the monitor visit findings.

Contracts with pharmaceutical companies must define the role of study monitors that is consistent with the requirements of the above procedure.

If a study monitor requires direct access to electronic medical records, appropriate permissions and clearances must be obtained in advance of the visit, working in coordination with the Administrative Officer/Research or his/her designee.

## 12. HUMAN SUBJECT RESEARCH ELIGIBLE FOR EXPEDITED REVIEW

The Chairperson, Co-Chairperson or experienced IRB member designee will be authorized to act on behalf of the IRB to conduct expedited review and grant approval for:

Categories of research published in the Federal Register Vol. 63, November 9, 1998

Minor changes in previously approved research during the period for which approval is authorized

An *experienced* IRB member designated by one of the Chairpersons will be a voting member of the IRB, have one or more years of IRB experience, and will be knowledgeable about the requirements and regulations for full, expedited and exempt reviews.

Certain types of research protocol applications submitted to the IRB for initial or scheduled continuing review, requests for amendments, advertisements, or adverse event reports will be eligible for "expedited review". The basic element determining the eligibility for expedited review is the magnitude of the risks to which the human subjects of the research will be exposed.

Only protocols involving no more than minimal risk will be considered for expedited review. As defined by Federal regulatory agencies, "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."

When a study involves "usual care," in the protocol or a separate document in the IRB application the researcher must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject's health care provider) responsible for relevant aspects of both the research and the usual care.

## 12.1 IRB Process for Expedited Review

Expedited review of a new protocol or previously approved protocol may be requested by the Principal Investigator at the time of submission of the application, by indicating the applicable criterion for expedited review. Alternatively, the Chairperson or Co-Chairperson, or their designee may choose to process an application by expedited review.

Expedited review will be carried out by the Chairperson or Co-Chairperson, or one or more experienced members of the IRB in accordance with the requirements set forth in 38 CFR 16.110. The reviewer will have the authority to approve the protocol, without a vote of the IRB membership. If the reviewer believes that there is reason for disapproval, or the nature of the protocol is not suitable for expedited review, the reviewer will defer any decision, and submit the protocol to a full review by the IRB. An individual reviewer cannot disapprove a protocol. All protocols approved under expedited review procedures are subject to continuing review.

Upon approval based on expedited review, the IRB membership will be informed of the approval at the time of a regularly scheduled meeting, and it will be recorded in the minutes of that meeting. At that time, questions may be raised by IRB members regarding the list of approved expedited reviews.

### 12.1a Research Considered by IRB as Suitable for Expedited Review

**FDA ACTIVITIES APPROPRIATE FOR EXPEDITED REVIEW**
(FDA and DHHS only differ slightly in that certain types of behavioral research is not included)
**(Listed in Federal Register Vol., 63 November 9, 1998)**

The following types of research, considered to have no more than minimal risk, and not involving children, fetuses, neonates, pregnant women, or prisoners*, have been explicitly identified by IRB as eligible for expedited review. The categories apply regardless of the age of subjects, except as noted, and pertain to both initial and continuing review.

**(*The IRB will not review or approve any research focused on prisoners.)**

Research activities that:

[1] Present no more than minimal risk to human subjects

[2] Involve only procedures listed in one or more of the following categories may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.100 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure where the specific circumstance of the proposed research involves no more than minimal risk to human subjects.

The categories in this list apply regardless of the age of subjects except as noted.

**The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing and appropriate protections will be**

**implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.**

The standard requirements for informed consent or its waiver, alteration or exception apply regardless of the type of review (expedited or convened) utilized by the IRB.

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

Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

[1] Clinical studies of drugs and medical devices when one of the following conditions is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risk or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

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

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

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

(b) from other adults and children, considering age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

[3] Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted

prophylactic techniques: (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

[4] Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical device for new indications. Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinograph, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

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

**Procedures that involve more than minimal risk or do not fall into categories (1)-(7) of research that could be reviewed using the expedited procedure (see list in preceding section) must undergo review by the full IRB Committee.**

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

(a) (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

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

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

NOTE: For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b) or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that “no subjects have been enrolled” is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that “no additional risks have been identified” is interpreted to

mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

**When using the expedited review procedure for continuing review, the reviewer will receive and review the same information that the convened IRB received.**

[9] Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories [2] through [8] do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

## 12.2 Research Considered Eligible for Exemption from IRB Review

Before a protocol is evaluated for exemption, it should first be determined if the activity is 1) research (using worksheet *Step 1: Is it Research?*), and 2) human research (using worksheet *Step 2: Is it Human Research?*).

As defined in 45 CFR 46.101, federal regulatory agencies have recognized certain types of research as having no or negligible risk to the subjects and considered by them to be eligible for exemption from review by institutional review boards. Exempted review of a new protocol may be requested by the Principal Investigator by submitting the *Step 3: Is It Exempt?* form and a protocol to the IRB. Alternatively, the Chairperson or Co-Chairperson or their designate, may choose to process an application submitted for full or expedited review by exempted review if applicable.

*Exemption determinations may not to be made by investigators or others who might have a real or apparent conflict of interest regarding the study.*

Exempted review will be carried out by the Chairperson or Co-Chairperson, or another experienced voting member of the IRB (see definition of "experienced" in previous Section 12, 2nd paragraph) designated by them. The *Step 3: Is It Exempt?* form is used for this purpose. The reviewer will also determine whether the exempt research fulfills the organization's ethical standards[12], including:

- The research holds no more than minimal risk to subjects.
- Selection of subjects is equitable.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- If there are interactions with subjects, the IRB should determine whether there should be a consent process that will disclose such information as:
  - That the activity involves research.
  - A description of the procedures.
  - That participation is voluntary.
  - Name and contact information for the researcher.

[12] Minneapolis VA Medical Center Patient Rights and Organizational Ethics (RI) Policy RI-11C, Statement of Organizational Ethics.

- There are adequate provisions to maintain the privacy interests of subjects

The reviewer will have the authority to declare the protocol exempt from IRB review, without a vote of the IRB membership and will provide documentation to declare the protocol exempt, specifying the category for the exemption. The protocol will then be forwarded to the R&D Committee for review and final approval and oversight.

If it is determined that the study does not meet exempt criteria, the IRB will provide documentation to this effect, specifying the reason exempt criteria is not met, and directing the investigator to submit a full IRB application.

Projects meeting an exempt category and approved by an experienced member of the IRB will be subject to continuing review process by the Research and Development Committee.

### 12.3 Previously Approved Research Eligible for Expedited Review

Research approved previously by expedited review will be considered eligible for expedited review at the time of its regular continuing review, if, during the course of the study, the risks of the study have not increased.

Prior to the scheduled date of regular continuing review, changes may have to be implemented in an approved protocol. Amendments to a previously approved research protocol of administrative or logistical nature, revisions in the text of an informed consent document, or corrections in text of documents, all of which are minor in nature and do not increase the risks involved, will be considered eligible for expedited review.

## 13. NON-COMPLIANCE

The Research Compliance Program SOP 10-Research-004 and Reporting Research Events for Members of the Research Community and Research Compliance Officers (RCOs) SOP 10-Research-001describe the auditing and reporting processes. Findings of apparent serious or continuing non-compliance are reported to the IRB and other oversight committees as described in these policies. The determination of whether non-compliance is *serious* or *continuing* will be made by the convened IRB.

If the convened IRB determines that serious or continuing non-compliance has occurred, the IRB may require one or more of the following actions:

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

- Referring the problem to other organizational entities (e.g. legal counsel, risk management, institutional official, RCO, etc.), especially in cases of serious or continuing non-compliance
- Alteration of the frequency of continuing review
- Observation of the research or the consent process
- Requiring additional training of the investigator and/or the research staff
- Notification of investigators at other sites
- Reporting the event to institutional officials and/or regulatory agencies
- Suspension or termination of the research
- Obtaining additional information
- Revise policies and procedures
- Taking no action

The IRB's decision will be documented in the meeting minutes and the Investigator will be notified of the findings of the IRB.

If the reviewer has immediate concerns about the safety and welfare of research subjects that cannot wait until the next fully convened IRB meeting, the reviewer will immediately notify the Institutional Official, the Chief of Staff, or the ACOS/Research or his/her designee in his/her absence, who has the authority to take immediate actions (e.g. call for an emergency meeting of the convened board, suspend study procedures, etc, as appropriate, as long as the justification for such actions is documented. The Investigator will immediately be notified of the immediate actions to be implemented and will cooperate with the HRPP to protect the welfare of the affected research subjects. A report of the action will be reviewed at the next convened IRB meeting, or a specially convened IRB meeting. The IRB will review the report, with the reviewer's recommendations at the next meeting and make a determination as described above.

## 14. EMERGENCY USE OF A TEST ARTICLE

21 CFR 56.104(c) 21 CFR 50.23

### Definitions and authority

**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.

An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval. The emergency use exemption is for treating patients and cannot be used to otherwise get around requirements for prior IRB review of research.

The following conditions must be met for this type of emergency use:

1. A human subject is in a life-threatening situation.
2. No standard acceptable treatment is available.
3. There is insufficient time to obtain IRB approval.

The investigator must obtain written informed consent from each individual or legally authorized representative prior to the use of a test article. The consent used with emergency use needs to include all required elements as described in Section 9.1 "Elements of Informed Consent". An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

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

The FDA requires an Investigational New Drug number (IND), for emergency use and does not allow a waiver of this policy. If the intended patient does not meet the criteria for an existing study protocol or if an approved study protocol does not exist, the investigator must contact the manufacturer to determine if the drug or biologic can be made available for the emergency use under the manufacturer's IND. If the manufacturer does not allow the investigator to reference its IND, the investigator must contact the FDA directly for an IND.

Within VA, emergency use of a test article is not considered to be research. Therefore, the patient is not a research subject, the emergency care cannot be claimed as research, and the outcome of such care cannot be included in any report of research activity subject to 38 CFR Part 16.
<u>The exemption allows for one emergency use of a test article without prospective IRB review</u>. FDA regulations require that any subsequent use of the investigational drug or biologic at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

**Procedures:**
The investigator is responsible for consulting with the IRB Chair or designee prior to use of the test article if time allows. The IRB Chair or designee will review the use to assure that appropriate FDA regulations have been followed.

The investigator will notify the Chief of Staff or designee prior to use of a test article without informed consent. The Chief of Staff or designee will certify that the conditions allowing for exemption are met. If time is not sufficient to obtain certification before use of the test article, the actions of the investigator must be reviewed the Chief of Staff or designee and evaluated in writing within 5 working days.

The emergency use must be reported to the IRB within five working days using the Unanticipated Problem Form. The emergency use event will be placed on the agenda of the next convened IRB meeting. IRB Reviewers are responsible for verifying that the use of the test article in an emergency falls within the emergency use criteria, conducting a thorough review,

securing appropriate consulting expertise as needed, and making appropriate approval recommendations for consideration by the IRB. If it is the determination of the convened IRB that appropriate FDA regulations were not followed then procedures to address non-compliance to federal regulations would apply.

## 15. APPROVAL FOR HUMAN SUBJECT RESEARCH INVOLVING RADIOACTIVITY

The protocol of research studies involving the administration of radioactive substances to human subjects, for research purposes, will be reviewed and approved by a Radioactive Drug Research Committee (RDRC). This committee will be formed as needed to review protocols to ensure that radiation risks are properly documented in the consent form and that the appropriate level of review is carried out for protocols that involve radiologic procedures in addition to what would normally be required for standard clinical care. When applicable, the IRB will require prior certification by this subcommittee as a condition for approval. To prevent delays in the total review process, at its discretion, the IRB may accept concurrent review by the IRB and the RDRC, but defer the final decision until a notice of certification has been received.

## 16. INVESTIGATIONAL DRUG SERVICE

The Minneapolis VA Health Care System Pharmacy Service will be responsible for safekeeping, dispensing and monitoring of investigational drugs administered to human subjects within the confines of the institution as stated in the 05/04/07 policy “Pharmacy Service Policy and Procedure Manual”. In addition to an investigational drug designated by the FDA, an investigational drug is defined in VHA Handbook 1200.05 as “an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.”

Before dispensing investigational drugs to human subjects, the Investigational Drugs Pharmacist will have:

[1] Approved protocol and a copy of VA Form 10-1223.

[2] The original copy of VA Form 10-9012, Investigation Drug Information Record with the signature of the Principal Investigator, the Chairperson, Institutional Review Board, and the Chairperson, R&D Committee and

[3] A copy of the informed consent document with the signature of the subject.

<u>Investigational Drug Service Fee</u>
On all industry-sponsored pharmaceutical protocols a one-time set up fee for study initiation and closure activities, and a dispensing fee will be charged for each prescription.

## 17. CONFLICT OF INTEREST

Conflict of interest is managed by the Minneapolis VA Health Care System HRPP Policy #08-001 and the VA R&D policy for Conflict of Interest which is currently under revision at a federal level.. All investigators, co-principal investigators, and collaborators are required to complete a Research Financial Conflict of Interest Statement as part of their submission to the IRB.

A financial conflict or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings. Concerns related to conflicts of interest have increased as relationships of investigators with private corporations, pharmaceutical companies, and outside institutions have become more complex. These concerns are based on the potential effects that the conflicts may have on the actual or perceived quality of the research and the treatment of research participants.

The main conflict of interest statue in the federal criminal code, 18 U.S.C. §208, prohibits all VA employees (full-time, part-time, WOC, and IPA) from participating personally and substantially, as part of their official duties, in any particular matter, including research, that directly and predictably affects their own financial interests or any financial interests imputed to them. Financial interests that are imputed to a VA employee include the financial interests of a spouse; minor child; general partner; an organization in which the VA employee serves as an officer, director, trustee, general partner, or employee; or an organization with which the VA employee is negotiating or has an arrangement for prospective employment. Imputed financial interests are treated as if they were the VA employee's own financial interests for purposes of this prohibition.

In addition to the disclosures required in the form entitled Research Financial Conflict of Interest Statement, all VA employees are subject to the criminal conflict of interest statutes at Title 18, United States Code (U.S.C.) Chapter 11, and the Executive Branch Standards of Conduct at Title 5 Code of Federal Regulations (CFR), part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

Getting Ethics Advice

The IRB Executive Committee comprised of Chairs of both IRB Committees, Chair of R&D, ACOS/Research, Administrative Officer, Research Compliance Officer & IRB Administrator will evaluate reported potential conflicts of interest and may seek ethics advice. VA Regional Counsels and the Assistant General Counsel for Professional Staff Group III (023), the designated agency ethics official, maintain ethics expertise and provide ethics counseling services to employees. Employees with questions regarding these requirements are encouraged to contact the Regional Counsels at the Minneapolis VAHCS.

**Important Note: When completing the Research Financial Conflict of Interest Statement, question 7, regarding publically traded companies: 1) you must aggregate the interests of yourself, spouse and dependent children when determining if you have reached the threshold amount; b) If your research involves human subjects, the threshold amount is $10,000 (not $15,000). (This information is included in a cover sheet which accompanies the Research Financial Conflict of Interest Statement.)**

## 18. EDUCATIONAL AND CREDENTIALING ACTIVITIES OF RESEARCH

It is the expectation of the Human Research Protection Program that individuals involved in research at the Minneapolis VAHCS will understand and be able to apply ethical principles that guide individual and organizational decisions. This includes situations where the answer cannot be found in the law, professional standards, or policies and procedures.

The IRB will provide services to inform the research community on issues related to the protection of human subjects in research and ethics in research, and to make researchers aware of applicable Federal regulations.

When a research protocol is submitted for review, the IRB Administrative staff will ensure all of the research employees involved with the conduct of the protocol, as documented on the protocol submission forms, have been credentialed and completed the required research training. If the investigators and coordinators are connected with a VAHCS other than the Minneapolis VAHCS, dates of their training and a statement verifying their credentials from their human resource department or research department must be included in the protocol submission.

Investigators and coordinators at other institutions outside of the VA that are connected with VA research but do not come to the Minneapolis VAHCS to perform any research functions or interact with VA research subjects, will not be required to provide verification of their human studies education, good clinical practice or their credentials.

### 18.1 IRB Educational Activities and Credentialing Aimed at the Research Community at Large

The following credentialing, validation of qualifications, certification of mandatory education, scopes of practice, and background investigations will be monitored and documented by Research Administrative staff utilizing a database and hard copy records containing the information ensuring these requirements have been satisfied. Only IRB and Research Administrative staff have access to the hard copy records containing sensitive information such as employee social security numbers.

### 18.2 Validation of Credentials for Research Employees

Credentialing, as stated in VHA Directive 2003-036, “is the formal, systematic process of verifying, screening, and evaluating qualifications and other credentials that include education, licensure, relevant training and experience, and current competence.”

All employees involved in human subject research taking place at the Minneapolis VAHCS must have been credentialed or had their qualifications validated, and the licenses of individuals in positions requiring a license verified for currency.

A Scope of Practice form outlining the authorized duties of research employees, other than Principal Investigators and co-investigators, is created for each research employee, not each protocol. The Principal Investigator will complete this form with the research employee.

All research employees will complete the “Questionnaire for Non-Sensitive Positions,” Standard Form 85 with the following exceptions: when the research employee will only be employed for 90 days or the University of Minnesota has verified the credentials of their students/interns/residents/fellows. The level of the background investigation will be commensurate with the employee’s position.

### 18.3 IRB Educational Activities Aimed at Research Employees of Projects Involving Human Subjects

All Investigators, Study Coordinators and other research employees regardless of appointment, except for secretarial support, involved in human subjects research will have documented training in good clinical practice and human subjects protection prior to receiving approval for any new studies and at least once every 2 years (730 days) thereafter.
The training will include the ethical principles and regulatory requirements associated with research involving human subjects and is available at https://www.citiprogram.org/, choosing Department of Veterans Affairs (Minneapolis-618) as the affiliation. Training through CITI is recommended, however a listing of alternative coursework is available at: http://www.research.va.gov/programs/pride/training/. Completion of CITI training is verified electronically by IRB staff with each project's continuing review, therefore copies of completion certificates are not required to be sent to the Research Office. If human subjects and Good Clinical Practice (GCP) training are obtained from a source other than CITI, copies of completion certificates must be forwarded to the Research Office.

The HRPP staff will regularly present education sessions providing research staff with pertinent information regarding the submission of research protocols; conducting research; and research regulations. The information presented will also be available on the IRB SharePoint site and the shared VA server, will be disseminated through emails to research staff, and will be announced on the IRB SharePoint site.

The IRB will periodically broadcast to researchers who have active research protocols involving human subjects, using electronic mail or hard-copy correspondence, reviews of the rationale for selected regulatory policies, and reminders of periodic actions expected by the IRB from the researchers.

### 18.4 IRB Educational Activities Aimed at Members of IRB

At the time of induction, new members will receive reference material including the Institutional Review Board Guidebook, the 1998 FDA Information Sheets, the "Common Rule," (FDA) 21 CFR 50, 56, (DHHS) 45 CFR 46, VHA Handbook 1200.05 and the HRPP Standard Operating Procedures. New members will be oriented by the Chairperson and the IRB Administrator.

All IRB members, IRB staff, and other individuals with responsibility for human research protection will have documented training in human subjects' protection at least every 2 years (730 days). The training will include the ethical principles and regulatory requirements associated with research involving human subjects and good clinical practice training. Documentation of the completion of training will be maintained in the Research Administration database. In addition, IRB members will be required to read the Belmont Report on an annual basis.

The IRB will subscribe to "IRB: Ethics & Human Subjects Research" which is distributed as part of IRB member review packets six times a year. Articles relevant to the committee's discussion or of general interest to the committee's role will be included in the monthly agendas.

## 19. PARTICIPATION OF SPONSOR REPRESENTATIVES AND USE OF EQUIPMENT PROVIDED BY THE SPONSOR IN RESEARCH CONDUCTED AT THE MINNEAPOLIS VAHCS

When equipment to be used for research purposes is brought in to the Minneapolis VAHCS by an outside sponsor and the sponsors' representatives will be operating the equipment, the following requirements must be met before allowing sponsor representatives to be present and involved in the conduct of any research procedure.

1. The Sponsors' Human Resource Department must provide written confirmation of the education credentials and completion of applicable training necessary to perform the indicated research functions of sponsor representatives participating in the research study at the Minneapolis VAHCS.

2. Sponsor representatives must complete the required VA HIPAA, data security, human studies and good clinical practice training before participating in the research study.

3. The guidelines outlined in the Network Policy Memo V13-27, April 4, 2001 titled "Visitors in the OR and Other Areas Where Procedures are Performed," must be followed.

4. Equipment used for research purposes must be inspected by Acquisition and Material Management Service (AMMS, ext. 2122) and Biomedical Instrumentation Service (Biomed, ext. 2012) before the equipment is used for research purposes.

## 20. RESEARCH DATA SAFEGUARDING REQUIREMENTS

The VA continues to emphasize the importance of privacy and security of VA research. All VA researchers and staff must be familiar and comply with existing policies, procedures and directives, including any required initial and ongoing education regarding the protection of human subjects in research and the use and disclosure of individually-identifiable information. For additional information please refer to:
http://www1.va.gov/resdev/resources/policies/cybersecurity.cfm.

<u>VA Sensitive Information:</u> VA Directive 6500 defines "VA Sensitive Information" as data that require protection due to the risk of harm that could result from inadvertent or deliberate disclosure, alteration, or destruction of the information. This includes:

1) Information whose improper use or disclosure could adversely affect the ability of the VA to accomplish its mission.

2) Proprietary information

3) Records about individuals requiring protection under various confidentiality provisions, such as the Privacy Act and the HIPAA Privacy Rule.

Information that can be de-identified in accordance with VHA Handbook 1605.1, would not be considered sensitive information.

If data is not de-identified, names, addresses, and social security numbers (real or scrambled) must be replaced with a code to share or transport off-site. The key to the code must remain within the VA.

The Principal Investigator has overall responsibility for data safeguarding. This includes being responsible for training and providing oversight for all members of the research team (including trainees) on the data security rules. The PI is responsible for protecting all VA-sensitive data that is identifiable for any private individual; assuring paper and electronic VA-sensitive data are only accessible to authorized individuals; and that storage and security are maintained as approved by the IRB.

VA Protected Information (VAPI) must not reside on non-VA systems or devices unless specifically designated and approved in advance by the Minneapolis VAHCS ISO and the Privacy Officer.

## 21. IRB DOCUMENTATION AND RECORDS

(a) The IRB Administrator, IRB Coordinators, and other Research office staff will maintain an archive of files for all research protocols approved by the IRB. Each protocol folder will include all versions of the following types of documents:

[1] Application forms
[2] IRB-approved consent documents
[3] Research protocol
[4] Investigator's brochure for test articles, if any
[5] Certification documents from other subcommittees
[6] Text of advertisements for subject recruitment, if any
[7] Notifications of IRB decisions & correspondence between the IRB and the investigator Records of continuing review activities,
[8] Reports on amendments and adverse events,
[9] Statements on significant new findings, including data and safety monitoring reports, if applicable,
[10] Minneapolis VAHCS PHI and Sensitive Information Use Statement,
[11] Correspondence between IRB and investigators of the protocol,
[12] DHHS-approved sample consent document and protocol, when they exist,
[13] Progress reports submitted by investigators,
[14] Reports of injuries to participants,
[15] For initial and continuing review of research by the expedited procedure:
   a. The specific permissible category.
   b. Description of action taken by the reviewer.
   c. Any findings required under the regulations.
[16] For exemption determinations the specific category of exemption.
[17] For initial review, unless documented in the IRB minutes, determinations required by the regulations and protocol-specific findings supporting those determinations for waiver or alteration of the consent process.

[18] For each protocol's initial and continuing review, the frequency for the next continuing review Correspondence between the IRB and the Research and Development Committee Subject complaints
[19] Internal (local) serious adverse events
[20] Unanticipated problems involving risks to subjects or others and protocol deviations.
[21] For continuing review, unless documented in the IRB minutes, determinations required by the regulations and protocol-specific findings supporting those determinations for waiver or alteration of the consent process.
[22] Scientific evaluations by IRB reviewers addressing the quality of the research design and an assessment of whether the research design is expected to yield the expected knowledge.
[23] Documentation of non-compliance

IRB records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.

The IRB files on a research protocol will be retained for at least five years after completion of the research. If a protocol is cancelled without participant enrollment, IRB records will be maintained for at least five years after cancellation of the study. IRB files not relating to research will also be retained for a least 5 years. All IRB records will be retained in accordance with VHA's Records Control Schedule (RCS 10-1) and will be destroyed by shredding when appropriate.

Research protocol files are the property of the Research Office and will be stored as required to protect the privacy and confidentiality of research participants. Storage will be in locked files and/or in locked offices.

(b) In addition, the IRB Administrator or IRB Coordinators will prepare and maintain adequate documentation of IRB activities, including the following:

[1] Minutes must include components as described in Section 6.3 IRB Meeting Minutes

[2] All decisions about a research protocol are reported to the Principal Investigator and R&D Committee including terminations and suspensions. Terminations and suspensions are reported to institutional officials responsible for the assurance and HRPP, and appropriate VACO officials, Federal agencies or departments.

[3] When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically and the research is automatically suspended.

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

- Once notified of the suspension, the PI must immediately submit to the IRB Chairperson, 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.

- If the study is FDA-regulated, the COS and IRB Chairperson must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.
- The sponsoring agency, private sponsor, ORD, ORO, or other Federal agencies must be informed, as appropriate.
- Once suspended, IRB review and re-approval must occur prior to re-initiation of the research.

[4] All previous IRB membership lists and resumes for IRB members; FWA documentation

[5] Standard Operating Procedures and other related policies

[6] Emergency Use Reports

[7] Research audit results

### 21.1 IRB Relational Database

To facilitate tracking of the steps involved in accepting, reviewing and monitoring research protocols involving human subjects, and evaluation of its activities statistically, the IRB will maintain a computerized database on all research protocols submitted to it for review. The database will be stored on the computer of the IRB Administrator, IRB Coordinators, and other designated Research Office staff. It will be maintained indefinitely.

The database will be monitored monthly and as needed by IRB staff to assure that all continuing review approval dates are current.

### 21.2 IRB Meeting Records

Agendas and minutes of the IRB meetings will be stored in digitized-electronic form on the computer and on hard copy in the office of the IRB Administrator or IRB Coordinators. They will be maintained indefinitely.

### 21.3 IRB Member Records

*Curricula vitae* (CV) of active members of the IRB will be maintained in the files of the IRB, and updates will be requested annually. Each member's membership term status will be monitored and updated, as necessary.

### 21.4 Informational Documents

The IRB will make available to the entire research community of the Minneapolis VA Health Care System copies of various informational documents relevant to human subjects research, by storing them on the reference bookcase in the Research Office.

Federal Regulatory & Advisory Documents

[1] "Protection of Human Research Subjects" Title 45 Code of Federal Regulations Part 46 (45 CFR 46), 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] “Requirements for the Protection of Human Subjects in Research” VHA Handbook 1200.05, July 15, 2003.

[4] “Credentials and Training of Employees Involved in Human Subjects Research” Veterans Health Administration (VHA) Directive 2003-036, July 7, 2003, defines the policy for credentialing and validating the qualifications of employees involved in human subjects research.

[5] "Institutional Review Boards" Title 21 Code of Federal Regulations Part 56 (21 CFR 56), issued by the United States Food & Drug Administration.

[6]"Investigational Drugs" Title 21 Code of Federal Regulations Part 312 (21 CFR 312), issued by the United States Food & Drug Administration).

[7] "Investigational Devices" Title 21 Code of Federal Regulations Part 412 (21 CFR 412), issued by the United States Food & Drug Administration.

[8] "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 Services.

[9] "Protecting Human Research Subjects: Institutional Review Board Guidebook", prepared by the Office for Protection from Research Risks of the National Institutes of Health.

[10] "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).

[11] "The Nuremberg Code", derived from the Trial of Criminals of World War II by the International Military Tribunal (1949).

[12] "World Medical Association Declaration of Helsinki" (adopted in 1964; most recently amended in 2000).

[13] “Standards for Privacy of Individually Identifiable Health Information, Regulation Text”, US Department of Health and Human Services, Office for Civil Rights, 45 CFR Parts 160 and 164 12/28/00 as amended: Part 160, 5/31/02; Parts 160, 164, 8/14/02

[14] “Research”, Office for Civil Rights HIPAA Privacy, 12/3/02

[15] “HIPAA Privacy Rule Compliance Steps”, Office of Research and Development of the VHA, 4/4/03

[16] Food and Drug Administration Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update

Minneapolis VA Health Care System IRB Documents

[1] Assurance: FWA00001480, approved 11/14/01

IRB-A (1) – IRB00000211

IRB-B (2) – IRB00002431

Assurance components:

Twin Ports VA Outpatient Clinic; Superior, WI

St. Paul Community Based Outpatient Clinic (CBOC); Maplewood, MN

Eau Claire CBOC; Chippewa Falls, WI

Rochester CBOC; Rochester, MN

[2] Operational Procedures of the IRB.

[3] List of members of the IRB.

[4] Guidelines for Investigators for Submission of Applications to the IRB.

[5] IRB application forms, including instructions for their preparation and processing.

## 22. OUTREACH PROGRAM FOR HUMAN RESEARCH PARTICIPANTS AND COMMUNITY OUTREACH ACTIVITIES

Several activities and efforts are available to ensure that participants, prospective participants and the community have an understanding of human research at the Minneapolis VA Health Care System.

A. The following informational pieces are available for display and distribution throughout the MVAHCS:

Research Kiosk: Recruitment posters for IRB approved protocols and other informational pieces regarding research participation are posted on a kiosk located in the Flag Atrium near the Cafeteria entrance.

Booklet: “I’m a veteran. Should I participate in research? Here are some things you NEED to know.” Department of Veteran Affairs, Center on Advice and Compliance Help (COACH) www.research.va.gov/programs/PRIDE. The accompanying VCR tapes (in English and Spanish) and DVD also available for viewing in Patient Education.

Brochure: "Volunteering in RESEARCH. Here are some things you need to know" Department of Veterans Affairs, Center on Advice and Compliance Help (COACH) www.research.va.gov/programs/PRIDE. Handouts and posters have also been distributed throughout the institution.

Spanish versions of all the above materials are also available from COACH.

B. Information about participating in research is available online through the Research Service website at http://www.research.va.gov. The following links to other informational resources about research are included:

1. Clinical Trials.gov
2. US Department of Health and Human Services
3. Food and Drug Administration (FDA)
4. National Institutes of Health (NIH)
5. Office of Research Oversight (ORO)
6. The President's Council on Bioethics
7. MyHealth*e*Vet

C. Community News

News releases are prepared by the MVAHCS Public Affairs Office as events surface. These releases of information to the community cover the research activities currently being conducted.

D. VA Research Week and MVAHCS Research Day

The Department of Veteran Affairs celebrates research annually. This gives each local program a chance to share with employees, patients, and the community information about research being conducted at that facility. It also affords the opportunity to share with the community and research partners what the VA has done in research in the past.

Investigators are encouraged to present their research protocols and discuss the numerous opportunities for research at this facility. Investigators and staff have the opportunity to display posters they have submitted and presented at various conferences, as well as other informational pieces about their research.

General posters provided by VA celebrating Research Week along with locally generated information highlighting the current research foci are displayed in lobby areas in the hospital, throughout the research laboratories, and distributed to employees.

The Minneapolis VAHCS conducts an annual Research Day. Medical center staff and the community members are invited to attend formal presentations of the work of several investigators and posters are displayed presenting the research work of the many disciplines and specialties throughout the facility. Public officials are invited to this event, which includes media coverage.

E. Community Outreach

Investigators are encouraged to present information relating to their research at local community and veteran support groups. The directory of Veterans Service Organizations and their contact information is available at: http://www1.va.gov/vso/.

The information presented is general and relates to the investigator's field of research. If the presentation is specific to an active enrolling research protocol, the information presented will be approved by the IRB.

F. Periodic Review

The ACOS/Research or his/her designee will review the activities of Research Day after the event in an effort to improve the next year's efforts. Informally, the research office discusses what worked well, what did not work well, and what can be done to improve for future events. Investigators and attendees are informally surveyed for their added comments and ideas. Research Day typically includes all areas of research. Ideas for future events are welcomed and if practical, implemented.

The ACOS/Research or his/her designee will periodically review all other outreach activities (at least annually, and when new materials become available) and coordinate with the Public Affairs Office to ensure a constant flow of information to the public about the potential of research, at the same time ensuring efforts are maintained to safeguard individuals' participation in research. The goal of Research Service is to keep individuals informed as much as possible through the use of various available media.

As new materials and ideas arise, the outreach program makes appropriate changes under the direction of the organization.

## 23. RESEARCHER CONTACTS WITH VETERANS

VA Researchers have been directed by VACO to restrict their telephone and other contacts with veterans to only those procedures and data elements outlined in IRB-approved protocols. In these contacts, researchers must not request social security numbers.

During the recruitment process, researchers must make initial contacts with veterans in person and/or by letter prior to any telephone contact and provide a telephone number or other means that veterans can use to verify the validity of the study. One source of information about clinical trials that can be shared with the veteran is http://www.clinicaltrials.gov, where VA clinical trials are listed. Informed consent documents need to include information about where and how a veteran could verify the validity of a study and authorized contacts. The investigator may use written documentation that the participant is willing to be contacted by telephone about the study in question or a specific kind of research.

After recruitment and during the follow-up phase, a researcher should begin calls by referring to previous contacts and the information provided on the informed consent document. The scope of the telephone contacts will be limited to topics outlined in the IRB-approved protocols and consent documents.[13]

## 24. REVIEW OF POLICIES AND PROCEDURES

### 24.1 POLICY

These Minneapolis Standard Institutional Review Board Operating Procedures (SOP) must remain current and in compliance with all applicable regulations. To remain current this SOP must be reviewed and periodically updated as needed. The IRB Administrator and the Research Compliance Officer will review these policies and procedures for compliance with the most recent VA and federal regulations. Proposed changes will be presented to the IRB for input. Revisions will be implemented upon review and approval of a majority of each of the IRB committees. The revised version will then be forwarded to the R&D Committee for approval. Notifications of changes and an updated SOP will be distributed to researchers as appropriate.

Other documents used by the IRB for its day-to-day functions, including, but not limited to the IRB Application, Continuing Review of Approved Human Studies Protocol form, Amendment forms, checklists, etc., will also be reviewed and revised as needed.

### 24.2 PROCEDURE

**IRB Chairs, IRB Administrator, IRB Coordinators, and RCO:**
1) Review this SOP at every 2 years, and at other times as needed, as determined by the Chair, the IRB Administrator, or a majority of the IRB members.
2) Document the SOP continuing review and updating.
3) Notify members of changes by memo when implemented.
4) Provide updated copy of SOP to members.

**IRB Members:**
1) Discuss and vote on proposed changes to SOP.

**IRB Administrator and IRB Staff:**
1) Retain file copies of current SOP and archive copies.

**IRB Administrator and RCO:**
Update policies and procedures to comply with the most recent VA and federal regulations.

### 24.3 Applicable Regulations and Guidelines

| | |
|---|---|
| VA Handbook 1200.05 | 45 CFR 46.108 (a) |
| 38 CFR 16.194 (b) (4) | 45 CFR 46.116 (6) |
| 38 CFR 16.108(a) | 21 CFR 56.108(a) |

[13] Memorandum dated July 10, 2006, to VA Research Community, from the Principal Deputy Under Secretary for Health and Chief Research and Development Officer, Department of Veterans Affairs, Subject: Researcher Contacts with Veterans.

38 CFR 16.115 (6) 21 CFR 56.115 (6)
45 CRF 46.103 (b) (4)

**25. MEMORANDUM OF UNDERSTANDING WITH THE UNIVERSITY OF MINNESOTA IRB**
A Memorandum of Understanding has been agreed to by the Minneapolis VA Health Care System and the University of Minnesota concerning jurisdiction and collaboration between the Institutional Review Boards of the two institutions. It sets forth the conduct of human subject research involving investigators who have appointments at one or both of these institutions, or involving the facilities, records or patients of these or other institutions.

**26. QUALITY ASSURANCE/CONTINUING IMPROVEMENT AND PERFORMANCE REVIEW OF HRPP COMPONENTS**
The R&D Committee will review the IRB performance on an annual basis and when necessary take action to improve the performance. Criteria to be used in the evaluation include, but are not limited to, the following:

- The number of new full board studies reviewed by the IRB annually in order to assess whether additional boards are needed due to the volume of work or whether additional expertise is needed in a certain area.
- The findings of the audits conducted by the RCO and others to determine if there are common areas of noncompliance that could be improved upon with education, clarification of policy or development of new policies.
- The performance evaluations of IRB members which consider contribution to discussion, attendance, thoroughness of review, volume of work reviewed, and participation in educational activities.
- The performance evaluations of IRB staff members which consider contribution to achieving the goals of the office, level of service provided to faculty, students and staff, and professional development activities.
- The nature, number and outcome of participant complaints to determine if proper action was taken or if improvements can be made.
- The educational opportunities with IRB members and staff attended throughout the year and whether opportunities were foregone due to lack of funding.
- The principal investigators' (PI) responses to the Investigator Satisfaction Survey.
- The results of past QI/QA projects completed by the IRB and plans for upcoming evaluations.

The performance of IRB members will be evaluated as needed but not less than every 2 years. Elements taken into consideration will include attendance, number of studies reviewed (new and continuing), the ability to apply ethical principles to the review process, the thoroughness and clarity of presentations, contributions to discussions, and participation in educational activities.

## Appendix 1. ELEMENTS OF INFORMED CONSENT FOR SPECIAL PURPOSES

I. RISKS AND/OR DISCOMFORTS

A. Blood Drawing: Approximately _____ tablespoons of blood will be drawn from your arm at each visit. Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of the puncture. There is also a slight possibility of infection.

B. Female Participation: The medication/procedure used in this study may involve risks to an embryo, fetus or nursing infant which are not known at this time. Therefore, if you are pregnant, planning to become pregnant, or nursing, you should not participate in this study. If you are a female of childbearing age, you must be using an approved form of birth control.

C. Radiation: You will be given a prescribed amount of radiation. The amount of radiation is less than what is encountered in daily activity over the course of several years. However, since the effects of radiation add up, it is important for your regular physician to know about your participation in this study and any other studies involving radiation, including x-rays. The researcher will talk with you regarding radiation. Ask if you have any special concerns.

II. OTHER INFORMATION

I understand in unusual cases there is the possibility that some of the material removed from my body may be developed or processed into something that has potential for profit. For example, a group of cells may grow for years in a laboratory. Currently the court rulings are that I have no property right or financial interest in what might be developed. I agree to the removal and use of my tissue for that purpose.

III. SAMPLES STORED FOR FUTURE RESEARCH

During this research study, biologic samples will be stored for future research studies. The samples may be stored for a long time, even after your death. Your samples will be stored at the Minneapolis VAHCS or at a VA-approved tissue bank at another location and will be given a code, (rather than labeled with your name). You will be asked for your permission to have your samples stored on the authorization form.

All future research on your samples will only be done after approval by a special committee (Institutional Review Board) that protects the interests of research participants and after your approval if samples are identified.

IV. INFORMATION TO BE INCLUDED IF YOU ARE USING MRI SCANS FOR RESEARCH PURPOSES

The MRI scanner consists of an enclosed tube in which you will lie down for the research study. Since metallic jewelry, clothing and metal dental material may interfere or even be dangerous with these measurements, you will be required to remove certain metallic jewelry, garments and removable dental material containing metal (including metal dental braces, belts, undergarments having metal hooks, and shoe buckles) to participate in this study. If you have tattoos with metallic dyes, you should not participate in this MRI scan.

You will want to avoid bringing any credit cards, driver's licenses, cassettes, or watches into the scanning area as the magnetic field may damage these articles. MRI measurements can only be made while you lie very still. You will be made as comfortable as possible. Support such as pillows and cushions may be used to aid in making you feel comfortable and in helping you to remain still.

If you have metallic tattoos, you will not be allowed to be scanned.

Most people experience no ill effects from the magnetic field present during the MRI. However, some people do report dizziness, mild nausea, headaches, a sensation of flashing lights, or a metallic taste in the mouth. These symptoms, if present, disappear shortly after leaving the scanner.

## Appendix 2. VA POLICY ON BANKING, STORAGE AND REUSE OF SPECIMENS

Human biological material is not considered to be "banked" (stored) if the specimens are used for only the specific purposes defined in the protocol and are destroyed either when the specific use is completed or at the end of the protocol. Specimens collected and stored for future research purposes are considered "banked" specimens. These specimens must be banked in a VA-sponsored or VA-approved tissue bank. Reuse of specimens must be consistent with the consent under which they were collected, and the reuse must only occur through a VA-approved protocol.

If the specimens are sent to a non-VA institution for testing or use as defined in a VA-approved protocol, a written understanding between the VA investigator and the non-VA institution must specify the use of the specimens as defined in the protocol and that the specimens will be destroyed or returned to the VA once the analysis is completed. A copy of this written understanding must be on file before work may commence.

Once the specific analyses are performed, the remainder of the specimens must be destroyed or returned to the VA for destruction. The remaining quantity may not be retained or stored by the non-VA institution. If the specimens are destroyed at another institution, that institution must certify in writing to the VA Investigator the destruction of the specimen. The investigator will include this information with the final report at study closure to the IRB.

The investigator storing the banked specimens must retain a copy of the original consent, a record of the use of the specimens, and the protocols under which they were used.

Linking of the data generated by the specimen and clinical data should occur within the VA by the VA Investigator whenever possible. When this is not possible, the minimal amount of clinical data necessary should not contain any unique identifiers, if possible. In some cases the IRB may require that a Certificate of Confidentiality be obtained.

If specimens are to be sent outside the MVAHCS for testing or use, the MVAHCS Investigator must obtain approval of a determination of exemption before the work may begin. In addition, the investigator must provide a written letter of assurance between the VA investigator and the non-VA investigator, indicating that samples were collected with appropriate institutional approvals and certifying that confidentiality will be maintained. The outside investigator will provide documentation of IRB approval or documentation of a determination of exemption. Consent forms, or protocols from the outside investigator may also be required. A copy of these documents will be placed in the study file.

<u>Applicable Regulations and Guidelines</u>
VA Directive 200-043; Banking of Human Research Subjects' Specimens Report and Recommendations of the National Bioethics Advisory Committee,1999.
45 CFR 46.110

## Appendix 3. ADDITIONAL ELEMENTS FOR RESEARCH INVOLVING DEPARTMENT OF DEFENSE

**1. The Minneapolis VA Health Care System (MVAHCS) has entered into a formal agreement (Assurance) with the DoD for the conduct of research involving a DoD component. Details of institutional responsibilities are spelled out in that document. In addition, a formal agreement between organizations will be required when multisite research is conducted to specify the roles and responsibilities of each party.**

**2. For research involving any DoD component the following additional requirements are necessary in addition to all other applicable IRB requirements under 45 CFR 46, 21 CFR 50, 56,312, and 812:**

**a. Research requiring consent by a legal authorized representative (LAR): Per DoD Directive 3216.02 section 4.2.1, informed consent may be provided by LARs (LARs) of subjects if:** (1) the subject lacks capacity, due to age, condition, or other reason, to make a decision regarding consent to participate in the research; AND (2) the IRB has determined that the research is intended to be beneficial to the individual subjects. Examples of situations where LARs might provide consent: parents consenting on behalf of children; proxies or family members consenting on behalf of incapacitated subjects.

**b. Independent Medical Monitor for greater-than-minimal risk research Per DoD Directive 3216.02 section 4.4.3, for research involving more than minimal risk (as defined in 32 CFR 219.1 02(i)** - "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 exams'), an independent medical monitor shall be appointed by name.

(1). Medical monitors shall be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate.

(2). Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: subject recruitment; subject enrollment; data collection; or data storage and analysis.

(3) At the discretion of the IRB, the medical monitor may be assigned to discuss research progress with the principal investigator, interview subjects, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the medical monitor's reports.

**c. Additional protections for greater-than-minimal risk research involving subjects who are military personnel:**

Per DoD Directive 3216.02 section 4.4.4, for research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers (NCOs) shall not influence the decisions of their subordinates to participate or not to participate as research subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

**d. Waiver of consent:**

Per 10 U.S.C. 980(b) and DoD Directive 3216.02 section 4.2.2, the requirement to obtain prospective consent may not be waived for research involving a human being as an experimental subject unless such waiver is approved by the head of the DoD component involved in the research. For research not meeting the definition of research involving a human being as an experimental subject, the IRB may waive consent as described in 45 CFR 46116(d).

**e. Limitations on compensation to military personnel using 000 funds:**

The Dual Compensation Act limits compensation for U.S. military personnel participating in research during active duty hours. This prohibition applies to U.S. military personnel paid from either appropriated or non-appropriated funds, or a combination thereof, and includes temporary, part-time and intermittent appointments. U.S. military personnel may not receive compensation for research while on active duty hours. U.S. military personnel may be compensated for research if the participant is involved in the research while not on duty. If the research involves compensation for blood donations, payment cannot exceed $50 per blood draw (24 USC 30).

**f. Surveys and interviews administered to 000 personnel:**

Research involving the administration of surveys to, or interviews of, DoD personnel (military or civilian) may require DoD approval of the surveys or interview questions (for example, see the Navy Survey Policy entitled OPNAV Instruction 5300.8D).

**g. Research involving captured or detained prisoners of war:**

Per DoD Directive 3216.02 section 4.4.2, research involving captured or detained prisoners of war is prohibited. No research involving DoD which includes captured or detained prisoners of war will be initiated at the MVAHCS.

**h. Submission of records to DoD**

DoD may require submission of records to Department of Defense for archiving.

**3. Additional Requirements for Research Involving Department of Navy Component For research involving Department of Navy the following additional requirements are necessary in addition to all other applicable IRB requirements under 45 CFR 46, 21 CFR 50, 56, 312, and 812.**

**a. Surveys and interviews administered to Department of Navy personnel:**

A Privacy Act Statement must be displayed prominently on all Navy personnel surveys without exception regardless of whether personal identifiers are requested. The statement will identify the authority for survey administration (including OPNAV RCS), advise respondents of the purpose and routine uses of the survey, indicate that the survey is voluntary, explain the intended use(s) of the data, and describe measures used to safeguard confidentiality.

**b. Independent scientific review prior to IRB review:**

Per SECNAVINST 3900.39D section 8(c)(6), research involving a Department of the Navy component requires an independent review of research for scientific merit or scholarship prior to IRB review. For clinical research, review by the Scientific Review Committee (SRC) satisfies this requirement. For other greater-than-minimal risk research, an equivalent review by an independent scientific review committee is required (e.g. NIH Peer review), and documentation provided to the IRB prior to review of the research. For non-clinical, minimal risk, and exempt research; review and approval by the division head is satisfactory to meet this requirement.

**c. Compensation for Injury in greater than minimal risk research:**

Per SECNAVINST 3900.390 section 6(5), research involving a Department of the Navy component that is greater than minimal risk shall include an arrangement for emergency treatment and necessary follow-up of any research-related injury. The IRB will determine whether minimal risk research also might include a similar arrangement for research related injury as appropriate.

**d. International research locations:**

Per SECNAVINST 3900.390 section 6(i), research involving human subjects who are not U.S. citizens or 000 personnel, conducted outside the United States, and its territories and possessions, requires permission of the host country. The laws, customs, and practices of the host country and those required by this instruction will be followed. An ethics review by the host country, or local NavaliRB with host country representation, is required. FHCRC investigators conducting international research involving DoD are required to submit documentation of local host country approval to conduct the research and documentation of local ethics review and approval.

**e. Principal Investigators and INDIIDE research:**

Per SECNAVINST 3900.39D section 6(h), research involving DoD may not be sponsored by an investigator who also is the holder of the IND or IDE for which the research is being done.

**4. Additional Requirements for Research Involving Department of Defense - Personnel and Readiness**

For research involving Department of Defense - Personnel and Readiness the following additional requirements are necessary in addition to all other applicable IRB requirements under 45 CFR 46,21 CFR 50,56,312, and 812.

**a. Human subjects training for research personnel:**

Per HA Policy 05-003, for research involving a DoD component which falls under the purview of the Under Secretary of Defense (Personnel and Readiness) all investigators and research staff directly involved in human subjects research shall have Annual training on human subjects protections.

**5. Additional Institutional Reporting Requirements:**

**a. Institutional Reporting Requirements for all DoD Components:**
Consistent with the institutional reporting requirements under DoD Directive 3216.02 section 4.10 all events requiring notification to outside institutions under Policy 2.81RB Reporting Requirements to Institutional and External Officials shall be copied to the Human Research Protection Office at the DoD component involved in the research.

**b. Additional Institutional Reporting Requirements for Department of Navy:**

**The following specific events will be reported to Department of Navy (DoN) Human Research Protection Office for research involving Department of Navy consistent with SECNAVINST 3900.39D section 8(d)(2a-g).**

(1). All suspensions or terminations of previously approved DoN-supported research protocols.
(2). The initiation and results of investigations of alleged non-compliance with human subject protections.
(3). Unanticipated problems involving risks to subjects or others, or serious adverse events in DoN-supported research.
(4). All audits, investigations, or inspections of DoN-supported research protocols.
(5). All audits, investigations, or inspections of the institution's HRPP conducted by outside entities (e.g., the FDA or OHRP).
(6). Significant communication between institutions conducting research and other federal departments and agencies regarding compliance and oversight.
(7). All restrictions, suspensions, or terminations of institutions' assurances.

## Appendix 4. RESEARCH USING HUMAN BIOLOGICAL MATERIAL AND GENETIC RESEARCH

### 1. POLICY

Research involving material that can be linked, directly or indirectly by a code, to personal information concerning the source of the material constitutes research that is subject to federal regulations and IRB approval. Research using unlinked samples may require IRB review, as the IRB needs to ensure that the process by which the material is rendered unidentifiable is appropriate and secure. Research using only unidentified samples may be exempt from IRB review if other criteria for exemption are met. Research using human genetic material or genetic testing poses special concerns and always requires IRB review.

**A. IRB Review Procedures:**
The Committee will consider the application by means of an expedited or full-committee review process. A protocol involving human biological materials may be reviewed through the expedited review process providing that the protocol meets the criteria for such review as described in Section 12. **Genetic research may not be reviewed by expedited review.**

In order to facilitate review of the protocol, the investigator will set forth the following in the Application for IRB Review:

a) A thorough justification of the research design, including a description of procedures used to minimize risk to subjects

b) A full description of the process by which samples will be obtained

c) Any plans to obtain access to medical records of the subjects

d) A full description of the mechanisms that will be used to protect against inadvertent release of confidential information

The investigator should address the relevant aspects of these issues in an appropriate manner in the Informed Consent Document. The sections on use of human biological material and/or use of genetic material on the initial application form must be completed.

The principal risk of such research is primarily psychosocial in nature, resulting from the inappropriate release of information to the subject and third parties. The IRB will consider the research to be of minimal risk if:
a) The study adequately protects the confidentiality of personally identifiable information, and isolates research results from the subject's general medical records, and
b) The study does not involve the inappropriate release of information to third parties, including other researchers and institutions, and
c) If appropriate, the study design incorporates a plan for whether, when and how to reveal findings to the sources or their physicians, with disclosure to the subject permitted only when all the following apply:

i : the findings are scientifically valid and confirmed
ii : the findings have significant implications for the subject's health concerns, and

iii : a course of action to ameliorate or treat these concerns is actually available
Expedited review may be permitted if it is determined that the investigator has adequately addressed these issues.

**B. Informed Consent Requirements:**

Informed consent from the subject is generally required for research involving human biological material and genetic research. In the case of research involving existent identified or coded samples, it may not be feasible to obtain such consent. If in the original consent document subjects anticipated and agreed to further participation in this way, then additional consent is unnecessary. However, documents may not exist or, when they exist, they do not address the possibility of such research. In such cases, unlinking, or new consent may be necessary to conduct the research, unless a waiver of informed consent is possible.

The IRB may waive the requirement for informed consent if the requirements in Section 9.5 are met. The determination of minimal risk must be made, as described above. In determining whether a waiver of consent would adversely affect the rights and welfare of subjects, the IRB will consider whether:

a) The waiver would violate any state or federal statute or customary practice regarding an entitlement to privacy or confidentiality;

b) The study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects; and

c) The study's results might adversely affect the welfare of the subject's community (if applicable). If the study poses more than minimal risk and consent cannot practicably be obtained, the removal of identifiers may be required.

In general, a separate informed consent form should be used. In addition to the required and optional elements of informed consent described in Section 9.5, the informed consent form should contain the following additional elements, if applicable.

a) If research results of the reuse of the specimen will be conveyed to the subject.
b) If the subject will be re-contacted after the original study is completed.
c) If the subject requests, the specimen and all links to the clinical data will be destroyed.
d) That refusal to participate does not affect the subject’s ability to participate in any associated therapeutic research.
e) If the proposed research study involves the potential for psychosocial harm to the subject's family members, relatives or members of the subject's ethnic group
f) If the research has a reasonable likelihood of leading to the development of a commercial product, subjects should be informed that they might not benefit from the product.
g) If the investigator has any commercial interest from which he/she may benefit

financially, directly or indirectly.

h) If the specimen will be used for future research and allow the subject the choice of how the specimen will be used. The consent should provide subjects with a sufficient number of options to help them and fully clarify the present and future uses of their samples. Options might include:
   - refusal to use their samples in any research
   - permitting use of their samples only in unidentified or unlinked form
   - permitting coded or identified use of their samples for the present study only, with further contact required to do further studies
   - permitting coded or identified use of their samples for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies
   - permitting coded use of their samples for any future study

## 2. APPLICABLE REGULATIONS AND GUIDELINES

VA Directive 2000-043; Banking of Human Research Subjects' Specimens Report and Recommendations of the National Bioethics Advisory Committee,1999. 45 CFR 46.110

## 3. PROCEDURE

**Investigator:**
Provides necessary information and documentation

**IRB Members:**
1) Review the information provided and the informed consent form according to the criteria outlined in Section 9.5.
2) Ensure that informed consent documents and methods are in compliance with regulations
3) Make assessments as to risks, benefits and the adequacy of subject protections
4) Make recommendations as to the appropriate IRB action