VA NEBRASKA-WESTERN IOWA
HEALTH CARE SYSTEM

Omaha, NE (636)

SUBCOMMITTEE of HUMAN STUDIES (IRB) STANDARD OPERATING PROCEDURES

for the
PROTECTION of HUMAN RESEARCH SUBJECTS

A MANUAL

for

Principal Investigators

IRB Members

& Staff

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I. DEFINITIONS

A. What is Research and when is it Human Subjects Research?

Research – as defined by VA regulations means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. [38 CFR 16.102(d) and 45 CFR 46.102(d)] The VHA Handbook 1200.05 defines research 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.

- When determining whether an activity is or is not a **systematic investigation**, there are numerous questions that can be asked. These questions include but are not limited to the following:

Is the activity:
1) referred to as a "research" activity
2) designed to address a research intent?
3) using an organized method (e.g., methodical, purposeful, carried on by using step-by-step procedures, or characterized by the use of logically and carefully planned succession of steps)?
4) designed to answer a question or test a hypothesis that addresses a Research intent even though it is not specifically stated?

- When determining whether an activity is or is not designed to develop or contribute to **generalizable knowledge**, there are numerous questions that can be asked. These questions include but are not limited to the following:

Is the activity:
1) designed to be used for operational purposes only?
2) applied to populations or settings different from the ones from which it was collected?
3) going to be published or presented? If so, what kind of publications will the manuscripts be submitted to and/or what is the type of conference?

Research – as defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

! "Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act"

means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

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

! "Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]"

Research involving human subjects - means any activity that either:

- Meets the VA definition of "research" and involves "human subjects" as defined by VA; or
- Meets the FDA definition of "research" and involves "human subjects" as defined by FDA.

Human Subject – as defined by VA regulations means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. [38 CFR 16.102(f) and 45 CFR 46.102(f)]

- "Intervention" as defined by VA regulations means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(f)]
- "Interaction" as defined by VA regulations means communication or interpersonal contact between investigator and subject. [45 CFR 46.102(f)]
- "Private information" as defined by VA regulations means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). [45 CFR 46.102(f)]
- "Identifiable information" as defined by VA means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

The definition provided in the Common Rule includes investigators, technicians and others assisting investigators when they serve in a "subject" role by being observed, manipulated, or sampled. As required by 38 CFR 16.102(f) an intervention includes all physical procedures by which data are gathered and all physical, psychological or environmental manipulations that are performed for research purposes. [VHA Handbook 1200.05]

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

B. When does research with human specimens (Reference Appendix QQ), cells, cell lines, or data involve human subjects?

In order for research with human specimens, cells, cell lines, or data to involve human subjects, the specimens, cells, or data:

1. Must be or must have been obtained from individuals who are alive; AND
2. Must be or must have been obtained by an investigator conducting research; AND

The investigator EITHER:

1. Must be obtaining or must have obtained specimens, cells, or data through interaction or intervention with living individuals; OR
2. Must be obtaining or have obtained individually identifiable private information.

IF providers of **coded** human specimens, cells, cell lines or data:

1. Obtained or will obtain the specimens or data, AND
2. Can link the specimens or data to living individuals, AND 3) Will also collaborate on other activities related to the conduct of a proposed research project with the investigators who obtain the specimens or data;

THEN **both** the providers and recipients will be considered to be involved in the conduct of the research and are conducting human subjects research.

C. What is FDA-regulated "Human Subject Research?"

1. Activity is "research" as defined by FDA:
   a. The activity involves the use of a drug, other than the use of a marketed drug in the course of medical practice, where "drug" means:
      1) An article 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. **OR**
      2) An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals. **OR**
      3) An article (other than food) intended to affect the structure or any function of the body of humans or other animals. **OR**
      4) An article intended for use as a component of any article specified in the above items
   b. The activity will involve the evaluation of the safety or efficacy of a medical device where "medical device" means:
      1)Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them. **OR**
      2) Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals. **OR**
      3) Intended to affect the structure or any function of the body of humans or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of humans or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes
   c. Data from the activity will be submitted to, or held for inspection by, the FDA.

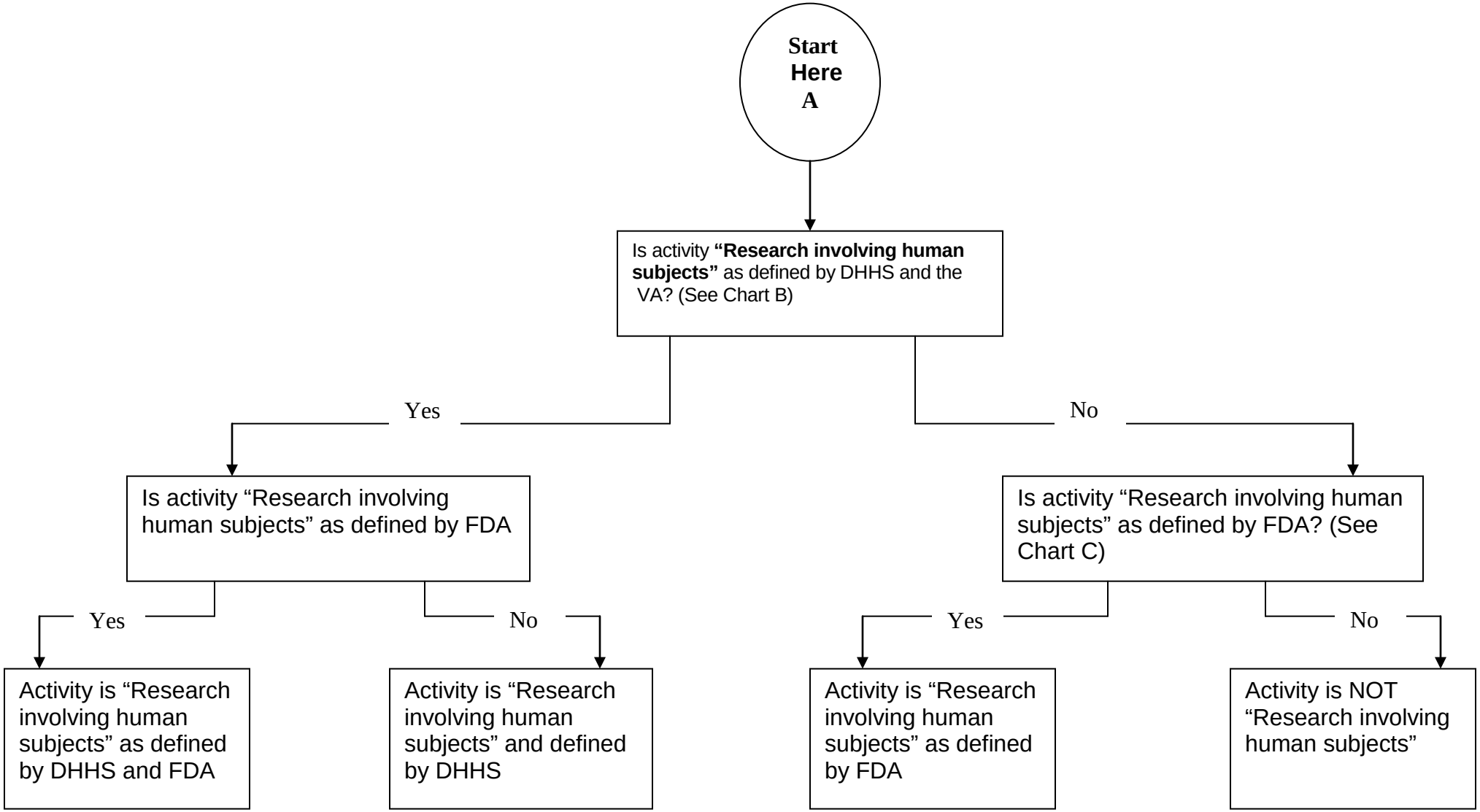
2. Research involves “human subjects” as defined as FDA.
    a. The test article will be used on one or more humans; **OR**
    b. A medical device will be used on human specimens; **OR**

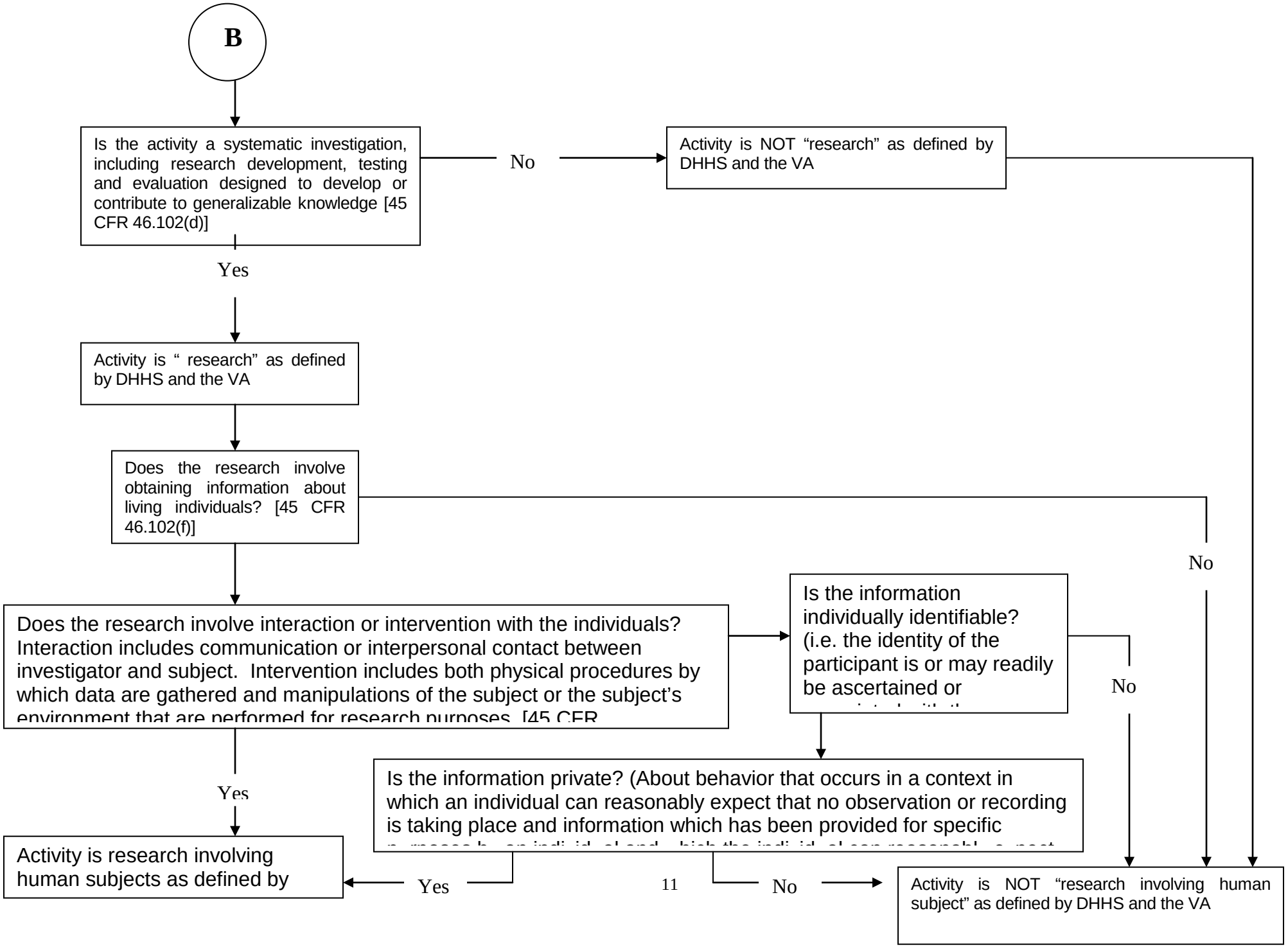
Humans on whom a test article will not be used who will serve as controls for one or more humans on whom a test article will be used.

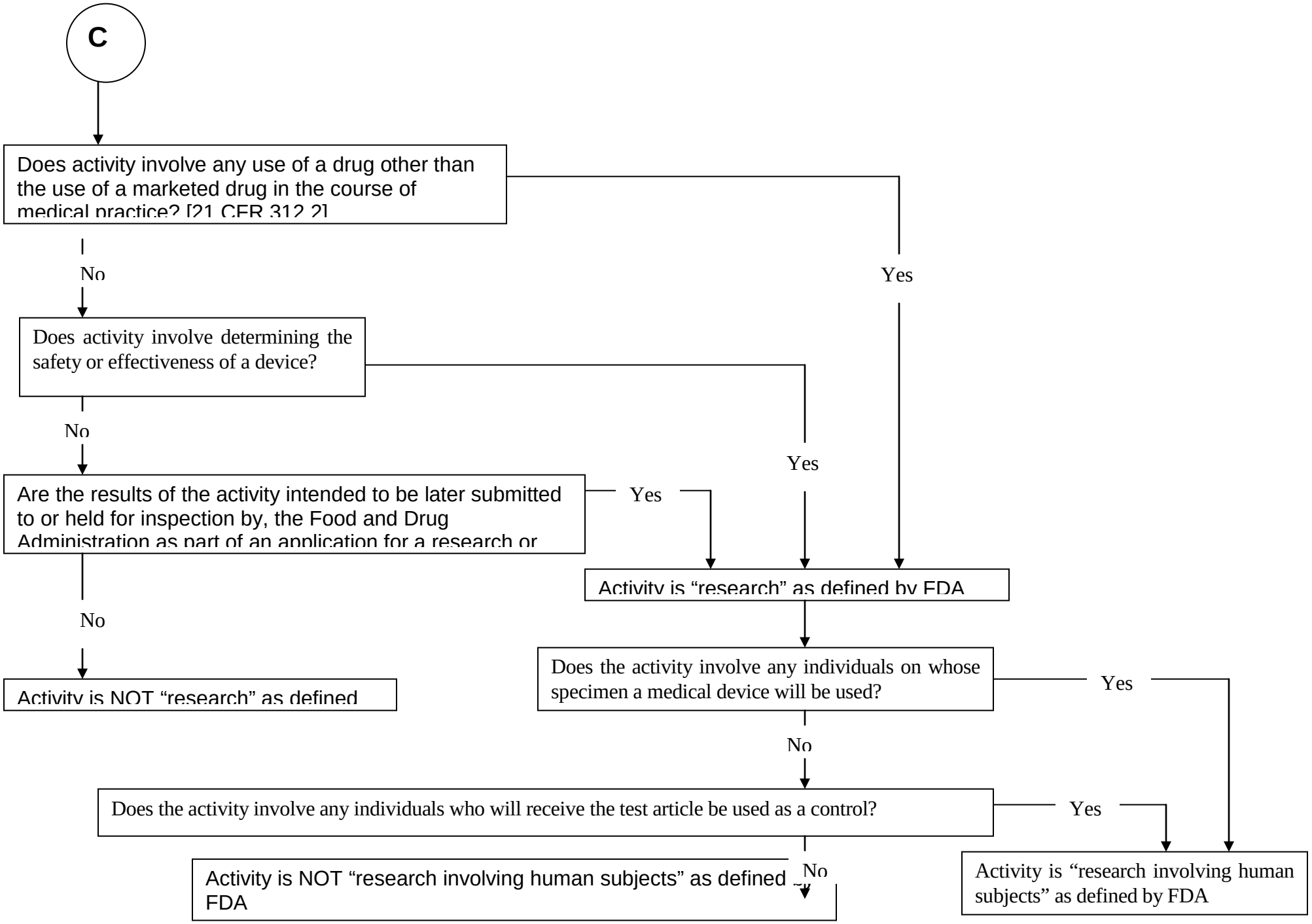
D. When is research involving human subjects eligible for exemption?

Exempt research is research determined by the IRB to involve human subjects only in one or more of certain minimal risk categories (38CFR 16.101(b). The exemptions for categories (1)-(5) are not applicable to research governed by FDA regulations (21CFR50.20). Following determination of exempt status by the IRB, the proposal is reviewed by the R&D Committee prior to initiation and included in their annual continuing review of research projects. (See VIII. IRB Review Process, Paragraph L)

E. The following charts A, B and C should be referenced in determining whether something is human subjects research under the VA, DHHS and FDA definitions when preparing a protocol submission to the IRB.


Start Here A
Is activity **"Research involving human subjects"** as defined by DHHS and the VA? (See Chart B)
Yes
No
Is activity "Research involving human subjects" as defined by FDA
Is activity "Research involving human subjects" as defined by FDA? (See Chart C)
Yes
No
Yes
No
Activity is "Research involving human subjects" as defined by DHHS and FDA
Activity is "Research involving human subjects" and defined by DHHS
Activity is "Research involving human subjects" as defined by FDA
Activity is NOT "Research involving human subjects"


B
Is the activity a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge [45 CFR 46.102(d)]
No
Activity is NOT "research" as defined by DHHS and the VA
Yes
Activity is " research" as defined by DHHS and the VA
Does the research involve obtaining information about living individuals? [45 CFR 46.102(f)]
No
Does the research involve interaction or intervention with the individuals? Interaction includes communication or interpersonal contact between investigator and subject. Intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's
Is the information individually identifiable? (i.e. the identity of the participant is or may readily be ascertained or
No
Yes
Is the information private? (About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place and information which has been provided for specific
Activity is research involving human subjects as defined by
Yes
No
Activity is NOT "research involving human subject" as defined by DHHS and the VA


C
Does activity involve any use of a drug other than the use of a marketed drug in the course of medical practice? [21 CFR 312.2]
Yes
No
Does activity involve determining the safety or effectiveness of a device?
Yes
No
Are the results of the activity intended to be later submitted to or held for inspection by, the Food and Drug Administration as part of an application for a research or
Yes
No
Activity is "research" as defined by FDA
Activity is NOT "research" as defined
Does the activity involve any individuals on whose specimen a medical device will be used?
Yes
No
Does the activity involve any individuals who will receive the test article be used as a control?
Yes
No
Activity is NOT "research involving human subjects" as defined by FDA
Activity is "research involving human subjects" as defined by FDA

F. Determination to Submit to the IRB

1. When to ask: When preparing a protocol for submission to the IRB, the IRB Coordinator may be contacted for assistance with this determination after reviewing the definitions and the decision charts. The IRB Chair may be consulted as well.

2. What Information to Submit: The definitions and decision charts are reviewed by the Principal Investigator in communication with the IRB coordinator to determine if the proposed research is human research under VA, DHHS and/or FDA regulations. If the proposal is already prepared, submit it to the IRB.

3. Persons with Authority to make a determination: The IRB Chair/Vice Chair has the authority to make a determination on behalf of the IRB whether an activity represents human research.

4. Notification of Decision: Following this determination, communication is provided in writing to the Principal Investigator. If the proposal meets the definition of human research, it must be submitted to the IRB and other applicable committees for review and approval prior to initiation.

G. General Definitions

Ad Hoc Review – a review conducted by a consultant who serves as an ad hoc reviewer with appropriate expertise and is not a voting member of the committee,

Adverse Event (AE) – Any untoward occurrence (physical, psychological, social or economic) in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Assent – Agreement by an individual not competent to give legally valid informed consent to participate in research (e.g., a child).

Assurance – A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with regulations governing the protection of human subjects in research. Assurance is the word used in the Federal Policy (Common Rule).

Belmont Report – A statement of basic ethical principles governing research involving human subjects issued in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Children – are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. (VHA 1200.05) Legal age of majority is nineteen (19) in the State of Nebraska.

Clinical investigation means 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 Food and Drug

Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. (21CFR50.3c)

Certificate of Confidentiality - A Certificate of Confidentiality (CoC) helps researchers protect the privacy of human research participants enrolled in biomedical, behavioral, clinical and other forms of sensitive research. Certificates protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a research participant.

Cognitive Impairment – Some disorder that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished.

Compensation – Refers to payment or other benefits that will be given to subjects who volunteer to participate in research protocols.

Data and Safety Monitoring Board (DSMB) – A group of people who monitor a clinical trial for adverse events and other trends. The Data and Safety Monitoring Board looks for any information that might warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

Declaration of Helsinki – A code of ethics for clinical research approved by the World Medical Association. It has been widely adopted by medical associations worldwide and has been revised numerous times.

DHHS – Acronym for U.S. Department of Health and Human Services.

Exemptions – The Federal Policy for the Protection of Human Subjects contains six exemptions. (38CFR16.101(b)). These exemptions must be requested and granted by the IRB. FDA regulations contain an exemption from IRB review requirements for the emergency use of a test article [21 CFR 56.104(c)] and for certain taste and food quality evaluations and consumer acceptance studies [21 CFR 56.104(d)].

FDA – Acronym for the Food and Drug Administration, a component of DHHS.

HRPP - Human Research Protection Program.

Institutional Review Board (IRB) – An IRB is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with the Common Rule, DHHSs regulations and FDA regulations the IRB has responsibility for approving, requiring modification in (to secure approval), or disapproving research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common Rule, DHHS regulations and FDA regulations, or its own findings. Within VHA, an IRB is a subcommittee of the Research & Development Committee.

Institutional Official (IO) – The individual at an institution who is responsible for ensuring the

effective administration and implementation of the institution's system for the protection of human subjects. The Medical Center Director serves in this capacity at the NWIHCS.

Interaction - Includes communication or interpersonal contact between investigator and participant [38 CFR 16.102(f) (2) and 45 CFR 46 102(f) (2).

Intervention – Includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes [38 CFR 16.102(f) (2) and 45 CFR 46.102(f) (2)].

Investigator – An investigator is an individual under the direction of the Principal Investigator (PI) who is involved is some or all aspects of the research project, including the: design of the study, conduct of the study, analysis and interpretation of the collected data, and writing of resulting manuscripts. An investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970. The FDA considers an investigator and a PI to be synonymous. (VHA 1200.05) The individual who actually conducts a research investigation [21 CFR 50.3(d) and 56.102(h)].

Licensed Independent Practitioners - Individuals permitted by law and the facility to provide patient care services independently, i.e., without supervision or direction, within the scope of the individual's license and in accordance with individually granted clinical privileges

Minimal Risk (Federal Policy, DHHS Subpart A, and FDA) – The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.102(i); and, 21 CFR 50.3(k) and 56.102(j)].

Minimal Risk (DHHS Subpart C - prisoners) – The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons [45 CFR 46. 303(d)].

Monitoring – A mechanism for keeping track of any part of the research process: data analysis, recruitment of subjects, informed consent process, to ensure its compliance with Institutional Review Board dictates and the federal regulations.

National Bioethics Advisory Commission (NBAC) – A Presidential appointed commission that issues reports and makes recommendations relating to the protection of human subjects in research.

NIH – Acronym for National Institutes of Health.

Non-Affiliated Member – Member of an IRB who has no ties (and whose immediate family members have no ties) to the parent institution, its staff, or faculty. This individual is usually from the local community [45 CFR 46.107(d); and 21 CFR 56.107(d)].

Non-Scientist – Member of an IRB who does not have a scientific background, but may be affiliated with the institution [45 CFR 46.107(c); and, 21 CFR 56.107(c)]. At least one non-

scientist member must be present at convened meetings to approve research [45 CFR 46.108(b); and, 21 CFR 46.108(c)].

Nuremberg Code – A code of research ethics developed during the trials of Nazi war criminals following World War II and widely recognized as a standard during the 1950s and 1960s for protecting human subjects.

Office for Human Research Protections (OHRP) – An office within the DHHS that was created in June of 2000. OHRP is responsible for the implementation of the DHHS regulations [45 CFR Part 46] governing the protection of human subjects in research.

Office for Protection from Research Risks (OPRR) – Until June 2000, this office was within the DHHS as part of the National Institutes of Health (NIH). OPRR was responsible for the implementation of the DHHS regulations [45 CFR Part 46] governing research involving human subjects. The Office for Human Research Protections supercedes OPRR.

Phase 1,2,3,4, Clinical Trials – Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to post-marketing studies (Phase 4).

Phase 1 Clinical Trials – Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; however, where the drug is intended for use in patients with a particular disease, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness. They are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. Typically, Phase 1 investigations involve anywhere from 20-80 subjects [21 CFR 312.21(a)].

Phase 2 Clinical Trials – Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects [21 CFR 312.21(d)].

Phase 3 Clinical Trials – Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and

effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand subjects [21 CFR 312.21(c)].

Phase 4 Clinical Trials – The FDA, when it gives market approval, may seek an agreement from the sponsor to conduct certain post-marketing studies to ascertain additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR 312.85].

Public Health Service (PHS) – A division within the DHHS. PHS agencies include the National Institutes of Health, Centers for Disease Control, the Indian Health Service, and the Substance Abuse and Mental Health Services Administration.

Placebo – In biomedical research, a chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than the actual power of a drug. In social and behavioral research, a condition that mimics the experimental context but does not include the experimental manipulation under study. As in biomedical research, the control condition is used to confirm that observed effects are the result of the experimental manipulation rather than the research context itself.

Principal Investigator (PI) – Within VA, a PI is an individual who conducts a research investigation, i.e., under whose immediate direction research is conducted, or in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (VHA 1200.05) The FDA considers a PI and an investigator to be synonymous.

Public Responsibility in Medicine and Research (PRIM&R) – A non-profit organization that organizes conferences, workshops, and other activities to further the protection of human subjects in research.

Prisoner – An individual involuntarily confined or detained in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution; or (4) incarcerated in a penal institution [45 CFR 46.303(c)].

Protocol – The formal design or plan of an experiment or research activity. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

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

SAE - Serious Adverse Event [defined later in this SOP]

Sponsor – Typically refers to the entity that initiates a clinical investigation but does not actually conduct the investigation [21 CFR 50.3(e) and 56.102(j)].

Sponsor-Investigator – An individual who both initiates and actually conducts a clinical investigation [21 CFR 50.3(f) and 56.102(k)].

UAE – Unexpected Adverse Event [defined later in this SOP]

II. ETHICAL PRINCIPLES

The VA Nebraska-Western Iowa Health Care System is guided by the ethical principles regarding all research involving humans as set forth in the Declaration of Helsinki, the Nuremberg Code and the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research often referred to as the "Belmont Report."

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The three basic principles contained in The Belmont Report are central to the ethics of research involving human subjects and guide the IRB in assuring that the rights and welfare of subjects are protected:

- **Respect** for persons is applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- **Beneficence** is applied so that possible benefits are maximized and possible risks are minimized to the persons involved.
- **Justice** is evidenced in the equitable selection of subjects.

All research activity associated with the VA Nebraska-Western Iowa Health Care System will be obligated by this institution to conform to ethical principles which are at least equivalent to those of this institution, as cited in the previous paragraph or as may be determined by the Department of Veterans Affairs Secretary or the Department of Health and Human Services (DHHS) Secretary. This includes all research performed by any individual associated with the VA Nebraska-Western Iowa Health Care System whether pertinent at this institution or other performance sites, domestic or foreign.

Before any human subject is involved in research in exempt research or non-exempt research relationship to this institution, an Institutional Review Board (IRB) will give proper consideration to:

- the risks to the subjects,
- the anticipated benefits to the subjects and others,
- the importance of the knowledge that may reasonably be expected to result, and
- the informed consent process to be employed.

III. REGULATORY MANDATE TO PROTECT HUMAN SUBJECTS

References throughout this guidance manual include but are not limited to:

- **38 CFR 16** (i.e., Title 38 Code of Federal Regulations Part 16: Protection of Human Subjects) applies to research involving human subjects conducted by the Department of Veterans Affairs

- **45 CFR 46** applies to research involving human subjects conducted or supported by the Department of Health and Human Services (DHHS) Subpart A (56 FR 29003)

- **21 CFR 50 and 21 CFR 56** which apply to all research involving products regulated by the Food and Drug Administration (FDA), including research and marketing permits for drugs, biological products, or mechanical devices for human use, food and color additives, or electronic products. Federal funds do not need to be involved

- Department of Veterans Affairs **VHA Handbook 1200.05** available at website http://www.research.va.gov/default.cfm

- The **Federal Wide Assurance (FWA00000556)** signed by the Institutional Official for the Nebraska-Western Iowa Health Care System assures that all of its pertinent activities related to human subject research will comply with the DHHS and with all requirements of Department of Veterans Affairs regulations at 38 CFR. 16, Office of Research Oversight (ORO), and Office of Research & Development (ORD) issued manuals, handbooks and other relevant authorized directives.

When research involving products regulated by the FDA is funded by DHHS, both DHHS and FDA regulations apply, and the requirements of both sets of regulations must be met.

IV. THE HRPP STRUCTURE

A. Institutional Official Responsibilities

The Medical Center Director is the Institutional Official (IO) who is responsible for the Research & Development (R&D) program, advised and assisted by the R&D Committee. The IO is responsible for ensuring that the human subjects research program has the resources and support necessary to comply with all federal regulations and guidelines that govern human subject research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances and assumes the obligations of the Assurance. The IO is the point of contact for correspondence addressing human subjects research with OHRP, FDA, ORO and VHA Headquarters. The Director must ensure effective coordination by and among the various individuals, offices, committees and subcommittees that comprise the HRPP. Annually, the Director distributes a memorandum within the Medical Center describing guidelines to conduct human research. Authority and responsibility for the oversight of the Human Research Protection Program resides with the Institutional Official.

The Institutional Official also is responsible for appointing one or more research compliance officers to conduct annual research consent document audits and triennial regulatory audits, and to assist in facility assessments of regulatory compliance.

- Unless a waiver for a part-time research compliance officer is approved by the under secretary for health, each VA research facility must designate at least on full-time research compliance officer.
- The medical center director must report any appointment, resignation, or change in status of the facility research compliance officer to ORO VHA Central Office, with a copy to the relevant ORO research officer, within 10 business days after the appointment, resignation, or change takes effect.
- The Medical Center Director is responsible for appointing the Information Security Officer (ISO) and Privacy Officer (PO) to the IRB or R&D Committee. At the NWIHCS these individuals are appointed to the IRB.

The IO is responsible for reporting in writing within five business days after being notified of a research problem or event (including serious and continuing non-compliance, unanticipated problems involving risks to subjects or others, and suspensions and terminations) for which such reporting is required under handbook 1058.01.

- The medical center director's written report is required regardless of whether disposition of the event has been resolved at the time of the report.
- Follow-up reports detailing any additional findings and appropriate remedial actions must be provided to the relevant ORO office at intervals and in a manner specified by that office.

The IO must provide a copy of any ORO correspondence reports regarding the research program to the associate chief of staff for research, Research and Development committee, any relevant research review committee(s), and the research compliance officer in a timely fashion.

The facility director must report the following research events to ORO Central Office, with a simultaneous copy to the appropriate ORO research officer, as indicated in the following:

- IRB Changes. The proposed addition or removal of the IRB(s) of record designated in a facility's FWA must be submitted to ORO Central Office prior to submission to ORHP and in accordance with VHA Handbook 1058.03. Any change in IRB membership rosters must

be reported to ORO Central Office in accordance with VHA Handbook 1058.03

- Substantive MOU Changes. Any substantive change in an MOU with an affiliate institution or other entity related to the designation of IRB(s) or other human research protection arrangements must be reported to ORO Central Office within five business days.
- Accreditation Problems. Failure of the VA facility to achieve the accreditation status required by ORD for human research protections, and change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's human research protection program must be reported to ORO Central Office within five working days.

B. Jurisdiction of the IRB

In accordance with federal and institutional regulations, any research conducted by or under the direction of any employee, faculty, staff, student, or agent of the NWIHCS in connection with his/her institutional responsibilities; uses any VA property or facilities; uses any non-public data maintained by the VA facility; and/or receives a direct award to conduct the research, must seek approval. In all these situations, the VA facility is considered engaged in research and, therefore, the research is subject to its review and oversight. All human subject research and other activities which in part involve human subject research regardless of sponsorship (funded and non-funded) is subject to oversight by the NWIHCS human research protection program. Research that has been approved by the IRB is subject to review and disapproval by the R&D Committee and the Institutional Official, however those officials may NOT approve research that has not been approved by the IRB. IRB members should be free from coercion or undue influence. A member, who feels they are experiencing coercion or undue influence, should address this issue with the IRB Chair, RCO, R&D committee Chair or ACOS/Research. Corrective action will be taken as outlined in the process of filing a complaint in Memorandum 151-10 Research Service Policies and Procedures for Complaints and Allegations of Non-Compliance. Review by other committees (e.g., Safety, Radiation Safety) may be required to grant final approval.

C. IRB Membership

The VA Nebraska-Western Iowa Health Care System Subcommittee of Human Studies follows the following guidelines:

- The VA Nebraska-Western Iowa Health Care System prohibits the use of a commercial IRB for research.

- Each IRB must have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

- The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

- In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional;

conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

- When the IRB reviews research that involves a vulnerable category of subjects, such as pregnant women, handicapped or mentally disabled persons and persons with impaired decision-making capacity, the IRB coordinator with assistance from the IRB chair will confirm that a member of the IRB who is knowledgeable about and experienced in working with these subjects is assigned, as a reviewer of the protocol and is present for the review. If an appropriate member of the IRB is not available to review this type of research or any other research where particular expertise is needed, the IRB Chair will identify an ad hoc or consultant reviewer with expertise in the areas for assistance with the review.

- Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender.

- No IRB may consist entirely of members of one profession.

- Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas; a non-scientist always attends the meeting.

- Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

- An IRB may, at its discretion, invite ad hoc reviewers and/or consultants with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. These individuals are subject to the same conflict of interest policies as IRB members.

- All IRB members (regular and alternate) are appointed by the Medical Center Director in writing. The IRB roster is updated annually for the calendar year. Members may serve 3-year terms and may be re-appointed indefinitely. Members are responsible for ensuring that the rights and welfare of research subjects are protected. Members vote to approve, require modifications in, disapprove, or table research submitted to the IRB. Members are expected to attend IRB meetings on a regular basis, serve as primary reviewers for research within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings. Members are also expected to conduct expedited reviews on behalf of the IRB when so designated.

- At least annually, the Research Service Executive Team (ACOS/R, Deputy ACOS/R, AO and Chair of R&D committee) evaluates the performance of and provides feedback to IRB members including IRB Chair as a part of the process of recommending continued membership on the committee. A committee membership review and evaluation tool will be utilized for the annual review process and this tool will be reviewed with all committee members at a convened meeting during the year to explain its use and address any questions. The tool provides each member with information specific to their past attendance, education requirements and workload statistics. The tool requires members to do a self assessment of their annual performance and to provide feedback regarding the Committee Chair's

performance. All information will be reviewed by the Executive Team and communicated back to members by the end of their annual term. The Review and Evaluation tool can be accessed on the internet forms bank.

- The Chairperson and Vice-Chairperson are appointed by the Medical Center Director and must have a VA appointment. The Chairpersons are nominated by the IRB through the ACOS/R&D with concurrence by the R&D Committee. The Chair is appointed for a period of one year and may be reappointed indefinitely. In addition to the responsibilities of IRB membership, the Chairperson has primary responsibility for conducting IRB meetings according to regulatory requirements. The IRB Chairperson works with IRB members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are adequately protected. The Chairperson/Vice Chairperson or designee signs all official IRB correspondence.

- The ISO and PO are appointed by the Medical Center Director.

- The appointment and function of alternate members is the same as that for regular IRB members, and the alternate's qualifications are comparable to those of the primary member. The IRB roster identifies the primary member(s) for whom each alternate member may substitute. When alternates substitute for a primary member, the alternate member will receive and review the same materials that the primary member received or would have received. The IRB minutes will document when an alternate member replaces a primary member.

- The Research Compliance Officer (RCO) serves as a non-voting consultant to the facility's IRB. The RCO regularly attends the IRB meetings in a von-voting capacity at the NWIHCS.

- The ACOS/R&D, Deputy ACOS/R&D, AO and IRB Coordinator are non-voting members on the IRB.

D. HRPP Staff

The Research Service Administrative Officer provides support to the Subcommittee of Human Studies and Research and Development Committee. Responsibilities are:

- Directing and overseeing all IRB support functions and operations
- Training, supervising, and evaluating HRPP support staff
- Developing and implementing procedures to effect efficient document flow and maintenance of all IRB records
- Administrative liaison between the IRB and R&D Committee

The HRPP staff is composed of the IRB Coordinator, R&D Coordinator, and is assisted by other staff trained in human subject protection. The HRPP staff's responsibilities include:

- Maintaining the official roster of IRB members
- Scheduling IRB meetings
- Using a checklist, verify that all required documents have been received; if any items are missing, contact the PI

- Log protocol into database
- Distribute copies of protocols to IRB members with the agenda; assign primary reviewer(s) who act as presenters at the IRB meeting
- Process continuing review requests
- Compiling the minutes of IRB meetings in compliance with regulatory requirements
- Promptly reporting changes in IRB membership to the Office for Human Research Protections (OHRP) and to VA Office of Research Oversight (ORO)
- Maintaining all IRB documentation and records in files according to regulatory requirements
- Ensuring that all IRB records are secured and properly archived
- Facilitating communication between investigators and the IRB
- Maintaining a computerized database for tracking purposes
- Serving as a resource for investigators on general regulatory information, and providing guidance about forms and submission procedures
- Training research investigators and staff; tracking education and credentialing
- Maintaining training documentation and reference materials related to human subject protection requirements
- Maintaining and updating the IRB investigators' application and IRB forms
- Drafting reports and correspondence to research investigators on behalf of the IRB regarding the status of the research,
- Processing unanticipated problems involving risk to subjects/adverse event reports and modifications to ongoing research,
- Drafting reports and correspondence directed to research facility officials, federal officials, and others on behalf of the IRB or IRB Chairperson
- Keeping manuals and Standard Operating Procedures up to date
- Coordinate and assist during regulatory inspections and site visits
- Attending VA and national human subject protection training

E. Principal Investigator Responsibilities

It is the responsibility of the Principal Investigator (PI) to initiate the application and be involved in all aspects of the research proposal including the design of the study, conduct of the study, analysis and interpretation of the collected data and writing of resulting manuscripts. It is appropriate for the PI and persons in Research to promote the involvement of community members on the local, regional or national level, when appropriate, in the design and implementation of research and the dissemination of results. At the national level, Veterans are involved in various meetings and activities including the National Research Advisory Committee (NRAC). Locally, we work with our affiliates on studies that are conducted at both locations involving our VA patients and their community based participants. Veterans at our medical center are encouraged to provide comments and feedback about the research they are participating in and information about how to provide that feedback is provided to them.

The PI must have a VA NWIHCS staff appointment: 1) compensated by the VA, 2) works under a WOC appointment initiated by his/her clinical service, or 3) be an employee assigned to the VA through the Intergovernmental Personnel Act of 1970. The PI must be credentialed and complete the human subject protection training as directed by the Institutional Official.

Research conducted by students and other trainees, which includes residents and fellows, must have a VA investigator sufficiently experienced in the area of the trainee's research serve as the PI and is responsible for oversight of the research and the trainee. Only students and trainees, including VA employees, from schools with an academic affiliation agreement consistent with current VHA policy, may serve as research team members.

The PI must provide the IRB with all relevant forms in the protocol application to obtain approval to conduct human research. The PI must be knowledgeable of the required consent form elements, consent form process, and elements of review the SHS uses to evaluate the study. Reporting of protocol and consent form changes, serious and/or unexpected adverse events, complete and timely continuing review and proper documentation are all essential responsibilities of the Principal Investigator. Research protocols that require skills beyond those held by the PI must be modified to meet the PI's skills or have one or more additional qualified staff/faculty as Co-Investigator(s).

The PI must be knowledgeable of reporting requirements which includes amendments to an ongoing study and reporting problems promptly to the IRB. Timely continuing review and proper documentation are all essential responsibilities of the Principal Investigator.
To ensure the continuation of a research study in the event of the absence of the PI's short-term or long-term, an amendment would be required to change the study personnel. The qualifications of the investigator to continue the study will be evaluated by the IRB. Human subject protection training and verification of credentials are necessary to assume responsibility of the study ensuring the protection of every research subject, which must minimize risks to subjects while maximizing research benefits.

The Investigator's research records must maintain written documentation that the protocol is being implemented as approved by the IRB, R&D Committee and ACOS/R&D, and other applicable committees. These research records include the following when relevant to the study:

- IRB-approved versions of the protocol and amendments,
- Case report forms and supporting data including, but not limited to signed and dated informed consent forms and HIPAA authorizations.
- Documentation on each subject including, but not limited to: informed consent, interactions with subjects by telephone or in person, observations, interventions and other data relevant to the research study which includes but is not limited to progress notes, research study forms, surveys and questionnaires, reports of adverse events, data analyses, other reports such as abstracts and other publications.
- Correspondence (i.e., with funding source or sponsor, applicable oversight entities such as IRB, R&D Committee, ORO and FDA).
- Master list of all subjects for whom informed consent has been obtained in the study unless this requirement has been waived by the IRB.

1. Investigators must not add a subject's name to the master list of all subjects until <u>after</u>:
   (a) Informed consent has been obtained from that subject, <u>and</u>
   (b) When appropriate, informed consent has been documented using an IRB-approved informed consent form.
2. IRB may waive the requirement for the investigator to maintain a master list for a given study if <u>both</u> of the following conditions are met:
   (a) There is a waiver of documentation of informed consent, <u>and</u>
   (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.

3. 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.

Documents must be maintained so that they may be audited by the facility Research Compliance Officer or other entities according to applicable sponsor, local, VA and other Federal requirements.

An accounting of disclosure must be maintained for each and every disclosure of information from this study to a non-VA entity. The original documentation of this accounting of disclosures is maintained in the Research Administrative Office.

F. Sponsor

The sponsor is the person or entity who takes responsibility for, or initiates a clinical investigation. The Omaha VA medical Center seeks written assurances from sponsors via the CT CRADA that research is conducted according to applicable laws and regulations, good clinical practices and ethical standards. In agreements with sponsors, the VHA guidelines for Clinical Trial Cooperative Research and Development Agreements will be followed, including the explicit language regarding the protection of human subjects, dissemination of knowledge and health care to injured research subjects. The Human Research protection Program and all VA statutes, regulations and policies at the Omaha VAMC will apply to sponsored research, as well as, all research conducted at the facility. Compliance activities are conducted in accordance with VA requirements. The IRB acknowledges the sponsor's responsibility for the CRADA and that NEBRA serves as the Administrator. Regional counsel reviews all CRADAs and contracts.

V. HUMAN SUBJECT PROTECTION TRAINING

The VA Nebraska-Western Iowa Health Care System is committed to the ethical principles of the Belmont Report in its human subject protection program. The Institutional Official, IRB members, R&D Committee members, Principal Investigators, Research Team Members and HRPP staff must undergo human subject protection training. This training requirement also applies to Investigators and ResearchTeam Members conducting studies involving human subjects that are determined exempt from IRB review under one or more of the categories in 38 CFR46.101(b). The CITI course, which consists of web-based human subject protection and Good Clinical Practice education modules with associated testing, is required by the NWIHCS to participate in human subjects research. CITI is also being used as the training tool for both of our affiliates, the Creighton University School of Medicine and the University of Nebraska Medical Center. The VA-required modules as outlined on the website, www.citiprogram.org, must be completed with a passing score of 80% and a certificate of completion should be maintained by the individual with a copy provided to the Principal Investigator of the study.

Continuing education is required is required within 730 days after the previous training. All principal investigators, research team members, IRB and R&D committee members and research staff involved with human subject protocols must complete the web-based CITI CE course every two years (within 730 days).

The training requirements listed above must be met before a protocol will be initiated, continued review approval granted, or an applicable amendment approved. The IRB Coordinator verifies the completion of the education requirements.

IRB members, staff and principal investigators have the opportunity to attend IRB 101 and watch the video of this training. Public Responsibility in Medicine & Research (PRIM&R) and the Society of Research Administrators (SRA) are training opportunities available to committee members and staff.

The monthly publication, “Human Research Report,” is mailed to all human research PI’s, IRB and R&D Committee members, clinical service chiefs, Chief of Staff and Medical Center Director.

Principal Investigators and their team members must complete the institution’s HIPAA training as part of the VA appointment process.

VI. CONFLICT INTERESTS IN RESEARCH

A. Conflict Interests of IRB Members In Research

1. Purpose: To establish policy and procedures regarding Conflict of Interest (COI) in research which will enable adhoc/consultant reviewers or IRB contributors, and research committee members (i.e., Research and Development [R&D], Subcommittee of Human Studies [IRB], Subcommittee of Animal Studies [IACUC], and Subcommittee for Research Safety) to comply with applicable VA and other federal and state regulations regarding conflicts of interest in research.

2. Definitions: Any financial or non-financial interest not defined as a conflicting interest is not a conflicting interest. IRB members and consultants are **automatically** considered to have a *conflicting interest* when they or their spouse or dependent children have:

a. Involvement in the design, conduct or reporting of the research.
b. Ownership interest, stock options, or other financial interest related to the research unless it meets four tests:
   1) Less than $10,000 when aggregated for you and your immediate family.
   2) Publicly traded on a stock exchange.
   3) Value will not be affected by the outcome of the research.
   4) Less than 5% interest in any one single entity when aggregated for you, your spouse and dependent children.
c. Compensation related to the research unless it meets two tests:
   1) Less than $10,000 in the past year when aggregated for you, your spouse and dependent children.
   2) Amount will not be affected by the outcome of the research.
d. Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement.
e. Board or executive relationship related to the research, regardless of compensation.
f. Any other reason for which the member or consultant believes that he or she cannot provide an independent review.

3. Responsibilities: IRB members are responsible to know the definition of conflicting interest and to identify their conflicting interests before taking part in any review of research (initial review, continuing review, review of modifications, review of unanticipated problems involving risks to participants or others, review of serious or continuing non-compliance, review of a suspension or termination of IRB approval) including reviews by a convened IRB or reviews by the expedited procedure.

4. Procedures: Conflict interests of IRB members and consultants may not be evaluated or managed,

a. IRB members with a conflicting interest are to notify IRB staff, the IRB chair, or the convened IRB of their conflicting interests. IRB members with a conflicting interest are not counted towards quorum. The Chair will request a declaration of any conflicts with items on the agenda at the beginning of the meeting.

b. Consultants: IRB staff will go over this policy with any proposed consultant and determine whether the consultant had a conflicting interest. Consultants with a conflicting

interest must disclose that conflicting interest to the IRB before providing information.

c. IRB members and consultants with a conflicting interest may not be involved in the review of research except to provide information requested by the IRB. In the case of review by the convened IRB, the IRB will ask the member for information. After that the member leaves the room for the discussion and voting.

B. Conflict Interests of Investigators in Research

See Appendix D.

C. Institutional Conflict of Interest in Research

See Appendix E.

D. Investigator Compensation for Recruitment

Federal employee conflict of interest rules bar Principal Investigators from receiving, personally, compensation for enrollment performance. Finder's fees and bonus payments to encourage recruitment of subjects by investigators, physicians and other health care providers are prohibited. These payments may compromise the integrity of studies or may give an appearance of affecting the judgment of the investigator/research team member.

VII. OPERATION OF THE IRB

A. Types of Research Activities Subject to IRB Review

The following are some types of activities that may be subject to IRB review and approval and are not all inclusive of human subject research conducted within the NWIHCS.

1. Clinical Research. Clinical research involves research: (a) to increase scientific understanding about normal or abnormal physiology, disease states, or development and (b) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of clinical research.

2. Behavioral and Social Sciences Research. The goal of social and behavioral research is similar to that of clinical research — to establish a body of knowledge and to evaluate interventions — but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.

3. Epidemiological Research. Epidemiological research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, efficiency, interventions, or delivery of services to affected populations. Some epidemiological research is conducted through surveillance, monitoring, and reporting programs — such as those employed by the Centers for Disease Control and Prevention (CDC) — whereas other epidemiological research may employ retrospective review of medical, public health, and/or other records.

4. Repository Research, Tissue Banking, and Databases. Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review.

5. Quality Assurance/Quality Improvement Activities. Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities <u>may</u> constitute human subject research, and require IRB review, if they are designed or intended to contribute to generalizable knowledge. Quality assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, will probably not require IRB review or will qualify for an exemption.

6. Patient Record Research: Research involving access to patient medical records requires IRB review. The researcher must state whether the data will be collected with identifiers or recorded anonymously (coded data is not anonymous). The IRB will determine if the study requires informed consent, qualifies for a waiver of informed consent or is exempt from further IRB review.

7. Human Genetic Research: Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA

diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies.

B. IRB Meeting

- Schedule of meetings: Second Thursday of each month. The meeting is held at 3:00 p.m. in the Research Conference Room, R308. Agendas and accompanying materials are distributed one week in advance of the scheduled meeting to members and alternates to allow for sufficient review time.

- Proposed research must be reviewed at convened meetings at which a majority of the members (quorum) of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. The general attendance of the unaffiliated member is documented in the IRB minutes. The expectation is to have an unaffiliated member attend 10 of 12 monthly meetings per year. When an FDA-regulated article is involved, a licensed physician must be included in the quorum. In order for the research to be approved, it shall receive the majority vote of the voting members present at the meeting. The non-scientific community member(s) represent the general perspective and interests of subjects. It is the preference of the facility to have a Veteran in this capacity. The attendance is documented in the IRB minutes. The IRB Coordinator will monitor that a quorum is present throughout the meeting. A member who cannot attend the convened meeting may participate via videoconference or telephone conference, when that member has received a copy of the agenda and accompanying materials. This member is counted as part of the quorum.

- The Principal Investigator (PI) is invited to present the protocol and answer questions presented by the IRB members during the preliminary discussion.

- IRB primary reviewers describe the protocol, noting any needed changes, and make his/her recommendation for IRB action.

- Any new information that may affect the human research protection program (laws regulations, policies, procedures, emerging ethical and scientific issues) are distributed to the Committee members and principal investigators as appropriate.

- The IRB Chair opens the floor to discussion and, when completed, calls for the members' vote. Categories of vote are For, Against, Abstained, Recused (when conflict of interest) and Excused (when absent from meeting).

- No expedited reviews of initial protocol submissions are done. Only minor changes to ongoing research studies are done by expedited review by the Chairperson/Vice-Chairperson or designee. These are reported to the full committee via the agenda at the next regularly scheduled meeting.

C. Policy for Assigning Protocols for Review:

A systematic approach will be used to assign specific research protocols to members of the committee with the appropriate expertise to provide a reasonable and comprehensive review.

This policy includes the following elements:

- All IRB committee members will submit a CV/resume identifying their areas of expertise.

- The HRPP staff will use the committee members established expertise in assigning primary and secondary reviews based on the content of the protocol abstract.

- For protocols where questions might arise and additional expertise is needed, the IRB Coordinator will consult with the IRB Chair, and the ACOS/Research if necessary, prior to contact with potential protocol reviewers to determine whether their expertise is adequate to review the research content. The IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond, or in addition to, that available on their IRB. Consultants are not considered IRB members and do not vote. Any IRB member may request a consultant by making a verbal or written request to the IRB Chair or designee. The IRB chair or designee will review the qualifications of the consultant prior to the consultant's participation in the reviews of the research. The ad hoc reviewer/consultant is provided an agenda with accompanying materials and attends the IRB meeting or provides information to the IRB for the review. Whether the ad hoc reviewer/consultant attends the IRB meeting or provides written information regarding his/her assessment of the research, the key information provided will be recorded into the minutes of the IRB meeting.

- The IRB will assess the expertise of review at the specific time of protocol review and indicate this assessment in the elements of review documentation.

- If the IRB determines that inadequate expertise exists to review a protocol, it will be tabled, and additional ad hoc reviewers obtained for the next scheduled IRB meeting.

D. Outcomes of IRB Review

After full committee review, the IRB makes its determination, which is documented in the minutes and communicated to the principal investigator, from the following:

- Approved with no changes. The Date of Approval is the date of the meeting at which the research was approved. New research approved receives an interval of approval of no more than one year. The Date of Expiration is defined as the Date of Approval plus the recommended interval of approval minus one day. Example: A protocol was approved on June 15 with a continuing review in one year which means that you begin counting one year starting with June 15 which means the date of expiration would be June 14.

- Contingently approved with minor changes to be reviewed by the IRB Chair/Vice Chair or a designee (commonly the primary or secondary assigned reviewer). When the convened IRB stipulates specific revisions requiring simple concurrence by the investigator, the IRB Chairperson may subsequently approve the research on behalf of the IRB.

- Tabled. The IRB determines that it lacks sufficient information about the research to give approval. The research may not proceed until the convened IRB has approved a revised application incorporating necessary information.

- Disapproved. The IRB has determined that the research cannot be conducted at the VAMC or by employees or agents of the VAMC or otherwise under the auspices of the VA. The reasons for disapproval are outlined in the notification to the PI. The PI has the right to appeal the decision in writing, resubmit the proposal and provide justification for the appeal.

- Exempted. No further review by the IRB is needed. The continued review is conducted by the Research and Development Committee.

- Waive the requirements to obtain informed consent or the documentation of informed consent An IRB may waive the requirement for the investigator to obtain a signed consent for some or all subjects.

Protocols will be administratively withdrawn 90 days after initial review when contingencies are not met.

E. IRB Communication to the Principal Investigator

- All IRB actions will be communicated to the PI in writing.

- Human subject research must not be initiated until complete IRB and R&D approval as well as other appropriate committee review and approval are granted and communicated to the PI by the ACOS/R&D.

- Research that has been approved by the IRB is subject to review and disapproval by the Research & Development Committee and/or higher authority, but those officials may not approve research that has been disapproved by the IRB.

- Approved research is subject to continuing IRB review at least annually, or more frequently if specified by the IRB. The IRB considers factors in determining protocols which require review more frequently than annually such as: the anticipated risk to subjects, the likely medical condition of the proposed subjects, overall qualifications of the PI and research team members, specific experience of the PI, nature and frequency of adverse events or unanticipated problems involving risks to subjects observed in similar research, vulnerability of the population being studied and other factors the IRB deems relevant. The date of continuing review and expiration of approval are stated on the letter issued to the PI. The approval and expiration dates are clearly noted on the consent forms sent to the PI and must be strictly adhered to. By federal regulation, no extension of that date can be granted. Reminder: The Date of Approval is the date of the meeting at which the research was approved. New research approved receives an interval of approval of no more than one year. The Date of Expiration is defined as the Date of Approval plus the recommended interval of approval minus one day. Example: A protocol was approved on June 15 with a continuing review in one year which means that you begin counting one year starting with June 15 which means the date of expiration would be June 14.

- The IRB provides written communication to the PI regarding IRB decisions pertaining to the status of their grants. At any time when a PI has an issue with any decision made by the IRB regarding their protocol during an initial review, continuing review, modification, suspension or termination, that PI will have up to 30 days to respond in writing to the IRB. If a written

response is received within 30 days, it will be reviewed at the next scheduled IRB meeting. If a written response is not received within this 30 day, the PI forfeits the opportunity to contest or question that particular action. All responses to IRB decisions should be sent directly to the IRB Staff Coordinator for inclusion in the next scheduled IRB meeting.

- The IRB will determine whether the medical records of a protocol require flagging to protect the participant's safety by indicating participation in the study and the source of more information on the study. To ensure that the necessity and/or appropriateness of flagging a medical record is considered during the protocol review, the IRB will utilize the Appendix OO checklist. The IRB may not want to require the medical record to be flagged if:
    1. The subject's participation in the study involved:
        a. Only one encounter
        b. Only the use of a questionnaire, or
        c. The use of previously collected biological specimens
    2. The identification of the patient as a subject in a particular study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk.

- Research activities are subject to internal audit and verification from sources other than the PI since the last IRB review.

F. Reporting IRB Actions to the R&D Committee and the Institution

The minutes of each IRB meeting are distributed and reviewed by the Research and Development Committee. IRB minutes are included in the R&D Committee agenda packet distributed to all mentioned above, including the Chief of Staff and Director, who are members of the Executive Committee of the Medical Staff. A memorandum is received from the Executive Committee of the Medical Staff describing their acceptance.

G. Auditing Recurring Processes

The IRB has the authority to conduct audits of recurring processes in addition to the regulatory monitoring requirements. The IRB may audit that written procedures are being followed, review research records and research case histories for compliance with written procedures and regulations, observe the informed consent process, and audit the conduct of the research (initial approval, requirement for modifications, final approval granted, continued review conducted, etc.) and consider results of audits conducted by other entities within the institution. The HRPP grants some of these oversight auditing activities to the Research Compliance Officer. These audits are reported to the IRB and R&D Committee quarterly. As a result of these findings, areas for improvement and actions needed are identified.

H. IRB Record Keeping

The VA Nebraska-Western Iowa Health Care System IRB shall prepare and maintain adequate documentation of IRB activities, including the following:

- Copies of the complete research protocol application for initial review

- Minutes of IRB meetings, which shall be in sufficient detail to show:

  1. Attendance at the meetings
  2. When an alternate member replaced a primary member
  3. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document
  4. The approval period for initial and continuing reviews
  5. The name of IRB members who absented themselves from the meeting due to a conflicting interest along with the fact that a conflicting interest was the reason for the absence.
  6. Determinations required by the regulations, and protocol-specific findings justifying those determinations for waiver or alteration of the consent process, OR to waive the requirement to obtain written documentation of informed consent.
  7. The rationale for significant risk/non-significant risk device determinations
  8. The approval of research contingent on specific minor conditions by the chair or designee, to be documented in the minutes of the first IRB meeting that took place after the date of the approval.
  9. Attendance at the meetings including those members or alternate members who participated through videoconference or teleconference and document that those members received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.
  10. When an ad hoc/consultant provides a written or verbal review of a protocol based on their particular expertise, key information provided by the ad hoc reviewer/consultant will be documented in the minutes of that meeting.
  11. Actions taken by the IRB
  12. The vote on the actions taken, including the number of members voting for, against, abstaining, and when appropriate recusing because of conflict of interest
  13. Determination of risk level
  14. The changes required to approve research as well as the basis for requiring changes or disapproving research; and
  15. Written summary of the discussion of controverted issues and their resolution

- Documentation of human subject protection education by principal investigator, research team members, committee members and staff

- Records of continuing review activities

  - Copies of scientific evaluations
  - DHHS-approved sample consent documents (when one exists)
  - Progress reports submitted by investigators
  - Reports of injuries to participants
  - Statements of significant new findings provided to participants
  - Protocol violations submitted to the IRB

- Copies of all correspondence between the IRB and the PIs and the R&D Committee

- A roster and current resume or curriculum vitae of IRB members

- Changes in IRB membership appointed in writing by the Medical Center Director must be reported to OHRP and ORO as required by the FWA
- Standard Operating Procedures for the IRB
- Modifications to ongoing research
- Reports of unanticipated problems/adverse events
- Reports of non-compliance or research misconduct
- Subject complaints
- Subcommittee of Human Studies Elements of Review Checklist
- Consent Form Checklist including HIPAA Authorization Elements

IRB minutes will be available within one week after the meeting time and will be made available to the R&D Committee meeting that immediately follows the IRB meeting. Minutes cannot be altered by anyone including a higher authority once approved by the members at a subsequent IRB meeting.

The required records, including the investigator's research records must be retained in accordance with VHA Handbook 1200.05 and until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Record Control Schedule (RCS 10-1). All records are stored in a secured manner to protect the confidentiality of subject information and shall be accessible for inspection and copying by authorized representatives of the VA, OHRP, FDA and other authorized entities at reasonable times and in a reasonable manner.

VIII. IRB REVIEW PROCESS

A. Documents Required for Initial IRB Review

IRB members and alternates receive initial review materials specific to the study being proposed one week in advance of the convened IRB meeting. The Principal Investigator checks the applicable contents of the submission on the Human Studies Protocol Submission Checklist or the Review of Medical Records and/or VA Database Submission Checklist and submits them in typewritten format. Primary reviewers and other IRB members and alternates receive the following:

- the investigator data sheet for new principal investigator(s),
- the request to review form,
- abstract,
- conflict of interest statement,
- human research protocol worksheet,
- participating research team member list
- consent form,
- DHHS-approved sample consent (when one exists),
- waiver of consent form,
- HIPPA Authorization or waiver of authorization
- request for exemption,
- surveys or questionnaires,
- investigational drug information record or device form (when one exists),
- recruitment materials,
- research using stored human biological materials or DNA form
- protocol narrative or grant submission (VA, DHHS, industry-sponsored, etc. Include the DHHS-approved protocol, when one exists)
- budget,
- support letters (Pharmacy, Radiology, Pathology, Clinical Research Unit, etc.)
- research safety application,
- data security checklist

Primary reviewers receive the following in addition to the materials listed above:

- investigator's brochure (when applicable),
- curriculum vitae(s).

All IRB members and alternates are expected to review all provided materials in advance of the meeting in enough depth to be familiar with and prepared to discuss the protocol at the convened meeting.

Primary reviewers are expected to conduct an in-in-depth review of all provided materials.

B. Protocol Submission Deadline

The complete protocol application including all attachments and appropriate signatures for initial review are due in the Research Administrative Office to the IRB Coordinator by the 25th day of the

month for the following month's review. Signatures representing clinical support departments (e.g., Radiation Safety Committee, Pharmacy, Pathology and Laboratory Medicine, Radiology, etc.) or the Privacy Officer should be obtained prior to submission for IRB review. Final approval is not granted until all identified support is obtained. This submission deadline (25th of the month) is also applicable for all continued review applications.

C. Criteria for Approval

The Subcommittee of Human Studies Elements of Review Checklist **(Appendix OO)** is utilized by the IRB to ensure the committee follows a process to identify and analyze potential sources of risk and measure to minimize risk, including physical, psychological, social, legal or economic risks, and to determine that the risks to participants are reasonable in relation to potential benefits to participants and society. The IRB Reviewer uses Appendix OO to document and record the IRB discussion of each protocol and to ensure complete review of each research protocol at the convened meeting. The IRB determines that:

- Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and whenever appropriate, by using procedures already being performed on subjects for diagnostic or treatment purposes. Risks may be physical, psychological, social and economic (including legal and employment) harms to which subjects may be exposed.

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, consider only those risks and benefits that may result from the research as distinguished from those of therapies the subject would receive even if not participating in the research.

- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. Particular attention should be paid to the special problems of research involving vulnerable populations and the additional safeguards required.

- Informed consent will be sought from each prospective subject or the subject's legally authorized representative and appropriately documented. In addition to the use of Appendix OO to evaluate the consent form, the IRB might consider requesting observation of the consent process as a method to protect subjects based on considerations like the involvement of vulnerable populations, level of risk of the study, prior issues of noncompliance involving the PI, data breaches, Phase I or Phase II studies and/or any other like types of criteria.

- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. An independent data and/or safety monitoring board are or are not needed.

- Adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data.

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such

as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

- Research Investigators/staff have appropriate expertise to perform their responsibilities in the study.

- Costs/compensation for participating in the study is addressed when applicable.

- Human subject education and training requirements have been met.

- Risk level is determined: minimal, greater than minimal and significantly greater than minimal. An appropriate continuing review interval is established (must not be greater than one year).

- Flagging of the medical record is determined to be necessary or not necessary based upon risk to protect the subject's safety.

- Conflict of Interest has been evaluated and appropriate action taken when a conflict is identified

- The protocol was reviewed with appropriate expertise based on protocol content.

The review of the scientific and scholarly validity of the proposed research (risk/benefit ratio) is conducted by the IRB and can be assisted by ad hoc review (person or persons with appropriate expertise). This review determines whether:

- The research uses procedures consistent with sound research design.
- The research can be reasonably expected to answer its proposed questions.
- The importance of the knowledge that is reasonably expected to result is known.

The protocol is reviewed by the Research Subcommittee for Research Safety and, when deemed appropriate, the Radiation Safety Committee. As part of the R&D Committee oversight of all proposals, the R&D Committee reviews and discusses the actions documented in the IRB minutes. When modifications or disapproval are recommended by the R&D Committee, this is promptly communicated back to the IRB Chair via the R&D Committee minutes.

D. Modifications to Secure Approval to Contingently Approved Research

Modifications must be documented in sufficient detail by the IRB to allow the IRB staff to verify the changes required by the IRB Chair/designee and/or committee. A Notification of Approval with Contingencies letter is generated after the IRB meeting and sent to the PI(s) listing all required modifications and conditions for approval. The PI(s) responds to the RAO with a copy of all modified documents within 90 days. The IRB reviews the modified documents for confirmation of all modifications required by the IRB. If the submitted documents have not been modified as required, the PI is contacted by IRB staff and asked to submit the complete revision as requested. Once the IRB Chair or an experienced IRB designated by the chair determines that the documents contain all required modifications, the IRB Chair or designee signs and dates the final approval letter indicating the interval of approval. If the PI(s) does not return the required modified documents within the specified 90 days, the protocol will remain unapproved, the subcommittees will be notified and the PI(s) will have to resubmit the entire protocol.

The IRB will utilize Appendix OO Subcommittee of Human Studies Elements of Review Checklist to ensure that the IRB is following the regulatory criteria for approval of research for modifications to previously approved research. Appendix OO will also be used when determining what information relating to protocol changes should be communicated to participants when such information might relate to their willingness to continue to take part in the research.

E. Recruitment of Research Subjects

Since recruitment is a part of a research protocol, it cannot occur until after the IRB has approved the protocol. The VA does not consider recruitment to be an "activity preparatory to research." Activities preparatory to research would include, for example, reviewing records to determine whether there is a sufficient number or type of record or a sufficiently large pool of prospective subjects to conduct the research. This activity takes place during the course of the preparation of the research protocol. Per VHA Handbook 1605.01, neither written authorization from the research subject nor an IRB or Privacy Board waiver of authorization is required for a VA Investigator to conduct a review of individually-identifiable information in preparation of a research protocol.

When an investigator is accessing and screening patient records/databases and recording identifiable private information for the purpose of identifying potential research subjects, this constitutes human subject research activities according to the Common rule. Under the Common rule a clinical investigation begins with screening, but is not part of the clinical investigation per FDA regulations. If identifiable private information is needed for recruiting, then IRB approval must be obtained. If informed consent is not obtained, the IRB may approve an appropriate waiver of informed consent and waiver of HIPAA authorization before identifiable information can be recorded and used for recruitment purposes. It does not matter if the PI or his/her agent is obtaining information from his/her own patient records or not.

The plan for recruitment of subjects must be described in the application to the IRB. For example, this may be a clinic visit, referral by other physicians, advertisement via newspaper, TV, radio ads, flyers, etc.) Advertisements and Recruitment Incentives must include the word "research" and be limited to the information the prospective subjects need to determine their eligibility and interest.

Recruitment Materials

1. All recruitment materials **must include** the following:

    a. The official ORD Research logo/emblem (microscope) and VA NWIHCS logo (PR to place on flyer)
    b. What type of study (diabetes, arthritis, etc.)
    c. Target audience
    d. Statement that it is "Approved by the NWIHCS Institutional Review Board (IRB)" can be in small print but must be included
    e. Limited to the information the prospective subjects need to determine their eligibility and interest.
    f. Clear statement that this is research and not treatment

g. Contact name and/or number
h. If materials will be posted outside the hospital, external posters/flyers should also include a statement indicating "This Research is being conducted through the Nebraska-Western Iowa Heath Care System (NWIHCS) and approved by the NWIHCS VA Institutional Review Board

2. Recruitment materials **can include** the following
   a. Name and address of the clinical PI and/or location of research facility
   b. The purpose of the research
   c. Time or other commitments required of the subjects
   d. Title of Study
   e. Protections/confidentiality statement if sensitive study (mental health, AIDS, sickle cell or like)
   f. The term "voluntary participation" in research
   g. When applicable, that "reimbursement may be available"…minimal statement

3. What **is not appropriate** for recruitment materials (avoid perception of enticements)
   a. Leaving off any of the items that **must** be included from above list
   b. Dollar amounts regarding compensation
   c. Mention of free testing, free medication, etc….---don't reference "free"
   d. Statements that suggest participants will benefit from the study beyond what is outlined in the consent document and the protocol.
   e. Do not include anything about "new treatment", "new medication", "new drug", "free medical treatment" or like. You can state that the study involves medicine for hypertension, COPD or whatever.
   f. No claims, explicitly or implicitly, that the drug, biologic or devise is safe or effective or known to be equivalent or superior to any other drug, biologic or device.
   g. Statements that entice by offering money or incentives to participate
   h. Home or cell phone numbers for contacts

4. Submission Process for PIs/Study personnel to follow:
   a. PIs must submit a completed Appendix X Research Recruitment Advertising Template to the IRB for review and approval. The approved Appendix X will then be submitted to Medical Media for formatting using the process below; no formatting by the PI is required.

   b. PI or designee must complete a Medical Media Request Form which is located on the Learning Resources Services Department SharePoint site. This will require access and use of a VA computer. If you have any problems with this, please contact the Research Administrative Office.
      i. Go to the NWIHCS Homepage at http://vaww.nebraska.va.gov
      ii. Select NWI SharePoint site on left
      iii. Go to Learning Resources Services Department field
      iv. Select Request for Services Forms on left
      v. Select Medical Media Request Form
         1. You will need a Job/Project title
         2. Date requested
         3. Date needed

4. Goal/purpose of Project
5. Category of Services: photography, design and/or finishing services you will select
6. You'll attach Appendix X and your IRB approval letter or approved amendment

c. PI or designee must attach a copy of the IRB approval letter or IRB approved Amendment form to your Medical Media Request Form.

d. Medical Media will create flyers (for building locations and elevators) and digital media using the information submitted. They will also provide you with copies of the draft for your final approval.

vi. Remember, the general guideline of using minimal text – ideally less than 100 words.
vii. You can request specific graphics, if needed, but do not include your own graphics. PR will use graphics that have no copyright issues.
viii. Send information in a word document only.
ix. PR will post the flyer or digital media for a minimum of one week. If you want this posted on a regular or monthly basis, you must continue to resubmit the PR work order – you can use the same work request and just resend. Be sure to indicate in the work order, however, if this is a new request or a repeat request.

e. If you want recruitment to include Facebook and/or Twitter, send request and copy of PR flyer to Public Relations..

f. Research Service has been given a display board on the 3rd floor by the canteen for posting recruitment materials. Please provide copy to Research Administrative Officer for posting in this display window.

For FDA regulated protocols, the IRB will insure that advertising follows FDA guidelines that also include the following:

1. Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational.
2. A phrase such as "receive new treatments" leads study subjects to believe they will be receiving newly improved products of proven worth and should not be used.
3. Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation.
4. Advertisements may state that subjects will be paid but **s**hould not emphasize payment or amount to be paid, by such means as larger or bold type
5. No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of FDA regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and of investigational devices [21 CFR 812.7(d)].

All recruitment materials must be approved by the IRB before use and all changes to approved materials must also receive IRB approval.

During the recruitment process, researchers must make initial contacts with veterans in person or by

letter **(Appendix V)** prior to any telephone contact and provide a telephone number or other means that veterans can use to verify the validity of the study. Informed consent documents need to include information about where and how a veteran could verify the validity of a study and authorized contacts. The office phone number of the Administrative Officer for Research will be used in the recruitment letter to potential subjects and in the informed consent to provide verification of the validity of a study and authorized contacts.

Payment for Research Subjects:

From the VA Handbook 1200.05, VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's medical care and when it makes no special demands on the patient beyond those of usual medical care. Payment may be permitted, with IRB approval, in the following circumstances:

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

Investigators who wish to pay research subjects must in their proposal:

1. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
2. State the terms of the subject participation agreement and the amount of payment in the informed consent form; and
3. Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or influence on the perspective research subjects to volunteer for, or to continue to participate in, the research study; and that the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study.

Generally speaking there is no prohibition against study subjects receiving payment for their participation in a research protocol. The only time an issue might arise is when the Veteran is also eligible for “Beneficiary Travel” and subject reimbursement is in the form of a gas card. Subjects/Veterans should be referred to the Travel Office for full details.

The IRB must review all proposals for payment of subjects to ensure conformity with VA policies. This issue is identified as an element of the scientific review on the IRB’s Elements of Review Checklist. The Research Administrative Office is responsible for ensuring that IRB-approved payment to subjects is made from a VA-approved funding source for research activities.

The IRB will review both the amount of proposed payment and the method and timing of disbursement to assure that neither are coercive nor present undue influence. The IRB will ascertain that:

1. Credit for payment accrued as the study progressed and not be contingent upon the participant completing the entire study.
2. Any amount paid as a bonus for completion was reasonable and was not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.
3. All information concerning payment, including the amount and schedule of payments, to be set forth in the informed consent document.
4. Compensation for participation in a trial offered by a sponsor does not include a coupon good for a discount on the purchase price of the product once it had been approved for marketing.

Recruitment of non-veterans in a VA research study:

It may be possible for you to include a select number of non-veterans in a VA-approved research study when there are insufficient veterans available to complete the study. The costs of the non-veteran participants should be absorbed by the study's sponsoring agency. Costs not covered by the sponsor will be covered by the VA and when appropriate, the medical care appropriation will be reimbursed from the research allocation. Their participation must be justified and not interfere or detract from the participation by the veteran population.

A memorandum must be drafted to the R&D Committee through the IRB which addresses the following:

1. How all costs will be covered for non-veterans? (This is addressed for veterans in the original submission)
2. How will these participants be recruited?
3. Why the inclusion of non-veterans is appropriate for the study (does not detract from veteran population).
4. Is this an interventional or non-interventional study?
5. Include an approval signature block for the ACOS/R&D

When participation of non-veterans in a study is requested at the onset of a study, this request must be included with the protocol submission to the IRB and R&D Committee. The R&D Committee oversees all initial submissions submitted to the IRB; therefore, the request for inclusion of non-veterans will be reviewed for approval by the R&D Committee as well as the IRB.

When participation of non-veterans is requested to an ongoing study, an Amendment/Revised Protocol Reporting Form **(Appendix MM)** will be required along with the memorandum outlining the requested information above. This type of amendment involving costs for non-veterans will also be reviewed by the R&D Committee for approval.

Following review by the IRB and R&D Committee, the memorandum will be signed by the ACOS/R&D when approval is granted. The ACOS/R&D will share the inclusion of the non-veteran participation with the Medical Center Director through the Chief of Staff for all interventional studies.

F. Recruitment to Off-Site Studies

The recruitment of VA patients to enter research studies at facilities off-site (outside of the Nebraska-Western Iowa Health Care System) is not allowed. Patient care providers may inform their patients about studies that are available outside the NWIHCS. It is the discretion of the VA patient to initiate contact with a Principal Investigator/Research Team Member regarding an off-site study. Systematic recruitment of VA patients is not permissible. When a question arises about this type of activity, the office of the ACOS/Research should be contacted.

G. **Protection of Privacy and Maintenance of Confidentiality of Human Subjects Participating In Research**

Protocols must include adequate provisions to protect the privacy interests of participants. Protocols must also include adequate provisions to maintain the confidentiality of collected data. Privacy and confidentiality are not the same. For the purposes of research involving human subjects, privacy relates to the interests of a *person* to limit access to themselves (e.g. be left alone and free of intrusions), confidentiality relates to the *data* and maintaining agreements to limit access to that data. Privacy is protected. Confidentiality is maintained.

<u>Privacy</u>
The IRB must assure there are adequate provisions to protect the privacy of the participant. This is evaluated on a continuing basis.

Privacy refers to the person's desire to limit the access of others to themselves, such as being seen at a certain clinic (for example, HIV or counseling center), or being seen talking to someone or a particular situation that may cause them embarrassment or feeling uncomfortable, The IRB will evaluate the Investigator's plan for recruitment and obtaining consent, and how and in what environment (among other patients, in a small hallway or in a private room) information is obtained about the participant. The IRB will consider these factors when using Appendix OO, the IRB Review Checklist, and assessing privacy provisions to protect the privacy interests of participants within the protocol.

<u>Confidentiality</u>
The IRB must assure there are adequate provisions to maintain the confidentiality of identifiable data. Confidentiality is about maintaining agreements with participants to limit the access to their data. This is evaluated on a continuing basis.

The IRB will evaluate the investigator's plan for handling, managing, storage and sharing of identifiable information. This also includes recruitment and obtaining consent and how information is obtained about the participant. Methods used to collect information about participants and the provisions for protecting the confidentiality of the research data must be identified. The IRB will consider these factors when using Appendix OO, the IRB Review Checklist, and assessing confidentially provisions within the protocol.

The VA Privacy Act and VA Privacy handbook 1605.01 provides more complete explanation of the regulations covering veterans' data. Section 13 4refers to research uses. One can access this information at http://www1.va.gov/vhapublications/ppublications.cfm?pub=2

Compliance for Researchers is guided by the following documents:
VHA HANDBOOK 1605.01 Privacy and Release of Privacy Information
Website – HIPAA Privacy Rule Guidance Document and HIPAA Privacy Rule Compliance

H. Data Safety Monitoring

1. Data Safety Plan:

The plan for monitoring the safety data collected to ensure the safety of participants must be described in the PI's application to the IRB for more than minimal risk research **(Appendix T)**. This monitoring may be conducted by a Data Safety Monitoring Board (DSMB) or a Data Monitoring Committee (DMC), or by the investigator. Adequate provisions for monitoring the safety data collection to ensure safety of subjects is evaluated by the IRB at initial review, continuing review and during modifications (when appropriate) to an ongoing study.

The monitoring plan should include at a minimum the following elements:

- Who will monitor the safety data?
- What safety data will be monitored?
- How frequently will safety data be monitored?
- What analyses will be performed on the safety data?
- What decision rules (e.g., stopping rules) will be considered?
- How will the PI promptly detect an increased frequency or severity of unexpected harms?

The IRB must carefully review plans for studies that are blinded, have multiple sites, enter vulnerable populations or use high-risk interventions and do not have a DSMB or DMC. When the investigator is the lead investigator of a multi-center study, or the organization is the lead site in a multi-center study, the application should include information about the management of information obtained in multi-site research that might be relevant to the participant protections, such as unanticipated problems involving risks to participants or others, interim results and protocol modifications.

2. External Site Monitoring

The Department of Veterans Affairs has published guidance regarding research studies conducted at VA facilities that are monitored by external entities (e.g. pharmaceutical companies and Contract Research Organizations (CROs). The Research Administrative Office must be notified of all monitoring visits (scheduled and unscheduled). The external study monitor or CRO must sign in as a visitor **(Appendix H)** in the Research Administrative Office (12th floor).

The Principal Investigator or other responsible investigator is to meet with the study monitor(s) prior to the monitors' beginning their work. During each visit by a monitor, the role of the monitor should be reviewed, including the new requirement that any potential or actual serious findings be conveyed to the investigator and the ACOS/R&D, AO/Research Service, or his/her designee during an exit interview.

Access to the computerized medical record by an external study monitor may be done by the VA employee "driver" method. This method allows the monitor to see only the information that is accessed by the VA employee and authorized for the specific trial. The other method is the

limited read-only access to selected data which requires approval by the ISO/IT staff.

Findings that require an exit interview include but are not limited to:

1. Any suspicions or concerns that serious non-compliance may exist.
2. All findings of serious non-compliance with the study protocol, IRB requirements or applicable regulations and policies (e.g., failure to consent subjects, entering subjects who do not meet inclusion criteria into protocols, failure to exclude patients that do not meet exclusion criteria at any time during conductance of protocol and failure to report serious or unexpected adverse events).

If the monitor records no serious findings or concerns as listed above, the Principal Investigator or research coordinator must notify the research office in writing that there were no such findings identified by the monitor.

The monitoring report titled External Site Monitoring Visit Report/Checklist **(Appendix I),** even if no serious findings are found, must be submitted to the IRB. A section titled "Study Monitor Reports" will appear monthly in the IRB minutes documenting these visits. A summary of the data safety monitoring findings must also be submitted at the time of continued review. When an issue of serious non-compliance occurs, The Research Service Memorandum No. 151-10 will be followed.

I. Continuing Protocol Review

1. Continuing review has to occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions and has to occur when the remaining research activities are limited to collection or analysis of private identifiable information. Upon initial or continuing approval of research, the IRB grants an interval of approval appropriate to the degree of risk, but no longer than one year. The expiration date of the research (last day of interval of approval) is the date of the most recent initial or continuing approval plus the interval of approval and minus one day. The date of the closest IRB meeting before the expiration date is the IRB meeting at which continuing review is scheduled to occur. As long as a protocol remains active, even when the research is closed to enrollment of new participants, continuing review must occur before the identified date of expiration based on the recommended interval of approval.

2. Approximately two months before the date of the IRB meeting at which continuing review is scheduled to occur, the IRB staff sends investigators a notice when continuing review materials are due and refers them to utilize **Appendix KK** Continuing Review Submission Form.

- The PI is expected to complete the form and provide all applicable attachments requested. The signature of the PI(s) on the form ensures that all changes in previously approved research will be reported to the IRB.
- Proposed changes will not be implemented without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

3. Upon receipt of the progress report from the PI(s), the RAO stamps it with the date of receipt and enters the request into the database.

4. If the IRB does not receive complete and accurate continuing review information from the PI by the expiration date, the IRB informs the PI(s) to stop all research activities immediately as explained in Section I following.

5. The IRB uses a primary reviewer system for conducting formal Continuing Review (CR). The IRB Coordinator conducts an initial audit of the continuing review submission. The expectation is that the primary reviewer will perform an in-depth review of all submitted materials. The primary reviewer reviews the complete protocol, the entire file and all documents submitted by the investigator for CR, including the following:

● "Continuing review submission" application including summaries of the research methodology, amendments since the last review, problems/local SAEs, information that may impact the risk/benefit ratio, data safety monitoring, number of subjects enrolled and withdrawn, gender, minority status, number considered to be a vulnerable population, complaints about the research, any recent literature and findings thus far. The application includes an assurance that all identified unanticipated internal or local SAEs have been reported as required by the IRB, and a statement signed by the PI certifying that all subjects entered onto the master list of subjects for the study signed an informed consent prior to undergoing any study interactions or interventions unless the IRB has granted a waiver of informed consent (38 CFR 16.116(c) and (d)), or a waiver of the signed informed consent form (38 CFR 16.117(c)).

- initial IRB application updated with any changes
- current approved protocol
- VA Project Data Sheet (generated by ePROMISE)
- updated abstract (generated by ePROMISE)
- current consent document and any newly proposed consent document,
- current HIPAA authorization document
- investigator's brochure when applicable
- any relevant multi-center trial reports

6. IRB members who are not assigned as a primary reviewer will receive all relevant information necessary to determine whether the proposed research continues to fulfill the criteria for approval including the following:

- "continuing review submission" application
- initial IRB application updated with any changes.
- VA Project Data Sheet (generated by ePROMISE)
- updated abstract (generated by ePROMISE)
- current consent document and any newly proposed consent document,
- current HIPAA authorization document

Additional information including a copy of the current approved protocol is available to any IRB member who wishes to review it. The expectation is that all IRB members will review the provided materials in enough depth to discuss the information at the convened meeting. The primary reviewer summarizes their review for the Committee. The above aspects of the review are covered. The protocol is then discussed, a recommendation made and a vote taken of the entire Committee. The vote may be to approve, defer for additional information or which may cause a lapse of approval, defer for education or suspend the project (at which time a decision

will be made about the disposition of current and future subjects until specified issues are resolved). The vote may also disapprove the research project. The IRB minutes will reflect the votes and discussion that ensued.

7. The IRB will determine, based upon study design and risks, if it will require verification from sources other than the investigator at the time of continuing review to assure that no additional risks have been identified. In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review. The IRB may consider the following factors in determining which studies require independent verification:

- Probability and magnitude of anticipated risks to subjects.
- Likely medical condition of the proposed subjects.
- Probable nature and frequency of changes that may ordinarily be expected in type of research proposed.
- Prior experience with the principal investigator and research team
- Other factors that the IRB deems relevant.

J. Study Closures:

1. Completion of continuing review documentation is required for study closures as described in the section above. PIs must report activities that have occurred since the last continuing review of the project. It is important to include an updated Findings summary and Impact/Significance statement that the Research Administrative office can download as a final report to the Central Office ePROMISE database. A study may be closed at any time when:

- there are no longer interactions or interventions with subjects;
- no additional data will be collected;
- data which includes identifiable private information will no longer be analyzed;
- individually identifiable specimens from the participants will not be tested or analyzed.

2. When a study comes up for continuing review and no activity has occurred since initiation (i.e., data collection or enrollment), a written notification may be sent stating the project was never initiated and closure is requested.

<u>or</u>

When a study closure occurs and there has been no activity (i.e., new enrollment or data collection) within 3 months or 92 days of the previous IRB review of the continuing review of an active study, a memorandum may be sent to the IRB for review and approval which addresses the following:

a. The name and study ID number.

b. Provide assurance that all activities have closed at this site (i.e., enrollment, patient follow-up, data collection and identifiable analysis).

c. A Findings summary: The main result of the study should be given. Describe measures that are not evident from the nature of the main results and indicate any blinding. If possible, the results should be accompanied by confidence intervals (most often the 95% interval) and the

exact level of statistical significance. For comparative studies, confidence intervals should relate to the differences between groups. Absolute values should be indicated when risk changes or effect sizes are given. State only those conclusions of the study that are supported directly by data, along with their clinical application (avoiding overgeneralization) or whether additional study is required before the information should be used in clinical settings,. Equal emphasis must be given to positive and negative findings of equal scientific merit.

d. Impact/Significance statement**:** Discuss the anticipated contributions of the proposed study in terms of products or outcomes; i.e., how the study results may be used in the VA health care system.

K. Expiration of Approval Period

If an accurate and complete Appendix KK Continuing Review Submission Form is not received by the submission deadline date and on or before the date of expiration indicated in the notice sent to the PI(s) by the IRB staff, a lapse and expiration of approval will occur. At this point, all research activity must stop on a study (including recruitment, advertisements, consent, data collection, data analysis, interactions and interventions). The ACOS/Research is notified of the lapse. Interventions or interactions on current participants may be continued if the safety of subjects already enrolled in a protocol would be compromised by the immediate cessation of the protocol. Enrollment of new subjects cannot occur; continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB Chair, in consultation with the Chief of Staff (COS), finds that it is in the best interest of individual subjects to do so. Once notified by the IRB of the expiration, the PI must immediately submit to the IRB Chair, a list of research subjects for whom discontinuation of the research would cause harm. In the event of an expiration or lapse of approval, suspension of approval and/or termination of approval, the IRB office staff notifies the sponsor. A copy of the IRB decision will be placed in the protocol file.

If a lapses of approval occurs, the following information should be included in the template letter used to notify investigators:

- All research activity must stop on a study (including recruitment, advertisements, consent, data collection, data analysis, interactions, and interventions).
- Interactions and interventions on current participants may be continued if the safety of subjects already enrolled in a protocol would be compromised by the immediate cessation of the protocol.
- Enrollment of new subjects cannot occur.
- Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB Chair, in consultation with the Chief of Staff (COS), finds that it is in the best interest of individual subjects to do so.
- Once notified by the IRB of the expiration, the PI must immediately submit to the IRB Chair, a list of research subjects for whom discontinuation of the research would cause harm.

L. Reporting Amendments to the IRB:

Changes in approved research must be reported promptly to the IRB and cannot be initiated

without IRB approval, except when necessary to eliminate apparent immediate hazards to the subject. When the investigator initiates changes to eliminate apparent hazards, these are to be reported to the IRB as soon as possible. The changes may be as simple as a title change or as complex as the addition of a study drug or other intervention that alters the risk-benefit relationship of the research. Reporting is done via the Amendment/Revised Protocol Reporting Form **(Appendix MM)** along with applicable attachments noted on the reporting form.

The IRB Coordinator reviews the amendment for completeness and entry into the MIRB database. It is the discretion of the IRB Chair/designee to approve the report by expedited review when it meets the criteria of a minor change in ongoing research, or recommend it for full board review. When an amendment is expedited, information about the amendment is provided to the full IRB Board via the agenda of the next regularly scheduled meeting.

Amendments receiving full board review are assigned a primary reviewer. The primary reviewer and other IRB members receive a copy of the amendment reporting form and applicable attachments. For example, when a consent form is revised, a highlighted copy is required. If the amendment requires a change to the protocol, the reviewer will receive a copy of the protocol.

The IRB notifies the PI in writing regarding the actions taken on an amendment report and a copy is retained in the appropriate protocol folder. Investigators may have additional reporting responsibilities outlined in individual contracts that are not covered by the standard FDA/sponsor procedures.

M. Expedited Review of Research

Expedited review is **not** done at NWIHCS for initial or continuing review of research.

N. Expedited Review of Minor Changes in Previously Approved Research

Expedited review may be done only for minor changes in ongoing previously approved research. These are reported to the IRB via the Amendment/Revised Protocol Reporting Form. The IRB Chairperson or one or more experienced reviewers designated by the Chair from among members of the IRB may review and approve minor changes in previously approved research on behalf of the IRB. If an amendment addresses an issue related to biosafety or radiation safety, the appropriate committee or subcommittee first approves the amendment.

An experienced reviewer would be an IRB member who possess the specific background applicable to the study being reviewed and/or is designated as a scientific member of the IRB versus a nonscientist member. The IRB Chair may also appoint a consultant to review minor changes and provide feedback to the IRB Chair who is then responsible to make the decision regarding the expedited review. The IRB Chair or designee conducting the expedited review has the final authority in deciding whether the revision qualifies for expedited review and/or may decide to recommend full committee review if the request exceeds the eligibility criteria. The reviewer, however, does not have the authority to disapprove the research. The reviewer can either determine that the expedited procedure can be approved as presented or the reviewer must refer it to the full committee for review and contingent approval. Whether processed by the

expedited process or referred to the full IRB committee for review, conflict of interest issues of the IRB reviewer, investigator and immediate family members and ad hoc/consultants must also be considered when reviewing all minor changes to existing protocols.

The IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented during the previously authorized approval period. A minor change is one which, in the judgment of the IRB Chair/designee, makes no substantial alteration in:

1. The level of risks to the subjects
2. The research design or methodology
3. The number of subjects enrolled in the research
4. The qualifications of the research team
5. The facilities available to support safe conduct of the research
6. Any other factor which would warrant review of the proposed changes by the convened IRB.

A substantial or major change is a revision involving more than minimal risk to the participant which must be reviewed and approved by the full IRB.

O. Research Requesting Exemption

A request for human research exemption **(Appendix DD)** from further IRB review may be submitted to the Subcommittee of Human Studies for full committee review and approval. The IRB determines that the proposed research qualifies for exemption and all ethical concerns of privacy and confidentiality are addressed. Exempt research is followed at the NWIHCS. The continued review of human research exempt from further IRB review is conducted by the Research and Development Committee. Categories of exempt research are listed in the Checklist for Criteria Allowing Exemption from Federal Regulations. The IRB determines whether the research can be granted an exemption determination by completing the Checklist for Criteria Allowing Exemption from Federal Regulations **(Appendix TT)** and by completing the Subcommittee of Human Studies (IRB) Elements of Review Checklist (Appendix OO).

P. IRB Review of Allegations of Serious or Continuing Non-compliance

All allegations of serious or continuing non-compliance are reviewed by the convened IRB. The primary reviewer system is used. The IRB Chair and IRB Coordinator assign a primary reviewer based upon their expertise.

1. The Primary Reviewer will receive the complete protocol, the entire file and all documents as follows:

- initial IRB application updated with any changes
- current approved protocol
- current consent document
- HIPAA authorization document
- investigator's brochure when applicable
- any relevant multi-center trial reports
- report of non-compliance

2. IRB members who are not assigned as a primary reviewer will receive all relevant

information including the following:

- initial IRB application updated with any changes.
- current approved protocol
- current consent document,
- HIPAA authorization document
- report of non-compliance

Additional information is available to any IRB member who wishes to review it. The expectation is that all IRB members will review the provided materials in enough depth to discuss the information at the convened meeting. The primary reviewer summarizes their review for the Committee.

3. The non-compliance is discussed and the IRB may consider a range of actions including:

- suspension of the research.
- termination of the research
- notification of current subjects when such information may relate to subjects' willingness to continue to take part in the research.
- modification of the protocol.
- modification of the information disclosed during the consent process.
- providing additional information to past subjects.
- requiring current subjects to re-consent to participation.
- modification of the continuing review schedule.
- monitoring of the research.
- monitoring of the consent.
- referral to other organizational entities.

If , after reviewing a report, the IRB finds that the report is serious or continuing non-compliance, its findings will be reported as outlined in Section XVI of the IRB SOP.

Q. Suspension or Termination of IRB Approval and Administrative Closure of Research

Any Termination or suspension of research (e.g., by the IRB or other research review committee, or by the ACOS/R or other facility official) related to concerns about the safety, rights or welfare of human research subjects, research staff, or others must be reported directly (without intermediaries) to the facility director within five business days after the terminator or suspension occurs.

1. The report must be made in writing with simultaneous copies, as applicable, to the ACOS/R, the Research and Development Committee, the IRB and any other relevant research review committee.
2. The facility director must report the termination or suspension to appropriate ORO research officer within five business days after receiving such notification.

All investigators are required to notify the IRB promptly of any serious unexpected adverse events or unanticipated problems involving risks to subjects or others. In addition, the IRB must determine if serious or continuing non-compliance with applicable regulatory requirements occurred.

1. The IRB may vote to suspend or terminate some or all approved research conducted by a Principal Investigator when:

a. The research is not being conducted in accordance with IRB requirements OR
b. The research is associated with unexpected serious risk or harm to subjects OR
c. The IRB finds reasonable cause to remove the PI from the study OR
d. There is an investigation as to whether research should be terminated or suspended and there is reasonable concern that subjects are at increased risk pending the outcome of the investigation.

2. Suspension refers to an action initiated by the IRB to stop temporarily some or all research procedures pending future action by the IRB or by the investigator or his/her study personnel. This term is typically used in the context of a federal agency taking action against an institution. For example, the Office for Human Research Protections can suspend an Assurance, preventing the institution from continuing to conduct studies support with federal funds.

3. Termination refers to an action initiated by the IRB to stop permanently some or all research procedures.

4. The IRB Chair or designee may temporarily suspend some or all approved research conducted by a PI when there is reasonable concern that subjects are at increased risk and there is inadequate time for convening an IRB meeting to determine if a suspension should take place.

5. If an approved study is suspended or terminated by the IRB, the IRB or the person ordering the suspension or termination must take into consideration the following actions to protect the rights and welfare of currently enrolled participants:

a. If suspended, will the subjects be allowed to continue?
b. What impact will the suspension or termination have on currently enrolled subjects?
c. What procedures should be taken to withdrawal enrolled subjects impact the subject--time frames, notification, options, etc.?
d. Should the participants be informed of the termination or suspension and how will that be communicated?
e. Have any/all adverse events or outcomes been reported to the IRB?

6. In addition, the IRB may vote to administratively close a study when no enrollment of subjects is occurring and no patients are being followed. Adequate resources may not be available to continue the study. This is not considered a type of event to be reported to regulatory agencies.

IX. INFORMED CONSENT REQUIREMENTS

Investigators and research staff should understand the concept of respect for persons and the obligation to obtain informed consent from prospective participants, or their legally authorized representative (LAR), prior to initiation of their participation in research unless explicitly waived. It is important to remember that consent is a continual process and that there is a difference between the actual consent process and the documentation of the consent process. Participants or their legally authorized representative should be kept informed during the research process and whenever appropriate, the subjects should be provided with additional pertinent information after participation in the research study. If someone other than the investigator obtains the informed consent, the investigator must delegate this responsibility on the application to the IRB. The investigator as well as the person delegated to perform this activity must have appropriate training and be credentialed by the NWIHCS.

A. Components of the Informed Consent Document:

The VA Form 10-1086 must be used for studies conducted at the NWIHCS and must contain all of the required basic elements and the applicable additional elements outlined in the consent form template **(Appendix Y)**. The consent form is written in a language that could be understood by a junior high student being careful to put technical jargon into lay terms. The consent form template is written in the second person (e.g. "You are being invited to participate.") with the exception of the signature statement on the last page which is written in the first person as a declaration for the participant or their legally authorized representative.

In addition to the consent form elements, the document must include:

1. Signature and date lines for the subject. **(**In Nebraska, the age of majority means nineteen years of age. Children may not participate in VA-approved research without permission of the VA Chief Research and Development Officer in Central Office.)

2. When applicable, signature and date lines for the legally authorized representative. (which may be a person appointed as a health care agent under Durable Power of Attorney for Health Care (DPAHC), court appointed guardian, next of kin in the following order: Spouse, Adult Child – 19 or older, Parent, Adult sibling – 19 or older, grandparent, grandchild or a close friend.
Note: An individual who is qualified as a LAR to provide informed consent on behalf of a prospective research subject may not always qualify as a personal representative for purposes of consent to use or disclose a human subject's PHI (i.e., signing the HIPAA authorization). The investigator must ensure the LAR meets the requirements of a personal representative (legal guardian or power of attorney) in HIPAA and the Privacy Act of 1974 prior to the LAR's signing a HIPAA authorization.

3. A witness to the signature of the subject is not required unless the IRB requires a witness signature when approving the research (i.e., surrogate consent or requirement of a sponsor).

4. Signature of the PI or a research team member obtaining informed consent.

5. The name of the subject <u>must</u> be printed on each page and dated.

B. Informed Consent Process:

1. Prospective participants must be given sufficient information about the risks and benefits of the research to make a decision to initially and voluntarily participate and must be provided information during participation to ensure they can continue to make informed decisions regarding their continued participation. The principles concerning research enrollment of human subjects by all persons obtaining informed consent are outlined below. Explain to the research subject: "You are being asked to take part in a research project." Emphasize the importance of reading and understanding these principles that apply to all individuals who agree to participate in the research project. Also explain that participants should never be forced or coerced to participate in a research study and provide them with constant encouragement to ask questions along the way to ensure their understanding of what is being presented to them. The consent form may be read to the participant or the participant's legally authorized representative.

2. The investigator must give either the participant or the participant's legally authorized representative adequate opportunity to read the consent document before it is signed and dated. The participant or the participant's legally authorized representative must sign and date the consent document. Also, a witness to the participant's legally authorized representative's signature is required to sign and date the consent document. If the sponsor or IRB require a witness to the consenting process in addition to the witness to the LAR's signature and if the same person is needed to serve both capacities, a note to that effect need to be placed under the witness's signature line. A copy of the signed and dated consent document should always be given to the person signing the consent document.

3. The subject may not personally benefit from taking part in the research but the knowledge obtained may help health professionals better understand the disease/condition and how to treat it.

4. The subject may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which he/she is otherwise entitled.

5. If during participation in the research project, new information becomes available concerning the subject's condition (disease), risks of the study, or concerning better therapies that would affect him/her being in the research project, the doctor will discuss this new information with the subject. This discussion will help the subject to make a decision about continuing in the research. The investigator is responsible for ensuring that any changes to the consent process, including the sharing of new information, is clearly documented and formally shared with the IRB (the content of the new information to be disseminated should be submitted to the IRB for approval first, as it is part of the ongoing consent process) as well as the participants.

6. The purpose of the research, how it will be done, and what the subject's part in the research will be, is described in the consent form. Also described in the consent form are the risks, inconveniences, discomforts, and other important information needed to make a decision about whether or not the subject wishes to participate. The potential risks of the research versus those associated solely with usual care provided by the subject's health care provider should be discussed during the consent process. Subjects are advised to review the risks with their health care providers. The information given to the subject or legally authorized representative must be in a language that is understandable. The subject or legally authorized representative is urged to

discuss any questions he/she may have about this research with the team members. The subject or legally authorized representative must give consent without coercion or undue influence.

7. No implication should be made (whether oral or written) to the subject or legally authorized representative to waive any of the subject's legal rights or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

8. Surrogate consent (consent from the subject's legally authorized representative): Under appropriate conditions investigators may obtain consent from the LAR of a subject. No individual who lacks decision-making capacity may participate in VA Research until the IRB has reviewed and approved that individual's, or that class of individuals', participation in a given study per the criteria for approval. The Investigator must 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 and provide information (i.e., informed consent process and HIPAA authorization) to the subjects' LARs.

a. Criteria for Decision Making Capacity: An individual is presumed to have decision-making capacity unless any one or more of the following apply:

(1) It has been documented by a qualified practitioner in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study. *Note: The qualified practitioner may be a member of the research team.*

(2) The individual has been ruled incompetent by a court of law.

If there is any question as to whether or not a potential adult subject has decision-making capacity, and there is no documentation in the medical record that the individual lacks decision-making capacity, and the individual has not been ruled incompetent by a court of law, the investigator must consult with a qualified practitioner (who may be a member of the research team) about the individual's decision-making capacity before proceeding with the informed consent process.

b. 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.

c. Criteria for Enrollment: Individuals who lack decision-making capacity may be enrolled in protocols if:

(1) The proposed research entails:

(a) No greater than minimal risk to the subject as determined by the IRB; or

(b) If the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject or

(c) Greater than minimal risk and no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition

that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

(2) The disorder (e.g., Alzheimer's) leading to the individual's lack of decision-making capacity is being studied, whether or not the lack of decision-making itself is being evaluated (e.g., an individual who lacks decision-making capacity as the result of a stroke can participate in a study of cardiovascular effects of a stroke), but only if the study cannot be performed with only persons who have decision-making capability.

(3) The subject of the study is not directly related to the individual's lack of decision-making capacity, but the investigator can make a compelling argument for including individuals who lack decision-making capacity in the study (e.g., transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in a nursing home where both individuals with, and those without, decision-making capacity are affected).

d. Responsibilities of LARs: LARs is acting on behalf of the potential subjects, therefore:

(1) LARs must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision.

(2) If the potential subject's wishes cannot be determined, the LARs must be told they are responsible for determining what is in the subjects' best interests.

(3) LARs generally assume the same rights and responsibilities as the individuals who lack decision-making capacity in the informed consent process (see 38 CFR 17.32(e)).

e. Dissent or Assent: If feasible, the investigator must explain the proposed research to the prospective research subject even when the surrogate gives consent. Although unable to provide informed consent, some persons may resist participating in a research (i.e., if they dissent) protocol approved by their representatives. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent.

9. The IRB and RAO staff must ensure that the IRB approval of the wording of the consent document is documented through the use of a stamp on each page of the VHA Form 10-1086 and that the dates reflects the most recent IRB approval of the document. If the consent document is amended during the protocol approval period, the consent document has to bear the approval date of the amendment rather than the date of the originally approved protocol.

C. Research Data Retention When a Subject Withdraws from a Clinical Trial:

The IRB determines the following regarding data retention when subjects withdraw from a clinical trial:

1. 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; however, for tissue banking, a subject must be given the option of withdrawing the specimen.
2. An investigator may ask a subject 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 would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentially of the subject's information.

3. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form.) IRB approval of consent documents would be required.
4. 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 investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator 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.

D. Progress Note Entry in the Medical Record:

In addition to a properly completed and signed consent form, the research team documents the process by generating a research consent note in the VA medical record (CPRS) Progress Note Properties section. The template in CPRS for the research consent note entry includes the following information:

1. The title of the study
2. The name of the Principal Investigator
3. The name of the Study Coordinator
4. Phone number
5. Pager number
6. A statement that the study was explained and
7. The study was discussed with (name of subject) with an opportunity for questions.
8. How the subject or legally authorized representative demonstrated comprehension (the subject verbalized understanding)
9. The person obtaining the subject's consent
10. The consent was obtained on (enter date) prior to initiating the study procedure.
11. The subject received a signed copy of the consent and HIPAA authorization.

An entry is placed in the progress note when the subject's participation begins, for all procedures performed for research, and when the subject's participation is terminated. Consent and entry into the study notes can be combined when both occur at the same visit.

E. Flagging of the Medical Record:

1. The patient health record <u>must</u> be flagged if the subject's participation in the study involves:
(a) Any invasive research procedure (e.g., muscle biopsy or bronchoscopy);
(b) Interventions that will be used in the medical care of the subject, or that could interfere with other care the subject is receiving or may receive (e.g., administration of a medication, treatment, or use of an investigational device);
(c) Clinical services that will be used in the medical care of the subject (e.g., orders for laboratory tests or x-rays ordered as a part of the study), or that could interfere with other care the subject is receiving or may receive; or
(d) 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 interests of the subject (e.g., an interview study

of victims of sexual assault).

2. In other situations, the IRB determines if flagging is necessary.

3. When the research consent note is completed by the principal investigator and his/her research team, the note is forwarded to the primary care physician for co-signature. This alerts the caregiver that the patient is in a research study. The flagging of the medical record in CPRS may not be required if the patient's participation is: 1) only one encounter, 2) only the use of a questionnaire, 3) the use of previously collected biological specimens, or the identification of the patient as a subject would place the subject at greater than minimal risk. The primary care giver will be informed via a co-signature note when the study is terminated. The IRB will determine if flagging is required and document its findings on the Elements of Review Checklist as well as communicate this to the PI.

F. Dual/Multiple Research Study Enrollment

It is the IRB's responsibility to ensure subjects who enroll in multiple studies are protected against increased risks due to their willingness to participate. Subjects who participate in dual and/or multiple research studies may not only be exposed to the risks of each study in which they participate but may also be exposed to any adverse or cumulative effects of dual/multiple enrollment (e.g., contraindicated medications, excessive radiation exposure, etc.). For this reason, both the PI and the IRB are required to take additional measures when enrolling a subject(s) into interventional studies which are greater than minimal risk. Although not all interventional studies with greater than minimal risk may present an issue of concern for the subject(s), cases of dual enrollment in interventional, greater than minimal risk studies require additional consideration by the PI and IRB and will be reviewed on a case-by-case basis.

Responsibility of the PI

Prospective subjects should always be asked directly whether or not they are participating in any other study as part of the study's eligibility screening process. If a prospective subject indicates that he or she is enrolled in another study, it is the PIs responsibility to ask the subject about the study in which they are participating. If the PI requires additional information, it is his/her responsibility to find out the specifics of the study from either the subject and/or the PI conducting the study. If the PI's study is interventional with greater than minimal risk and the subject is already enrolled in another interventional, greater than minimal risk study, the PI must submit a Dual/Multiple Research Study Enrollment Waiver form **(Appendix PP)** for IRB review and approval before enrolling the subject(s). PIs should be referencing the IRB's final determination of the level of risk for their study; the IRB may have modified the level of risk on a study based upon their review. In cases where the PIs of two or more interventional, greater than minimal risk studies are conducting their studies in collaboration, one Appendix PP can be completed to cover all enrollment of prospective enrollees into either of the studies.

If the waiver is approved by the IRB, investigators **must** document their compliance with this policy in the CPRS note.

Responsibility of the IRB

When an interventional greater than minimal risk study is being conducted, dual/multiple enrollment in another interventional greater than minimal risk study must be carefully reviewed, and all special circumstances considered, before a determination regarding approval by the IRB can be given. Each request for Dual/Multiple Research Study Enrollment Waiver **(Appendix PP)** will be evaluated on a case-by-case basis. NOTE: Each Principal Investigator responsible for the studies must agree that dual enrollment poses no increased risk to the subject and will not have a negative effect on the research in order for the waiver to be considered by the IRB.

The IRB Chairperson or his/her designee will review all requests for waivers of dual/multiple enrollment and make a determination as to whether dual enrollment poses any increased risk to the prospective research subject(s). The Chairperson, or his/her designee, has the authority to grant the waiver, deny the waiver, or defer the request to the fully convened IRB. The fully convened IRB may grant the waiver request, grant the waiver request with stipulations, or deny the request. The investigator will be notified of the IRB's decision in writing.

G. Obtaining Informed Consent from Non-English Speaking Subjects

The Common rule at 38 CFR 16.116 and 16.117 requires that informed consent information be presented in language understandable to the subject (or legally authorized representative) and, in most situations, that informed consent be documented in writing. When the consent interview is conducted in English, the consent document should be in English. When the subject population includes non-English speaking people or the investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB will require a translated consent document to be prepared and assured by the investigator, in writing, that the translation is accurate. A certified translator will perform translations. While a translator may facilitate conversation with a non-English speaking subject, routine translation of the informed consent will not substitute for a written translated informed consent. The appropriately translated consent documents must be submitted to the IRB for review and approval prior to their use in enrolling subjects. The IRB may utilize expedited review procedures in approving such documents if the English language consent document has already been approved, and the investigator attests in writing to the accuracy of the translation.

The short-form consent is not used at the NWIHCS.

Contracted foreign language interpretation services for a research participant and/or the legally authorized representative are provided to the NWIHCS through Precision Language Services. You may call the number below and provide the access code, station and language requested.

1) Dial 1-866-895-7375
2) Enter the Access Code applicable to your station:
   - PLS16 Omaha and its Community Based Outpatient Clinics
   - PLS08 Grand Island and its Community Based Outpatient Clinics
   - PLS15 Lincoln and its Community Based Outpatient Clinics

H. Alternative Forms of Informed Consent Requirements

1. Waiver or Alteration of Informed Consent Requirements:

Government Research**:** VA Regulations 38 CFR 16.116(c) permits IRB approval of a consent procedure which does not include, or which alters some or all of the elements of informed consent; or waive the requirement to obtain informed consent provided the IRB finds and documents that the research could not be practicably carried out without the waiver or alteration, **and**
The research is to be conducted by or subject to approval of state and local officials and is designed to study, evaluate, or otherwise examine procedures for obtaining benefits under public service programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs.
Request this waiver or alteration on **Appendix AA**.

Minimal Risk Research: VA regulations at 38 CFR 16.116(d) and the Common Rule permit an IRB to approve a consent procedure which does not include or which alters some or all of the required elements of informed consent, or to waive the requirement to obtain informed consent altogether when the research is non-FDA regulated. To approve such a waiver or alteration **(Appendix AA)**, the IRB must find and document that:

a. The research involves no more than minimal risk to the subjects,

b. The waiver or alteration shall not adversely affect the rights and welfare of the subjects.

c. The research could not practically be carried out without the waiver or alteration.

d. Whenever appropriate, the subjects shall be provided with additional pertinent information after participation.

These findings and their protocol-specific justifications shall be clearly documented in IRB minutes when the VAMC's designated IRBs exercise this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the VAMC's designated IRBs cannot approve such alterations or waivers for FDA-regulated research (21 CFR 50.20). For FDA regulated research, informed consent must be obtained except for: Emergency Use of a Test Article Without 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 under specific circumstances and stipulations.

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

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case,

each subject shall be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (The waiver provision is not applicable to FDA-regulated research). OR

b. The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the principal investigator to provide subjects with a written statement regarding the research. This policy is also applicable to FDA-regulated research. The IRB will consider and review a written description of the information to be provided to subjects when waiving the requirement for the investigator to obtain a signed consent form.

3. Short-form Consent: The short-form consent is not used at the VA Nebraska-Western Iowa Health Care System.

I. Compliance With Federal and State Law

The NWIHCS Research Service and NEBRA follow state law in determining who is a legally authorized representative for a possible research subject who is not competent to give an informed consent to participate in a study. National VA policy establishes a limited class and a strict priority among that class as to who can give such substituted consent. Those so designated by VA in order of priority are: a health care agent appointed by the person in a DPAHC; court-appointed guardians of the person, or the next-of-kin.

However, VA DPAHC policy defers to state law as to the validity of a state DPAHC. See VHA Handbook 1004.2, para. 4a(3). Nebraska DPAHC state law limits who can be designated as an agent under a state DPAHC to persons who are married or are at least 19 years of age. See Neb. Rev. Stat. sections 30-3402(1) and 3403. There is no age limit set by VA for a VA DPAHC. But VA policy on next-of-kin surrogate decision making defers to state law in this area as well, and Nebraska state law once again sets a minimum age of 19 years of age unless married. See Neb. Rev. Stat. section 43-2101. Therefore, because VA is silent as to a minimum age of the agent under a VA DPAHC and to avoid unwanted complexity, the state law requirement of 19 years of age or married is followed for all surrogate decision making. In addition, the state law on guardianships is followed. See Neb. Rev. Stat. section 30-2617, et. seq.

In stating the above, we note that there is no conflict between VA policy and state law as to the authority of a healthcare agent to give substituted consent in the research setting. Both VA policy and state law grant such authority to a properly designated healthcare agent.

J. Certificates of Confidentiality

What is a Certificate of Confidentiality (CoC) ?

A Certificate of Confidentiality (CoC) helps researchers protect the privacy of human research participants enrolled in biomedical, behavioral, clinical and other forms of sensitive research. Certificates protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a

research participant.

What is the effect of a Certificate? What protection does it afford?
Researchers can use a Certificate to avoid compelled "involuntary disclosure" (e.g., subpoenas) of names and other identifying information about any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect. It does not protect against voluntary disclosures by the researcher, but those disclosures must be specified in the informed consent form. A researcher may not rely on the Certificate to withhold data if the participant consents in writing to the disclosure.

How long does a Certificate's protection last?
Individuals who participate as research subjects (i.e., about whom the investigator maintains identifying information) in the specified research project during any time the Certificate is in effect are protected permanently- even if the subject gave the researcher data before the Certificate is issued.

In what situations may personally identifiable information protected by a Certificate be disclosed?
Personally identifiable information protected by a Certificate may be disclosed under the following circumstances:

- Voluntary disclosure of information by study participants themselves or any disclosure that the study participant has consented to in writing, such as to insurers, employers, or other third parties;
- Voluntary disclosure by the researcher of information on such things as child abuse, reportable communicable diseases, possible threat to self or others, or other voluntary disclosures provided that such disclosures are spelled out in the informed consent form;
- Voluntary compliance by the researcher with reporting requirements of state laws, such as knowledge of communicable disease, provided such intention to report is specified in the informed consent form (see Attachment D, which sets forth PHS policy on reporting of communicable diseases); or
- Release of information by researchers to DHHS as required for program evaluation or audits of research records or to the FDA as required under the federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.)

K. Consent for Use of Picture and/or Voice

VA Form 10-3203 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 NWIHCS and VHA policy.

1. 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 (VA Form 10-1086). Photography or recordings cannot occur prior to the patient’s granting such permission (VHA Handbook 1907.01).

2. 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 (i.e., VA Form 10-1086). 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.

L. Lay Language Examples for the Consent Form

The following are some examples of lay language to simplify the reading level of a consent form:

Term	Definition
acute	new, recent, sudden
adverse effect	side effect
assay	lab test
benign	not malignant, usually without serious consequences
bolus	an amount given all at once
cc	cubic centimeter, i.e., 10cc = 2 teaspoons
carcinogenic	capable of causing cancer
catheter	a tube for withdrawing or introducing fluids
chronic	continuing for a long time
clinical trial	an experiment with patients
controlled trial	a study in which the experimental procedures are compared to standard (accepted) treatments or procedures
culture	test for infection, or organisms that could cause infection
double blind	study in which neither the investigators nor the subjects know which intervention the subject is receiving
dysplasia	abnormal cells
edema	increased fluid
efficacy	effectiveness
extravasate	to leak outside of a blood vessel
hematoma	a bruise, a black and blue mark
heparin lock	needle placed in the arm with blood thinner to keep the blood from clotting
monitor	check on, keep track of, watch carefully
morbidity	undesired result or complication
mortality	death or death rate
necrosis	death of tissue
oncology	the study of tumors or cancer
percutaneous	through the skin
placebo	a substance of no medical value, an inactive substance
PRN	as needed
protocol	plan of study
random	by chance, like the flip of a coin
relapse	the return of a disease
retrospective	looking back over past experience

X. Vulnerable Populations and Special Studies

Department of Veterans Affairs (VA) regulations at and Food and Drug Administration (FDA) regulations require IRBs to give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
The IRB is also required to ensure that it has adequate representation on the committee to consider specific kinds of research involving vulnerable populations in a satisfactory manner when applicable.

Elements to Consider in Reviewing Research Involving Vulnerable Subjects**.** IRBs must pay special attention to specific elements of the research plan **(Appendix T)** when reviewing research involving vulnerable subjects.

- Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
- The IRB should carefully consider group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
- Investigators should not be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.
- IRBs must be knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.
- All studies that may require obtaining surrogate consent for patients judged incompetent should be in compliance with VHA Handbook 1200.05 or superceding state law.
- Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. The IRB shall look to see that such procedures are a part of the research plan and shall assess the plan for adequacy. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.
- The IRB may require additional safeguards that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversees the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

A. Women of Childbearing Potential

Pregnancy must be excluded whenever there is a potential hazard (more than minimal risk) to a fetus (e.g., most studies dealing with new drugs or radiation. In therapeutic research, a determination of

pregnancy must be made and, if positive, the purpose of the activity must be to meet the health needs of the mother, with the risk to the fetus at the minimum necessary to meet such needs. The consent form must indicate the potential hazard to the fetus.

Even in the case of research dealing with the treatment of serious life-threatening disease in women of childbearing potential (and where the accepted modes of therapy are ineffective), a determination of pregnancy must be done. If the test is positive, the subject should be informed of the danger to the fetus so that she may come to an informed decision as to whether to undergo the investigational therapy. For example, a woman has the right to forego investigational therapy in the hope of delivering a viable infant even though this course could lead to her death.

If pregnant women are to be excluded from a study which includes women of childbearing potential, the consent form should include the equivalent of the following: For women of childbearing potential - Since this research may have an adverse effect on an unborn child and should therefore not be done during pregnancy, it is necessary that a pregnancy test be done first. "To my knowledge, I am not pregnant at this time." If the study involves a period of time (days, weeks), the consent form must indicate the need for contraception measures in sexually active women, such as: "If sexually active, I will take contraceptive measures for the duration of the research."

B. Pregnant Women

Research involving pregnant women as subjects is **not** approved unless:

- The research includes adequate provisions to monitor the risks to the subject and the fetus.
- Adequate consideration has been given to the manner in which potential subjects are going to be selected.
- Adequate provision has been made to monitor the actual consent process by procedures such as:
    - Overseeing the process by which the consent of individuals is obtained either by:
        - Approving enrollment of each individual.
        - Verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed.
    - 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.
- Appropriate studies on animals and non-pregnant individuals have been completed, and data for assessing risks to pregnant women and fetuses are provided.
- 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.
- The risk to the fetus is the least possible risk for achieving the objectives of the activity.
    - Individuals engaged in the activity have no part in:
        - Any decisions as to the timing, method, and procedures used to terminate the pregnancy.
        - 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.
    - No inducements, monetary or otherwise, are offered to terminate pregnancy for purposed of research.
    - One of the following is true:
        - The fetus is placed at risk only to the minimum extent necessary to meet the health care needs of the mother.
        - The risk to the fetus is minimal.
    - Consent is obtained from the mother and father, except that the father's 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 ascert5ained.
        - He is not reasonably available.
        - The pregnancy resulted from rape.

Research on fetus, fetal tissue, and neonates, or in vitro fertilization is not permitted at VA.

C. Prisoners

Proposed research involving prisoners is not conducted at the NWIHCS. Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted at the VA NWIHCS unless a waiver has been granted by the Chief, Research and Development Officer in VA Central Office (45CFR Part 46, Subpart C). If subjects become incarcerated while in a study, suspension or termination from participation in the study will result when medically feasible. Only when termination of the subject's participation is not feasible and the subject remains incarcerated at the time the study-related procedures or treatment are to be performed, the study would be re-reviewed with appropriate expertise as defined in 45 CFR Part 46, Subpart C.

D. Children

Research involving children is not conducted at the NWIHCS. A waiver from the Department of Veterans Affairs Office of Research and Development in Washington, D.C. must be granted in order to include children in VA-approved research. Research conducted with children requires approval by an IRB constituted in compliance with 45 CFR 46 Subpart D and incorporates all of the conditions for inclusion as listed in VHA Handbook 1200.05, Appendix D.

E. Persons with Mental Disabilities, Educationally or Economically Disadvantaged Persons

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. These populations, in addition to economically disadvantaged persons, are considered to be vulnerable to coercion.

Research involving incompetent persons or with impaired decision making should only be approved when the investigator demonstrates a compelling reason to include them as participants as outlined in VHA Handbook 1200.05. The criteria for decision-making capacity and the criteria for enrollment are outlined in Section IX. Informed Consent Requirements.

IRB determination: If the criteria for enrollment are met, the IRB may approve the inclusion of individuals who lack decision-making capacity in research studies on the basis of informed consent from LARs as defined in the Section IX. Informed Consent Requirements.

Before approving the study, the IRB must:

1. Ensure the study includes appropriate procedures for respecting dissent;
2. Consider whether or not the study needs to include procedures for obtaining assent; and
3. Determine whether any additional safeguards need to be used (e.g., consent monitoring).

The IRB must document its deliberations and the criteria it used to approve inclusion of individuals who lack decision-making capacity in the IRB minutes or IRB protocol file.

F. Additional Considerations regarding Vulnerable Populations: Suicide Prevention Efforts for Clinical Research

The VA Clinical Science Research and Development Service (CSR&D) program has established an agreement with the VA National Suicide Hotline Center as one aspect for managing remote cases of suicidal thoughts or expressions when study personnel may be talking with a research participant face-to-face or on a telephone. The "warm transfer" procedure is described in guidelines posted by the VA CSR&D. This is defined as transferring a call and giving the referring party an opportunity to share information over the phone prior to the call transfer. A warm transfer also allows for all three parties to on the line at the same time if needed. For any studies funded by CSR&D and Cooperative Studies, Principal Investigators should consider incorporating this procedure into your study safety plan. The guidance document published by the VA CSR&D program is on the IRB website.

The VA National Suicide Prevention Hotline is 1-800-273-TALK (8255).

XI. PARTICIPANT OUTREACH PROGRAM

It is VHA policy that each facility conducting human research establishes a Research Participant Outreach Program for current, prospective, or past research participants or their designated representatives.

1. **Facility Director**. The Director is responsible for ensuring the local Research Participant Outreach Program is established and implemented. The Program should include:

a. A reliable mechanism for research participants to communicate with research project investigators, and with an informed VA representative who is independent of the research project in question (e.g., providing contact information in the informed consent form).

b. Making available the informational brochure, "Volunteering in Research – Here are some things you need to know", to potential research participants in settings where participants may be recruited (e.g., clinic waiting areas), and to each prospective participant when that individual is approached to take part in a project.

c. Venues for participants and their designated representatives to obtain information, discuss their questions and concerns, and offer their input.

2. **Associate Chief of Staff (ACOS)**. The ACOS for Research and Development (R&D) is responsible for implementing the local Research Participant Outreach Program and ensuring local investigators have an adequate supply of the brochure. Placement of brochures and research materials within the hospital is done through the Public Relations Office (PRO). The ACOS/Research will meet at least annually with PRO to mutually evaluate the current activities and discuss opportunities for improvement.

3. **Research Compliance Officer (RCO).** The RCO is responsible for overseeing and evaluating the facility's Outreach Program. The RCO will conduct a "walk-through" inspection twice a year looking for the presence of the Research informational brochure, "Volunteering in Research – Here are some things you need to know", in clinics and common spaces throughout the hospital. The RCO will also use these walk-through opportunities to speak with research staff, especially those working in the Clinical Research Unit (CRU), about their outreach efforts and the effective placement of research materials.

4. **Investigator.** The investigator is responsible for making available the informational brochure to potential research participants in a setting where they may recruit participants (e.g. clinic waiting areas), and to each prospective participant, and surrogate where necessary, when an individual is approached to take part in a project. This requirement applies when written documentation of informed consent is waived, but not when informed consent has been waived. In addition, the investigator is responsible for ensuring that all consent forms must provide participants with contact information for the investigator and study staff, as well as a person independent of the research team for when the research staff cannot be reached, or if the participants which to talk to someone other than the research staff, and/or the participants wish to voice concerns or complaints about the research. The investigator is also responsible for informing the independent contact person regarding the relevant details of the study, and for documenting that this contact person has been informed, to ensure their ability to render proper assistance to potential subjects.

5. **Reference**.

a. Belmont Report “Ethical Principles and Guidelines for the Protection of Human Subjects of Research”.

b. VHA Handbook 1200.05

XII. USE OF INVESTIGATIONAL DRUGS, BIOLOGICS OR DEVICES

A. General FDA, DHHS and VA requirements

When an FDA regulated test article is used in research being done at VA Nebraska-Western Iowa Health Care System or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by the U.S. Department of Health and Human Services (DHHS), e.g., the National Institutes of Health (NIH), fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS and VA human subject regulations. Where regulations differ, the IRBs apply the stricter one.

<u>FDA Requirements Compared to DHHS and VA (the Common Rule) Requirements</u>
The human subject protection requirements found in FDA regulations are substantially the same as the Common Rule requirements. However, there are important differences:

1. The FDA has different definitions for "human subject" and "clinical investigation (research)",
2. FDA regulations contain no Assurance requirement,
3. Conditions for exemption, exception, and waiver of IRB review and informed consent requirements differ,
4. FDA regulations require specific determinations for the IRB review of device studies, and
5. FDA regulations include specific requirements for reporting adverse events that are not found in the Common Rule or DHHS and VA regulations.

In addition to the Common Rule, there are specific additional protections for pregnant women, human fetuses, and neonates (Subpart B); prisoners (Subpart C); and children (Subpart D) which are addressed in the VHA Handbook 1200.05. In April 2004, FDA issued revised regulations to protect children in research (21 CFR 50 Subpart D).

In addition to regulations governing human subject protection, the FDA also has regulations governing the investigational use of drugs and biological drugs (21 CFR 312) and devices (21 CFR 812).

<u>Additional Veterans Affairs (VA) Requirements</u>
VA policy (VHA Handbook 1200.05) requires that all research comply with the VA human subject regulations, as well as with all FDA applicable regulations regarding investigational drugs and investigational devices.

For research using an investigational drug as defined in VHA 1108.04, a VA Investigational Drug Information Record (VA Form 10-9012) **(Appendix EE)** must be completed by the principal investigator and submitted to Pharmacy Service. The pharmacy must be provided with a signed copy of the subject's informed consent form on VA Form 10-1086 prior to the pharmacy dispensing the initial dose of an investigational drug on an IRB-approved study. The principal investigator must also notify the Chief of Pharmacy Service and the Research and Development Committee when the IRB is notified that a study involving investigational drugs has been terminated.

B. Research Involving Investigational FDA Regulated Test Articles

Medical products, such as drugs, biologics, and medical devices need to be proven safe and effective before the FDA can approve them for sale to and use by patients. FDA reviews the results of laboratory, animal and human clinical testing to determine if a product to be put on the market is safe and effective. New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

The IND is an investigational new drug application and is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." Investigational new drug (or investigational drug) means a new drug or biological drug used in a clinical investigation. An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met.

An approved investigational device exemption (IDE) permits a device not approved by FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE from the FDA, but an assessment of the need for an FDA IDE is required by the sponsor, investigator and IRB. (see details in XIV of the SOP) With only a few exceptions, most clinical research being done on FDA regulated test articles with an IND will need initial review and continuing review at a convened IRB meeting. The PI must provide this IND or IDE number on the application to the IRB with supporting documentation.

C. Investigator and Sponsor Responsibilities

Under FDA regulations, the i**nvestigator** in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include:

1. Ensuring informed consent of each subject is obtained
2. Ensuring the investigation is conducted according to the investigational plan
3. Personally conducting or supervising the investigation
4. Protecting the rights, safety, and welfare of subjects
5. Preparing and maintaining adequate, current, and complete case histories or records
6. Retaining records for two years following the date the marketing application is approved or withdrawn
7. Furnishing the required reports to the sponsor, including reports of adverse events and study completion
8. Providing timely reports to the IRB, including reports of changes in the research activity needed to avoid immediate hazards to subjects, unanticipated problems involving risks to subjects or others, including adverse events to the extent required by the IRB
9. Ensuring that changes are not implemented without prospective IRB approval, unless required to eliminate immediate hazard to subjects
10. Complying with the requirements of the Controlled Substances Act
11. Complying with all FDA test article requirements
12. Adequately maintaining control of test articles, including appropriate tracking documentation for test articles to the extent that such control and documentation are not centrally administered
13. Supervising the use and disposition of the test article

14. Disclosing relevant financial information
15. Ensuring that all associates, colleagues, and employees assisting in the conduct of the investigation(s) are informed about their obligations in meeting the above commitments.

The **sponsor** takes responsibility for initiating the clinical investigation, and holding the IND or IDE, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical or biotech company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. An investigator at the NWIHCS is not permitted to hold the IND or IDE. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation. Some of the responsibilities of sponsors are:

1. Selecting qualified investigators
2. Providing investigators with the information they need to conduct the investigation properly
3. Ensuring proper monitoring of the investigation
4. Ensuring that the FDA and (for devices) any reviewing IRBs or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

D. Committee Approval

Any drug used for research purposes in a clinical investigation is considered investigational regardless of whether or not the research is conducted under an IND; therefore, a completed VA Form 10-9012, Investigational Drug Information Record, is needed for all drugs used for research purposes prior to the time of first dispending of the investigational drug. The PI must also forward a copy of the protocol to Pharmacy Service to request their support for the study prior to IRB approval.

An investigational drug can be: (1) a new chemical compound which has not been released by the Food and Drug Administration for general use, or (2) an approved drug that is being studied for an unapproved or approved use, dose, dosage form, administration schedule, or under an Investigational New Drug (IND) application, in a controlled, randomized, or blinded clinical trial. In clinical investigations where an investigational drug with an IND and an FDA-approved drug are being compared to evaluate safety and/or efficacy, a VA Form 10-9012 is needed for both of these drugs. A VA Form 10-9012 is not required for drugs not meeting the definition of an investigational drug, such as concurrent, rescue, or auxiliary medications. VA Form 10-9012 may contain information for more than one investigational drug if the drugs are commercially available and not blinded.

The IRB will utilize 21 CFR Part 312 to determine if an IND is required. Subpart B of this regulation states the requirement for an IND as follows:

1. A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a)
2. A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.
3. A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written

determination 30 days after FDA receives the IND or earlier.

The IRB will not approve a study if a drug/biologic is ***NOT*** FDA approved unless an IND has been secured. Whenever there is a question regarding FDA approval, the IRB Coordinator will contact FDA to obtain additional clarification. However the IRB will be guided by the fact that an IND is also required if the drug/biologic is FDA approved in the following circumstances:

1. the trial is intended as a well-controlled study in support of a new indication or intended to support any other significant change in the labeling of the drug;
2. The research is intended to support a significant change in the current advertising for an approved product;
3. The research involves a route of administration, dosage level, use in a subject population, or other factor that significantly increases the risk (or decrease the acceptability of the risks) associated with the use of an approved product.

The use of an investigational drug or biologic in a clinical investigation requires approval by the IRB and R&D Committee. Validation of the IND number is done by the IRB Coordinator prior to IRB review of the clinical investigation. This is done by evaluating the IND number on one of the following materials supplied by the investigator: (1.) sponsor protocol or sponsor correspondence or (2) FDA correspondence. A VA Investigational Drug Information Record (VA Form 10-9012) must be completed by the PI and submitted with the protocol for review by the IRB and R&D Committee. Research involving an FDA-regulated investigational drug will only occur after the IRB:

1. Has received documentation that the research will be conducted under an applicable Investigational New Drug Application (IND), or
2. The protocol meets one of the FDA exemptions from the requirement to have an IND. [Categories #1, #2 and #4 in 21 CFR 312.2(b) which apply to human studies]

- Exemption 1
  - The drug product is lawfully marketed in the United States.
  - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
  - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
  - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
  - The investigation is conducted in compliance with 21 CFR 50 and §56.
  - The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
- Exemption 2
  - A clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following:
    - Blood grouping serum.
    - Reagent red blood cells.
    - Anti-human globulin.
  - The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis

made by another, medically established, diagnostic product or procedure.
- The diagnostic test is shipped in compliance with 21 CFR 312.160.

o Exemption 4
- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

Upon approval of the research project by the IRB and R&D Committee, the original signed VA Form 10-9012, the IRB approved consent form, and a copy of the signed protocol are forwarded to the Chief of Pharmacy Service. Pharmacy Service Policy Memo 001 should be referenced for procedures followed for receipt, storage, and dispensing of the investigational drugs. A copy of the signed VA Form 10-9012 is sent to the PI and a copy is filed in the protocol folder. A copy of the VA Form 10-9012 is filed in the subject's medical record by the PI or research team member per VHA Handbook 1108.04.

E. Pharmacy Benefits Management (PBM) Program

1. The NWI Clinical Pharmacoeconomist sends out the PBM notice to a standard list serve which includes the Omaha VA Research Pharmacist, ACOS/Research and AO/Research. It also includes the VHAOMA Research Personnel listing of current Research PIs, technicians and staff.

2. When received by the AO/Research, the subject line is checked against all drugs used in current protocols using the IRB electronic tracking software.

a. If the drug is being used by any specific investigator, the AO/Research sends the notification to the PI asking them to acknowledge receipt and what actions will they take as a result of the PBM.
b. The notice is entered onto a spread sheet that lists all PBM notices during the fiscal year. This list is maintained in the PBM folder located on the shared drive.
c. The AO/Research and/or the ACOS/Research forward a copy of the notice to the IRB Coordinator for inclusion and discussion on the following IRB agenda/meeting.
d. The electronic notices are filed in the AO/Research office

3. The PBM is discussed at the next meeting following receipt of the notice as an informational item unless further action is required/deemed appropriate by the IRB. Documentation of discussions or additional actions would be included in the IRB minutes.

4. The VHA Directive 2008-072 may be referenced for procedures to follow when further action(s) are required.

XIII. INVESTIGATIONAL DEVICE RESEARCH

The IRB considers an investigational device to be one that is not currently marketed in the United States. According to 21 CFR 812, clinical evaluation of devices that have not been cleared for marketing requires an IDE approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA, informed consent from all patients, labeling for investigational use only monitoring of the study and required records and reports.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution. Sponsors need not submit a PMA or Pre-market Notification 510(k), register their establishment, or list the device while the device is under investigation. Sponsors of IDEs are also exempt from the Quality System (QS) Regulation except for the requirements for design control.

A significant risk device is defined by the FDA as an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A non-significant risk (NSR) device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

A. Submitting Investigational Device Studies to the IRB

Investigators submitting projects involving investigational devices must submit the following in addition to the standard materials required for IRB initial submission **(Appendix T)**.

- Reports of prior investigations conducted with the device
- The proposed investigational plan
- Subject selection criteria
- Monitoring procedures planned for the study
- Sponsor’s risk assessment and rationale
- Sponsor’s statement detailing any other IRBs that have reviewed the proposed study and

what determinations were made.

● Investigational Device Exemption (IDE) number and supporting documentation (if applicable)

The use of an investigational device in a clinical investigation requires approval by the IRB and R&D Committee. The IRB will refer to 21 CFR Part 812 when determining FDA requirements for an IDE and when FDA required an IDE. An investigator at the NWIHCS is not permitted to hold the IND or IDE. Validation of an existing IDE number is done by the IRB Coordinator from: (1.) sponsor protocol, (2) device brochure, (3) sponsor correspondence, (4) FDA correspondence. Research involving an FDA-regulated investigational device will only occur after the IRB:

1. Has received documentation that the research will be conducted under an applicable Investigational Device Exemption (IDE), or
2. Has formally determined that satisfactory justification has been provided by the investigator as to why an IDE is not required.

B. Significant Risk (SR) vs. Non-Significant (NSR) Risk Devices

1. Distinguishing Between SR and NSR Device Studies:

a. The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

b. If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, an IRB will review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

2. SR/NSR Studies and the IRB: The NSR/SR Decision:

a. The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should

inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

b. The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

c. The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, an IRB must consider the nature of the harm that may result from use of the device. 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 should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

d. FDA has the ultimate decision in determining if a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

C. IRB Determinations of Device Risk

1. If the IRB decides the study is Significant Risk:
   a. IRB Responsibilities:
   Notify sponsor and investigator of SR decision. After IDE is obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]
   b. Sponsor Responsibilities:
   Submit IDE to FDA or, if electing not to proceed with study, notify FDA Center for Devices and Radiological Health (CDRH Program Operations Staff 301-594-1190) of the SR determination; Study may not begin until FDA approves IDE and IRB approves the study. Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

2. If the IRB decides the study is Non-significant Risk:
   a. IRB proceeds to review study applying requisite criteria [21 CFR 56.111]
   b. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

3. IRB Determination of the risk of the device study:

a. Once the SR/NSR decision has been reached about the investigational device, the IRB will consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study [21 CFR 56.111]. The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

b. FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures [21 CFR 56.110].

D. Informed Consent Documentation and Process for IDE Research

1. Informed consent must meet the requirements outlined in the IRB Informed Consent policies and procedures **(Appendix Y)**.
2. No claims are to be made which state or imply, directly or indirectly, that the IDE is safe or effective for the purposes under investigation or that the device is in any way superior to any other device;
3. The informed consent document must contain a statement that the IDE is “investigational, meaning non-FDA approved”;
4. The informed consent document must contain a statement that the FDA may have access to the subject’s medical records as they pertain to the study; and
5. The Investigator must ensure that throughout the consenting process and study participation the subject understands that the IDE is experimental, and that its benefits for the condition under study are unproven.

E. Exemptions from IDE requirements

1. A device can be exempt from the IDE requirements. A claim that the device is exempt must reference the exemption category being claimed. There are seven exemption categories that may be claimed. Categories 3 and 4 are the most common. Full information regarding the seven exemption categories that may be claimed can be found in the FDA regulations 21 CFR Sec. 812.2(c).

2. Under category 3, (21 CFR Sec. 812.2(c)(3)), in addition to the sponsor’s compliance with applicable requirements in 21 CFR Sec. 809.10(c), the diagnostic device testing must

comply with the following:

a. Is noninvasive;
b. Does not require an invasive sampling procedure that presents significant risk;
c. Does not by design or intention introduce energy into a subject; and
d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

3. Under category 4, (21 CFR Sec. 812(c)(4)), to qualify for this exemption, the device testing must not be for the purposes of determining safety and effectiveness and must not put subjects at risk. The device testing must be limited to the following:

a. Consumer preference testing;
b. Testing of a modification; or
c. Testing of a combination of two or more devices in commercial distribution.

4. The sponsor or sponsor/investigator should provide sufficient justification to the IRB that supports the exemption category being claimed.

5. An exemption from the IDE requirement is not an exemption from the requirement for prospective IRB review or informed consent.

F. Investigator Responsibilities for Investigational Device Studies

The Investigator is responsible for the tracking and oversight of FDA-regulated devices in research and must meet the following requirements in order to use an investigational device in research conducted under the jurisdiction of the IRB:

1. The investigational device must be used only by the Investigator or under his/her direct supervision;
2. The investigational device must be used only as approved by the FDA and as described in the currently approved IRB documents;
3. The Investigator must not supply the investigational device to any persons not authorized under the IDE; and
4. Informed consent from the subject or the subject's legally authorized representative must be prospectively obtained.
5. Research with the use of an investigational device must be conducted under all IRB applicable policies and procedures.
6. Proper disposing or return of investigational devices
7. Storage of the investigational device under lock and key
8. The investigator shall maintain the following accurate, complete and current records related to the device:

a. Correspondence with the IRB, sponsor, monitor, other investigators and FDA
b. Records of receipt, use or disposition of a device that relate to:

(1) The type and quantity of the device, dates of receipt, and batch numbers or code marks
(2) Names of all persons who received, used, or disposed of each device
(3). The number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s)

c. Records of each subject exposure to the device, including;
   (1) Informed consent
   (2) All relevant observations
   (3) Adverse device effects
   (4) A record of the exposure of each subject to the investigational device, including the date and time of each use and any other therapy

d. Dates and reasons for any deviations from the protocol

G. Additional Reporting Requirements.

1. Devices may have an unanticipated adverse device effect to subjects or others. An investigator must submit to the sponsor and to the IRB a report of any unanticipated adverse device effect to subjects or others occurring during an investigation as soon as possible, but in no event later than 5 working days after the investigator first learns of the effect. Should the IRB determine that the new information gained in the adverse effect report changes its risk assessment, the IRB has the ability to reconsider its prior NSR decision and ask for FDA review.

2. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate or suspend all investigations or parts of investigations presenting that risk as soon as possible. Termination or suspension must occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

3. If the device is a significant risk device, a sponsor may not resume a terminated or suspended investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated or suspended investigation without IRB approval and, if the investigation was terminated or suspended for an unanticipated adverse device effect that presented an unreasonable risk to subjects or others, FDA approval.

H. Studies of Devices with the FDA 510 K Designation

FDA regulations allow a manufacturer/sponsor to claim that a new device is substantially equivalent to models that FDA has already approved for marketing. Safety and efficacy testing of 510K devices, or use of 510K devices in clinical protocols, requires review by the IRB and approval before the study may begin. Application to the IRB must include verification of the device's 510K status.

I. Humanitarian Use Devices (HUD) or Custom Devices

Investigators who wish to use devices classified by the FDA as Custom or Humanitarian Use must consult the IRB office for guidance before using such a device or submitting a protocol.

XIV. EMERGENCY USE OF A TEST ARTICLE

Emergency use is 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. The IRB acknowledges that there will be certain limited circumstances where IRB approval will not be obtainable prior to the first use of a test article. FDA requirements for emergency use must be met, and the IRB requires written notification to the IRB following the use **(Appendix F)**. FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had time to convene a meeting. However, if subsequent use of the test article is contemplated, a complete IRB application must be submitted for full board review prior to any additional use of the test

A. Definitions.

1. Emergency Use: 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.

2. Unapproved Use: Use of a drug in a way or on a population different from that in which it was approved by the FDA.

3. Test Article: Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

4. Life-Threatening: Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

5. Severely Debilitating: Diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

B. Prior to Emergency Use of the Test Article

1. Emergency use of an investigational drug or biologic requires an IND. Therefore, the treating physician (PI) must contact the manufacturer to determine if the product can be made available for use under the company's IND. If the company elects not to name the PI on the IND, the treating physician can contact the FDA for an IND or obtain evidence of an IND Exemption. The treating physician must contact the appropriate department at the FDA and provide to the IRB a letter from the sponsor-IND holder authorizing release of the investigational drug or biologic.

2. FDA information defines an unapproved medical device as a device that is used for a

purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 360(e)]. An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520(g) of the Act [21 U.S.C. 360(j)(g)] and 21 CFR part 812. Medical devices that have not received marketing clearance under section 510(k) if the FD&C Act are also considered unapproved devices which require an IDE.

The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

a. Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:
(1) the patient is in a life-threatening condition that needs immediate treatment;
(2) no generally acceptable alternative for treating the patient is available; and
(3) because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

b. FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

c. In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the FDA Office of Emergency Operations.

d. FDA would expect the physician to follow as many subject protection procedures as possible. These include:
(1) obtaining an independent assessment by an uninvolved physician;
(2) obtaining informed consent from the patient or a legal representative;
(3) notifying institutional officials as specified by institutional policies;
(4) notifying the Institutional Review Board (IRB); and
(5) obtaining authorization from the IDE holder, if an approved IDE for the device exists.

3. The physician must assure that the device sponsor/manufacturer notifies the FDA immediately after an unapproved device is shipped for emergency use. Call the main FDA number 888-463-6332 and select from the menu or visit the www.fda.gov website and view the contact list.

C. Informed Consent For Emergency Use of a Test Article

Even with emergency use, the treating physician is responsible for obtaining the informed consent of the subject or the subject's legally authorized representative. Informed consent is documented according to the NWIHCS patient care and treatment policy on Informed Consent (Policy COS-007) prior to administration of the test article.

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, and
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the PI must be reviewed and evaluated in writing by an independent physician within 5 working days. The investigator must complete Section III of the form: "Notification of Emergency Use of an Investigation Drug, Biologic, or Device" **(Appendix F)**.

D. Reporting Requirements Following Emergency Use of a Test Article

Emergency use of all test articles must be reported to the IRB. The following written materials documenting emergency use of a test article must be submitted to the IRB by the PI within 5 working days:

1. Notification of Emergency Use of an Investigation Drug, Biologic, or Device **(Appendix F)**
2. IND or IDE documentation from FDA or the sponsor (if applicable)
3. Other information about the patient or emergency use of the test article if not included in the preceding forms including any adverse events and unanticipated problems associated with the use of the test article.

E. IRB Chair Responsibilities Following Notification of Emergency Use of a Test Article

1. The IRB Chair is responsible for making the following evaluations:
   a) The emergency use of the test article met the FDA criteria allowing the

exemption from IRB review.

b) Written informed consent was obtained and documented.

c) If written informed consent was not obtained by applying the exception from informed consent requirements for emergency use of a test article, the situation met the FDA criteria.

2. If the IRB Chair determines that FDA regulations were not followed, the matter will be handled according to IRB policies and procedures for non-compliance (Memorandum No. 151-10).

3. The IRB Chair has the authority to require an additional follow-up report from the PI that includes information on the subject's outcome and any adverse events or unanticipated problems.

4. If subsequent use of the test article is contemplated on the same subject or others, a complete IRB application must be submitted for full board review prior to any additional use of the test article.

5. The IRB Chair is responsible for full committee notification on the next available IRB meeting agenda.

6. The IRB Chair will provide information to clinicians who are faced with a patient care situation involving the proposed use of a test article in a life-threatening situation without prior IRB review to determine that circumstances would follow FDA regulations. If the decision to use a test article is made by the clinician, he/she must then follow procedures noted above in sections B-D.

7. Emergency use is not research under the Common Rule that applies to all VA research. Therefore, the PIs and the IRB are reminded that data obtained in the course of emergency use may not be used as research data.

F. Planned Emergency Research

The VAMC does not allow planned emergency research studies that exempt informed consent requirements under 21 CFR 50.24 to be conducted at this institution.

XV. PROCESS FOR UTILIZING THE REPORT OF PROBLEMS FORM FOR INTERNAL EVENTS REQUIRING IRB REPORTING

A. Purpose: These procedures describe how the VA NWIHCS complies with VHA, DHHS and FDA regulations which state that unanticipated problems involving risks (UPRs) to participants or others must be reported to the IRB, institutional officials and relevant federal agencies and departments.

> **NOTE: Problems impacting on the privacy and/or confidentiality of patients are outlined in Section XVI of this SOP and require reporting to internal authority within one hour of discovery.**

B. Definitions:

Adverse event (AE): Any untoward occurrence (physical, psychological, social or economic) in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Adverse Device Effect (ADE): An ADE is any adverse event/effect caused by or associated with the use of a device that is unanticipated and has not been included in the protocol

Internal AE: An AE experienced by a participant in a study conducted at the NWIHCS.

External AE: An AE experienced by a participant in a study conducted at an external site (a site not under the jurisdiction of the NWIHCS).

Protocol Deviation/Violation: Any departure from the defined procedures described in the IRB-approved protocol.

Unexpected adverse event (UAE): An UAE is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

Related: An event is "related" if it is more likely than not to have been caused by the research procedures. (Events caused by progression of underlying disease are usually NOT related).

Serious Adverse Event (SAE): A SAE is an adverse event in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social or other intervention is needed to prevent such an outcome.

Unanticipated (unexpected) problems: The terms "unanticipated" and "unexpected" refer to an event or problem in VA research that is new or greater than previously known in terms

of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

1. Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; AND
2. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

C. Problems that Require Prompt Reporting to the IRB

Investigators are to report the following types of SAEs or problems involving risks to subjects or others to the IRB using the Report of Problem form (**Appendix LL**). Reporting should be done immediately when there is a high risk to subjects and all other problems should be reported as soon as possible but not later than five (5) business days of the discovery of the problem:

1. Local (occurring within the NWIHCS) Unanticipated SAEs.
   This requirement is in addition to other applicable reporting requirements such as the sponsor under FDA requirements.
   The unfounded classification of an SAE as "anticipated" constitutes serious non-compliance.

2. 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.

3. 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.

4. 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.

5. Any DMC, DSMB, or DSMC report describing a safety problem.

6. 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.*

7. 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.

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

9. An accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has the potential to occur again.

10. A change to the protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.

11. Publication in the literature that indicates an unexpected change to the risks or potential benefits of the research.

12. A complaint of a participant that indicates unexpected risks or that cannot be resolved by the research team.

13. Incarceration of a participant in the course of a study.

14. A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

15. Adverse events that are unexpected, and related to the study treatment or intervention.

16. In FDA clinical trials, any unanticipated adverse device effect occurring during the investigation. [21 CFR 812.150(a)]

17. A protocol deviation/violation which is a change or alteration in a procedure(s) as outlined in the IRB-approved [protocol or procedures at the NWIHCS.

D. Distribution of the Report of Problem

The IRB Coordinator, upon receipt, immediately forwards the problem reports to the IRB Chair or designee who then makes the determination of what process to follow as outlined in Section E below.

E. IRB Procedures for Reviewing and Evaluating Report of Problems

1. Within five business days after a report of a problem involving risks to subjects or others, or of a local unanticipated SAE, the Chair or designee or, if time allows, the convened IRB must determine and document whether or not the reported incident was serious and unanticipated and related to the research. “Related” means the event or problem may reasonably be regarded as caused by, or probably caused by, the research. If the Report of Problem was submitted by someone other than the protocol PI, the IRB Chair or designee must notify the PI regarding the evaluation being done.

2. One of two actions can be taken by the IRB Chair or designee:

a. If the reviewer determines the report does not constitute an unanticipated problem involving risks to participants, the Report of Problem form is not forwarded

to the IRB. One copy of the report is filed in the IRB protocol file and the original is returned to the PI of the protocol.

b. If the reviewer determines that the problem or event is serious and unanticipated and related to the research and/or is serious or continuing non-compliance, the IRB Chair or designee, in collaboration with the Research Compliance Officer, must report the problem or event directly (without intermediaries) to the facility Director within 5 business days after the determination. The report must be in writing with a simultaneous copy to the ACOS/Research, RCO and the R&D Committee. When a report suggests that participant safety is at risk, the IRB Chair may immediately suspend or terminate the protocol. The Medical Center Director must report the problem or event to the appropriate ORO office as follows:

i. ORO Regional Offices serve as the focal point for oversight of facility Human Research Protection Programs (HRPPs) and Research and Development (R&D) Committee Oversight Programs. Reports related to HRPP and R&D Committee matters should be sent to the ORO Regional Office responsible for the reporting Facility.

ii. Matters related to Federalwide Assurances (FWAs), other ORO-approved human research assurances, and Memoranda of Understanding (MOUs) related to human research protection arrangements should be sent simultaneously to the responsible ORO Regional Office and the ORO Central Office FWA/MOU Contact Person.

iii. The ORO Central Office Research Safety and Animal Welfare (RSAW) group serves as the focal point for oversight of facility research safety and animal welfare programs. Reports related to research safety, research laboratory security, Bio-Safety Level 3 (BLS-3) laboratories and laboratory animal welfare should be sent to the ORO Central Office RSAW group.

iv. The ORO Central Office Research Information Protection Program (RIPP) group serves as the focal point for oversight of facility research information protection programs. Reports related to research information protection should be sent to the ORO Central Office RIPP group.

3. The qualified IRB member-reviewer has the option to refer a report of problem to the next convened IRB meeting if deemed appropriate.

4. If the IRB finds that the problem or event is serious and unanticipated and related to the research involving risks to participants or others, according to the definition in the policy, the IRB considers the following actions:
   a. Requiring modifications to the protocol (If required, IRB must determine at a convened meeting whether previously enrolled subjects must be notified, and if so, when, how notification must occur and be documented.)
   b. Revising the continuing review timetable
   c. Modifying the consent process
   d. Modifying the consent document (If required, IRB must determine at a convened meeting whether previously enrolled subjects must be notified, and if so, when, how notification must occur and be documented.)

e. Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
f. Providing additional information to past participants
g. Requiring additional training of the investigator and/or study staff
h. Reconsidering approval
i. Requirement that current participants re-consent to participation
j. Monitoring of the research
k. Monitoring of the consent process
l. Referral to other organizational entities (e.g., legal counsel, risk management, institutional official)
m. Suspending the research according to IRB SOP Section XVI. B.
n. Terminating the research according to IRB SOP Section XVI. B. Other actions appropriate for the local context.
o. Determining the problem or deviation/violation is continuing or serious non-compliance and reporting according to IRB SOP Section XVI B.

XVI. PROCEDURES TO FOLLOW REGARDING EXTERNAL REPORTING OF REPORTABLE PROBLEMS

A. Purpose: There are numerous types of incidents/situations that must be reported externally. This Section will provide a guide and outline of procedures to follow in terms of **WHO** should report incidents, **WHEN** should it be reported, **WHAT** should be reported, HOW should it be reported, WHERE should it be reported and WHO should report it in these various situations. Included below are procedures regarding incidents discovered, identified and/or reported by the ISO/PO/similar internal areas, RCO audits, incidents of serious and/or continuing noncompliance, unanticipated problems, IRB identified issues and other basic situation that could occur. In addition, please refer to the Research Service Polices and Procedure for Allegations of Non-compliance as well.

B. WHO is responsible for reporting problems? Everyone has a role to play in the reporting process.

1. Everyone is responsible to be aware of any situations that may impact human safety and protection. This includes research personnel and non-research personnel.
2. Whenever an incident occurs or is suspected of occurring, it is everyone's responsibility to internally notify the ACOS/Research and/or the Research Compliance Office immediately. All research personnel must personally inform the ACOS/Research and/or RCO when any incident occurs. Do not assume that they will find out from other sources. Each research person must accept individual responsibility to report occurrences to the ACOS/R and/or RCO to begin the reporting mechanism.
3. Once notified, the ACOS/Research, RCO, ISO and PO work closely to keep each other informed of any and all incidents to ensure proper notification to all internal and external parties is made.
4. The RCO assists with reporting to external entities through the Director.
5. The ISO and/or PO report findings to the professional oversight areas in their chain of command but keep Research abreast of any/all research related incidents.

C. WHEN should something be reported? Any incident impacting on the safety and risk to patients should be reported immediately. There is an external reporting expectation that the ACOS/R, RCO, ISO and PO must follow for reporting as well.

1. Internal reporting to the Director must be done within 5 days.
2. External reporting to ORO and other applicable places must be done within 5 days.
3. NSOC reports must be filed within one hour of the incident to external entities by the ISO and/or PO and then reported internally to the Director.

D. WHAT should be reported? The basic rule of thumb is that anything outside the approved protocol or outside the norm should be reported internally and screened for the

need/appropriateness for additional external reporting. Some examples of reportable events/situations include the following:

1. As outlined in Section XV, Investigators are to report the stated types of SAEs or problems involving risks to subjects or others to the IRB using the Report of Problem form (**Appendix LL**). Reporting should be done immediately when there is a high risk to subjects and all other problems should be reported as soon as possible but not later than five (5) business days of the discovery of the problem. When appropriate, external reporting should be done in accordance with the chart available in this section.

2. Incidents discovered, identified and/or reported by the ISO/PO/similar internal areas which impact on the privacy and confidentiality of patient information and data. The ISO and/or PO may be required to file a National Security Oversight Committee (NSOC) report which then triggers the need for station follow-up with ORO, and when appropriate, other external entities. Important to note: When you are involved in an ISO/PO incident, you must self report to the ACOS/Research immediately.

3. The Research Compliance Officer (RCO) conducts research audits for informed consents, compliance and cause. RCO reports are shared with the PI and internal authorities and when appropriate/applicable, with external entities as well.

4. Incidents of serious and/or continuing noncompliance can be discovered through an allegation or an incident that becomes known by the ACOS, RCO, Research Administrative Office, and/or any research member. Section XV addresses IRB initiated discoveries but the external reporting is similar regardless of who identified the concern.

E. Requirements for Reporting to Regulatory Agencies

1. Policy: It is the policy of the NWIHCS to comply with all applicable local, state and federal regulations in the conduct of research studies and to communicate certain actions to entities that may have an interest in the status of the research being conducted. The following types of events are defined in the Definitions section of this manual and require reporting to appropriate regulatory agencies:

- Unanticipated problems involving risks to participants or others
- Serious or continuing non-compliance
- Suspension or termination*

2. Responsibilities: The IRB Chair/Designee is responsible for drafting a letter to be sent to the facility Director with a simultaneous copy to the ACOS/R&D, RCO, R&D Committee and any other relevant research review committee within 5 business days once the IRB Chair/designee or convened IRB takes any of the following actions:

- Determines that a problem or event is unanticipated and serious and related to the research involving risks to participants or others,
- Determines that non-compliance was serious or continuing, or

- Suspends or terminates approval of research.

3. Procedures:

a. The IRB Chair/designee prepares a letter than contains the following information:

- Nature of the event (unanticipated problems involving risks to participants or others, or serious or continuing non-compliance, or suspension or termination of approval of research*)
- Title of the research project and/or grant proposal in which the problem occurred
- Name of the principal investigator on the project
- Number of the research project assigned by the IRB and number of any applicable federal award(s) (i.e., grant, contract or cooperative agreement)
- A detailed description of the problem including the findings of the IRB, and if appropriate R&D Committee, and the reasons for the decision
- Actions the institution is taking or plans to take to address the problem (e.g., suspend subject enrollment, terminate the research, revise the protocol and or informed consent, inform enrolled subjects, increase monitoring, etc.)
- Plans, if any, to send a follow-up or final report by the earlier of: (1) a specific date, or (2) when an investigation has been completed or a corrective action plan has been implemented.

b. The Institutional Official (facility Director) is responsible for reporting the problem or event 5 business days after receiving notification. *(ORO requests a 48-hour telephone/e-mail "heads up" of events/problems determined to be serious and unanticipated and related to research.)*

**Any Termination or suspension of research (e.g., by the IRB or other research review committee, or by the ACOS/R or otherfacility official) related to concerns about the safety, rights or welfare of human research subjects, research staff, or others must be reported directly (without intermediaries) to the facility director within five business days after the terminator or suspension occurs.*

1. *The report must be made in writing with simultaneous copies, as applicable, to the ACOS/R, the Research and Development Committee, the IRB and any other relevant research review committee.*
2. *The facility director must report the termination or suspension to appropriate ORO research officer within five business days after receiving such notification.*

c. Communication documenting any reports should be filed in the Protocol folder/ Administrative Section in the Research Administrative Office.

4. Distribution of Report: The Research Compliance Officer sends copies of the letter to the following as appropriate:

- Institutional Official
- Chief of Staff
- IRB
- R&D Committee

- Office of Research Oversight Regional Office
- Office of Research & Development
- VISN Director (for incidents of serious or continuing noncompliance)
  Thru VISN 23 Research Service Line Director
- FDA, if the study is subject to FDA regulations
- OHRP
- Federal agency supporting the research
- Principal Investigator
- Service Chief of Principal Investigator
- Affiliate University, if faculty member
- Sponsor, if the study is sponsored
- Contract Research Organization, if the study is overseen by a contracting research organization
- VA Privacy Officer if the event involved unauthorized use, loss or disclosure of individually-identifiable patient information
- VA Information Security Officer if the event involved violations of information security requirements

Copies of the letter signed by the Facility Director within five (5) business days after notification from the IRB, and when appropriate R&D Committee, action with a follow-up report when the investigation has been completed or a corrective action plan has been implemented. This reporting could be expedited depending upon the event and agency's reporting requirements. The letter and reports will be sent to the appropriate officials, committees and agencies listed above.

5. References: References include VHA Handbook 1200.05, VHA Handbook 1058.01

XVII. Collaborative (Involves VA Data and Affiliate Data) Research Studies Separating VA Research from Non-VA Research

A. Separation of VA activities/research from affiliate/collaborator activities/research is critical when dual appointment investigators wish to conduct studies that require combining VA data with affiliate/collaborator data.

1. VA research is research conducted by VA investigators (serving on compensated, without compensation (WOC), or Intergovernmental Personnel Agreement (IPA) appointments) while on VA time, utilizing VA resources (e.g. equipment), or on VA property including space leased to, or used by VA. The research may be funded by VA, by other sponsors, or be unfunded. (VHA Handbook 1200.01 §3.b)

2. The protocol(s) for "collaborative" research studies must clearly separate VA research activities and data from non-VA research activities and data, including for example where applicable, recruitment procedures, strategies, and advertisements; procedures, interactions, and interventions related to the research; data collection, storage, access, use, disclosure, and analysis; uses and disclosures of Protected Health Information (PHI); researchers and study team members; VA clinics, units, and laboratory locations; and VA Information Security Officer (ISO) and Privacy Officer (PO) reviews.

3. "Off-site" VA research activities, including data collection and use, occurring at non-VA locations (i.e., locations not owned or leased by VA) must be clearly identified.

4. If VA data will be combined with non-VA data for "collaborative" studies, the protocol(s) must specify when and how this will occur and where the combined data will be stored.

5. Data security arrangements for the "collaborative" study are noted in the Checklist for Reviewing Privacy, Confidentiality and Information Security in Research, **Appendix NN**.

6. The informed consent document and HIPAA authorization from both VA and non-VA sites must clearly separate VA research activities from non-VA research activities, and clearly state that:
   a. Resultant data are to be used in a multi-site ("collaborative") study that combines VA data with non-VA data; ***and***
   b. The data are to be disclosed to the Coordinating Center site (located at either the VA site or the non-VA site) where the data will be combined and analyzed for the study.

B. 1. In summary it is critical to separate and document the following:
   a. Activities on VA time vs.
   b. Affiliate activities on affiliate time

2. The documentation as outlined in the Investigator's Memorandum of Understanding (MOU) with the affiliate clarifies:
   a. VA duties

b. VA duty locations
c. VA tours of duty <u>or</u> time allocations

3. The MOUs are updated when there is a change in the commitment.

4. The documentation in the Checklist for Reviewing Privacy, Confidentiality and Information Security in Research clarifies:
a. Data ownership issues
b. Data security requirements

XVIII. RESEARCH COLLABORATIONS

Requirements in research collaborations are specific to the role that VA NWIHCS assumes with respect to studies conducted at multiple sites. Each participating institution is responsible for safeguarding the rights and welfare of human participants and for complying with all regulations.

When VA NWIHCS is the Principal site for a multi-site study, the PI is responsible for the overall conduct of the study, for maintaining appropriate documentation for all sites and for being the primary point of communication to external agencies and participating sites.

When VA NWIHCS serves as the coordinating center for a multi-site research study, the VA NWIHCS IRB must review and approve the coordinating site protocol. The VA NWIHCS IRB must receive documentation of IRB review and approval from each participating site.

When VA NWIHCS serves as a participating site for a study, the VA NWIHCS PI is responsible for the conduct of the portion of the study that is occurring at NWIHCS. The local PI is responsible for reporting data to the principal site as required by the protocol, and for providing timely communications concerning the research at this site and at other sites to the NWIHCS IRB as specified in the locally approved protocol and local policies and procedures.

When the VA NWIHCS PI is the lead investigator on a VA Cooperative Studies Program, the role of the local facility must be clearly outlined in a protocol submitted to the local IRB (that role may not meet the description of a Principal Site or Coordinating Center). The local IRB must review and approve the research activities that will be performed as a part of the Cooperative Studies Program that are different than that of a participating site. The IRB's responsibilities in such a review are to evaluate items outlined in the Principal Site and Coordinating Center sections below that are related to the activities being performed at NWIHCS.

A. Investigator Responsibilities when VA NWIHCS is Principal Site

1. The VA NWIHCS PI is responsible for meeting all requirements listed under "coordinating center" below in addition to points B-H that follow.

2. The VA NWIHCS PI has ultimate responsibility for serving as liaison with outside regulatory agencies, with other participating sites, and for all aspects of internal review and oversight procedures.

3. For each site, the VA NWIHCS PI must provide documentation of assurance of compliance at each research site, and indicate whether the site has a local IRB.

4. The VA NWIHCS PI has ultimate responsibility for ensuring accuracy and integrity of data for the study, and for analysis and reporting of the data.

5. The VA NWIHCS PI is responsible for obtaining VA NWIHCS IRB approval for the protocol (all other sites must use the VA NWIHCS IRB-approved protocol), and for ensuring that all sites review, approve, and adopt all protocol modifications in a timely fashion.

6. The VA NWIHCS PI is responsible for maintaining documentation of all communications with participant sites and for ensuring that appropriate channels for communication with other sites are established and maintained.

7. The PI is responsible for monitoring study progress at all sites.

8. The VA NWIHCS PI may delegate some authorities to others on the study team but has overall responsibility for the conduct of the study at all sites.

B. Investigator Responsibilities when VA NWIHCS is Coordinating Center

1. Institutional activities of coordinating centers usually involve no direct interaction or intervention with participants. Where institutional activities involve no interaction or intervention with the participants, the principal risk associated with the activity is limited to a potential breach in confidentiality. Therefore, the VA NWIHCS IRB application for research involving an operations or coordinating center must include the following:

a. A description of the management and data analysis systems.+

b. A description of the recruitment strategy.

c. A description for monitoring the data collected to ensure the safety of participants. If coordinating center will serve for central analysis for adverse events explain in detail how this will be done. If the data will be monitored by Data Safety and Monitoring (DSM) board, include how the DSMB will be selected, how it operates, how often it convenes, and the reporting frequency to the VA NWIHCS IRB.

d. A description of the mechanism that will be used to communicate safety data back to the other participating sites.

e. A description of the mechanisms for protecting the privacy of participants (i.e., the participants' sense of being in control of the access of others to themselves) and for maintaining the confidentiality of data.

f. . The protocol and the prototype informed consent document(s) to be distributed to each local site.

g. Recruitment instruments, including flyers, newspaper ads, television spots, etc., that will be used nationally or as a prototype for local sites.

h. A copy of each local site's IRB approval including the FWA number or an itemized list of each local site, IRB approval and FWA number. The coordinating center is responsible for ensuring that each local site has IRB approval prior to enrollment of participants.

i. A description of the mechanisms that will be used to manage information flow and approval processes for protocol changes, reporting of unanticipated problems that are not adverse events, interim findings and other information that may affect the risk/benefit analysis of the study.

j. A description of mechanisms that will be used to communicate with all study participants if necessary.

2. Any justification for any substantive modifications by a local site of sample consent information related to risks or alternative procedures must be reviewed by the VA NWIHCS IRB as well as the local IRB.

C. IRB Committee Responsibilities when VA NWIHCS is Principal Site

1. The VA NWIHCS IRB is responsible for determining whether or not the PI has met all requirements listed under "coordinating center" below.

2. The VA NWIHCS IRB is responsible for ensuring that the PI has appropriately and adequately addressed the following:

a. Documentation of assurance of compliance at each participating research site, and whether each site has a local IRB or will rely on the VA NWIHCS IRB.

b. A clear means of communication has been established between the VA NWIHCS PI and all participating sites.

D. IRB Committee Responsibilities when VA NWIHCS is Coordinating Center

1. The VA NWIHCS IRB is responsible for ensuring that the PI has appropriately and adequately addressed the following:

a. A description of the management and data analysis systems.

b. A description of the recruitment strategy.

c. A description for monitoring the data collected to ensure the safety of participants. If coordinating center will serve for central analysis for adverse events explain in detail how this will be done. If the data will be monitored by the Data Safety and Monitoring (DSM) board, include how the DSMB will be selected, how it will operate, how often it will convene, and the reporting frequency to the VA NWIHCS IRB.

d. A description of the mechanism that will be used to communicate safety data back to the other participating sites.

e. A description of the mechanisms for protecting the privacy of participants and for maintaining the confidentiality of data.

f. The protocol and the prototype informed consent document(s) to be distributed to each local site.

g. Recruitment instruments, including flyers, newspaper ads, television spots, etc., that will be used nationally or as a prototype for local sites.

h. A copy of each local site's IRB approval including the FWA number or an itemized list of each local site, IRB approval and FWA number. The coordinating center is responsible for ensuring that each local site has IRB approval prior to enrollment of participants.

i. A description of the mechanisms that will be used to manage information flow and approval processes for protocol changes, reporting of unanticipated problems that are not adverse events, interim findings and other information that may affect the risk/benefit analysis of the study.

j. A description of mechanisms that will be used to communicate with all study participants if necessary.

E. 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.*

Multi-site trials are covered under this definition if any of the following apply:

1. VA is a sponsor;
2. VA functions as the coordinating center;
3. VA subcontracts to a foreign site;
4. The PI for the total study is a VA investigator; or
5. The VA investigator is specifically collaborating with an international investigator and the VA investigator sends data or human biological specimens outside the U.S., or receives them from outside the U.S.

NOTE*: This requirement does not apply if VA is only one of the participating sites and the trial does not meet the preceding conditions.*

Permission must be obtained from the CRADO, or designee, prior to initiating any VA-approved international research. This applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including agreements, MOU, Cooperative Research and Development Agreements (CRADA), grants, or contracts. The CRADO, or designee, will not grant permission for an international research study involving prisoners as research subjects.

All international sites must hold an international FWA, and the research must be approved by the IRB or Research Ethics Board of the participating site(s) that are listed on the international FWA.

The NWIHCS Medical Center Director is responsible for approving the request for permission to conduct international research prior to forwarding it to the CRADO for action and ensuring permission has been obtained from the CRADO, or designee, for the international research prior to its initiation by an investigator at the facility. *NOTE: Contact the Research Administrative Office for information on how to request permission from ORD.*

The Principal Investigator is responsible for:

1. Obtaining approval from the facility Director.
2. Obtaining permission from the CRADO, or designee, in writing before initiating an international research study.
3. Conducting research in compliance with VHA Handbook 1200.05, and all other applicable VA and other Federal requirements including those for protecting human subjects, tissue banking, use of databases, Federal criminal laws, and the Standards of Ethical Conduct for Employees of the Executive Branch.

XIX. REVIEW OF POLICIES AND PROCEDURES

The HRPP guidelines must remain in compliance with all applicable regulations. To remain current, this manual must be reviewed and periodically updated. The R&D Coordinator with the assistance of the IRB Chairperson, IRB Coordinator, HRPP staff, R&D Committee Chair, ACOS and Deputy ACOS/R&D, and AO/R&D will update these policies and procedures to comply with the most recent VA and federal regulations. Proposed changes will be presented to the IRB and R&D Committee for information and discussion. The ACOS/R&D assumes responsibility and oversight.

Revisions will be implemented once notification of changes and an updated SOP manual are distributed to investigators and committee members. All other documentation will be revised and distributed as needed. Changes are rolled out semi-annually unless more frequent distribution is required. Training sessions are conducted in conjunction with the rollouts to present updated forms and procedures to all individuals involved in the HRPP. The ACOS also provides updates at the Research Seminars and the monthly Principal Investigators' meetings.

XX. USING THE VHA CENTRAL IRB AS IRB OF RECORD

A. Purpose: The use of the VHA Central Office IRB to review select VA funded multi-site studies involving human subjects including initial, continuing review, amendments, monitoring, reporting and other relevant requirements are outlined in a Memorandum of Understanding (MOU) between VHA Central Office and the Nebraska-Western Iowa Health Care System (NWIHCS). The FWA Assurance number is amended to include the VA Central IRB as an IRB of record. The appropriate Office of Research and Development (ORD) funding Service (CSP, RR&D, HSR&D, QUERI, etc.) will determine if a study should be reviewed by the VA Central IRB.

B. Responsibilities: Responsibilities of the VHA Central Office Human Research Protections Program and VA Central IRB and the NWIHCS are outlined in the Memorandum of Understanding signed by both parties, the non-profit (NEBRA) signatory official, and the VISN 23 Network Director. The VA Central IRB will maintain current FWA registration, human protections accreditation, ensure appropriate training for its members and staff. They will meet at least monthly and maintain Standard Operating Procedures. Responsibilities at the NWIHCS are met by maintaining current FWA registration, accreditation and providing local accountability. All review of the research by the VA Central IRB to be conducted at the NWIHCS must be approved by the R&D Committee.

C. Procedures:

<u>VA Central IRB</u>
Functions of the Central IRB include the following:

1. The VA Central IRB reviews the PI application with members who have knowledge of the local research context or uses ad hoc advisors

2. Interacts regularly with the NWIHCS point of contact

3. Provides written notice to the NWIHCS of the Central IRB's action that requires a response from the NWIHCS

4. Works closely with the NWIHCS to investigate and take action on complaints, noncompliance and unanticipated problems

5. Coordinates required reporting to ORO and other regulatory agencies

6. A project disapproved by the Central IRB cannot be reviewed by the NWIHCS IRB.

<u>NWIHCS</u>
Functions of the NWIHCS include the following:

1. Provides the website and contact person to the NWIHCS investigator, http://www.research.va.gov/programs/pride/cirb/default.cfm, when preparing the Central IRB PI or Local Site Application which is reviewed and signed by both the Department Service Chief and the ACOS/R&D. The ACOS/R&D may not sign off on an application that was previously disapproved by NWIHCS IRB.

2. Maintains documentation that required training and credentialing is current for all NWIHCS HRPP staff and all applicable research team members of VA Central IRB approved projects. These records will be maintained by the respective coordinators.

3. The ACOS/R&D is the point of contact and holds local accountability to provide the protocol review and comments to the VA Central IRB on the proposed research study to be conducted at the NWIHCS. This review is completed within 15 calendar days from the date of receipt of the initial review considerations of the VA Central IRB. The ACOS/R&D will respond to VA Central IRB's final determination and serve as the liaison among the VA Central IRB, NWIHCS PI and the facility for oversight, compliance and monitoring purposes.

The project is reviewed and approved by the R&D Committee following receipt of the VA Central IRB-approved project. Approval by other subcommittees (i.e., Research Safety, Radiation Safety, etc.) must be secured for final approval to be granted.

4. The NWIHCS promptly informs the VA Central IRB of amendments to ongoing research and:

- complaints from subjects or others,
- unanticipated problems involving risks to subjects or others including serious adverse events that are unanticipated and related to the research,
- suspension or termination of research activities, and
- serious and/or continuing noncompliance

The Principal Investigator must report any unanticipated problems, protocol deviations or violations and amendments to ongoing research via forms at the VA Central IRB website.

5. Notifies VA Central IRB immediately of potential research impropriety, misconduct, suspension, debarment or restriction of any local research team member associated with Central IRB approved project.

6. The NWIHCS IRB cannot approve a project that has been disapproved by the VA Central IRB.

7. Maintains a protocol file of each VA Central IRB-approved project which includes initial application, the local site application, VA Central IRB-approved consent form and other associated documents with the initial application, final approval documents, R&D Committee approvals, monitoring reports/audits and subsequent correspondence as amendments, continuing review reports and approvals, etc.