

**MIAMI VA HEALTHCARE SYSTEM
INSTITUTIONAL REVIEW BOARD
INVESTIGATOR MANUAL**

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SECTION 1 - TYPES OF SUBMISSIONS

1.1 Overview of Manual

This Investigator Manual is intended to serve as a supplement to the “Miami VA Healthcare System (MVAHS) Standard Operating Procedures - Human Research Protection Program” (“HRPP SOP”). Individuals involved in the conduct of human subject research within the MVAHS are encouraged to consult the HRPP SOP for a comprehensive explanation of the policies and procedures described in this manual.

The IRB at the MVAHS is also called locally the Human Studies Subcommittee and these two designations should be considered interchangeable.

1.2 Website Containing MVAHS IRB Information

Copies of this Investigator Manual and the HRPP SOP are maintained at:

www.sfvafre.org

Periodic updates are posted on the website.

1.3 Research IRB Office Phone Number

305 575-7000 x4465

1.4 How to Obtain Forms

Instructions for preparing and submitting required materials are contained in this manual. All human subject research forms are available in the IRB Office; most may also be downloaded at www.sfvafre.org.

1.5 Time Frame for Submitting Materials

New research applications, amendments, and applications for continuing review should be submitted to the IRB Office two weeks or more before the next scheduled IRB meeting (schedules may be obtained at www.sfvafre.org). Other study-related documents must be submitted to the IRB Office according to the timelines specified in this manual. The Principal Investigator will be notified if the application packet or report is incomplete.

1.6 Definitions

Human Subject: A human subject as defined by VA regulations (38 CFR and VA Handbook 1200.05) 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)).

- Intervention as defined by VA regulations (38 CFR 16 and VHA Handbook 1200.05) 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. [38 CFR 16.102(f)]
- Interaction as defined by VA regulations means communication or interpersonal contact between investigator and subject. [38 CFR 16.102(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). [38 CFR 18.102(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).

Human Subject – FDA Regulations: For research covered by Food and Drug Administration (FDA) regulations (21 CFR 50 and 56), human subject means an individual who is or becomes a participant in a clinical investigation (as defined below in Research - FDA Regulations), either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In research involving devices, a human subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (21 CFR 812). **Note:** The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

Minimal Risk: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Research -VA Regulations: Research as defined by VA regulations means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge (38 CFR 16.102(d)).

Research- FDA Regulations: 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 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)]

Test Article: A test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

1.7 Determining Whether the Submission is Human Subject Research

The responsibility for initial determination as to whether an activity constitutes human subject research rests with the IRB or IRB Chair. The IRB or IRB Chair should make this determination based on the definitions of “human subject” and “research” in Section 1.6.

1.8 Determining Whether the Submission is a Quality Improvement Project

The determination as to whether quality assurance activities constitute human subject research rests with the IRB or the IRB Chair. Quality assurance activities attempt to measure the effectiveness of programs or services. Quality assurance activities that are designed solely for the purpose of internal program evaluation, with no external application or generalization, are not considered human subject research and do not require IRB review. If the activities meet the definition for human subject research, then R&D Committee and IRB review are required.

Before initiating a quality improvement activity, the principal proponent of the activity must submit a summary description of the project to the IRB and justify why the project does not require IRB review. Hospital personnel involved in the activity are encouraged to contact the IRB Office if they are unsure whether their project should be reviewed by the IRB.

The summary is forwarded to the IRB Chair (or designee) who determines whether:

1. The activity is considered research and if so, whether it would qualify for an exemption, expedited review, and/or waiver of informed consent. If the activity is determined to be research, the principal proponent is notified in a letter that a new research application must be submitted for IRB review.
(Procedures for processing new research applications as full committee review, expedited review or exempt review are described in Section 2.)
2. If the IRB Chair determines the activity is not research and therefore does not require IRB review, the principal proponent of the activity will be notified in writing.
3. If the IRB Chair determines that more information is needed, the principal proponent of the activity will be notified.

1.9 Research Activities vs. Innovative Treatments in Medical Practice

In the course of medical practice, sound clinical judgment sometimes leads physicians to employ “innovative” treatments where more common treatments appear to be ineffective or otherwise unsuitable in addressing a patient’s individual needs. Such innovative treatments, employed on an occasional basis and solely for clinical purposes, do not normally constitute human subject research and do not normally require IRB review. However, the use of innovative treatments as part of a systematic investigation designed, at least in part, to develop or contribute to generalizable knowledge does constitute human subject research and does require prospective R&D Committee and IRB review.

1.10 Research Activities vs. Medical Case Reports

Generally speaking, a case report is not considered research because it is not “a systematic investigation designed to develop or contribute to generalizable knowledge”; therefore, it does not come under the purview of the IRB or R&D Committee. Further, the case report presentation, whether by lecture or publishing, is executed by the physician of record, meaning that the patient's own physician is reporting the case and already has identified the patient and has access to the clinical data. If the presentation uses photographs, initials, or any other information that may possibly identify the patient, then a medical center consent form for this

purpose is required.

There does not appear to be a limit on the number of cases from one's own patients that form a case report and if exceeded, moves the situation into the category of retrospective chart review research and then requires IRB and R&D Committee review. Usually, a case report summarizes a small number of cases to emphasize a discrete instance of a disease. However, it is the nature of the report, not the absolute number of cases, that determines whether or not the activity involves human subject research. A non-research case report is limited to an account of an observation or a description of a disease process that has little scientific merit and is not subjected to scientific analysis. It is not presented as a systematic investigation designed to contribute to generalizable knowledge. A case report should be presented in such a way that it is readily distinguishable from a research report, which usually contains data with statistical analysis, or at least a systematic qualitative analysis, that substantiates the science and the conclusion and thus constitutes a contribution to generalizable knowledge.

1.11 Research Activities vs. Commercial Services

MVAHS facilities and laboratories may occasionally provide tests or other services to non-MVAHS researchers solely on a commercial basis (e.g., MVAHS performs MRIs for non-MVAHS investigators solely on a commercial basis).

Provision of such services solely on a commercial basis does not constitute human subject research and does not require MVAHS IRB review, provided that all of the following conditions are met:

- The research is not otherwise conducted at MVAHS;
- The research does not otherwise involve MVAHS employees or agents (e.g., as co-investigators, in planning or analysis, or receiving publication credit);
- The commercial services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges;
- The commercial services adhere to commonly recognized professional standards for maintaining privacy and confidentiality; and
- The commercial services are conducted under a valid contract.

However, if MVAHS personnel are involved in any way that is more than merely providing a commercial service, then prospective review and approval by the R&D Committee and IRB is required.

1.12 Research Involving Deceased Persons

Research involving deceased persons is not covered by VA or FDA human subject regulations or the Common Rule. However, such research may be covered under applicable state law. See also section 8.7 in this manual.

1.13 IRB and R&D Committee Approved Research

The IRB bases its actions relating to proposed research on the information contained in the research protocols and other documents submitted to the IRB Office. Research involving human subjects may not be conducted without an IRB-approved protocol. The R&D Committee must also grant final approval of any research protocol before the study is initiated, including IRB-approved studies. After the study is approved and initiated, the IRB has responsibility for

continuing oversight of human studies and carries out this responsibility by reviewing a variety of information including, but not limited to, reports of unexpected problems or adverse event reports, correspondence from sponsors and funding agencies, and continuing review applications. Investigators are notified in writing of all decisions reached by the IRB.

1.14 Review of Human Research Protocols

All new and continuing review applications are subjected to the following reviews:

1. IRB reviews: IRB reviewers make recommendations about the research and lead the discussion during the meeting.
2. Scientific reviews: Scientific reviewers provide feedback about the scientific merits of the research.
3. R&D Committee Reviews. This committee must give final approval for all research conducted at MVAHS.

During the review process, the reviewers may request additional information from the Principal Investigator.

1.15 IRB Determinations – New Protocols and Continuing Review

After careful review of the protocol and all accompanying materials and feedback from the reviewers, the IRB makes one of the following determinations:

1. **Approved** with no changes (or no additional changes). The protocol will be referred to the R&D Committee.
2. **Deferred for Non-substantive Issues (Contingent Approval)**
The protocol and/or consent form require minor revisions, such as wording changes, with replacement language provided. For protocols reviewed at a convened IRB meeting, the needed revisions are agreed upon at the IRB meeting. For protocols reviewed under expedited review, the needed revisions are designated by the reviewer(s). None of the required modifications can be related to the regulatory criteria for approval. These revisions are presented to the PI for incorporation by simple concurrence. Revisions must be made exactly as designated by the IRB or reviewer(s).

In order to receive approval for a protocol deferred for non-substantive issues, the following is required:

- For full review, the investigator's response, the revised protocol, and the previously submitted protocol are given to the IRB Chair, Vice-Chair, or a subcommittee of the IRB for review. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the IRB.
- For expedited, the investigator's response, the revised protocol, and the previously submitted protocol are given to the same reviewer(s) for re-review.

Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

The outcome of the IRB's deliberations is once again communicated to the investigator in writing. The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the next IRB meeting or in the file for expedited review.

Note: For full review, the expiration date for the protocol is calculated based on the date of the last convened IRB meeting and NOT on the final approval date.

3. **Tabled for Substantive Issues**

This action is taken if substantial modification or clarification is required, or insufficient information is provided to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). IRB approval of the proposed research must not occur until subsequent review of the revised materials is conducted by the convened IRB or the expedited reviewer(s).

In order to receive approval for a protocol deferred for substantive issues the following is required:

- For full review, the investigator's response must be submitted for review at a subsequent, convened meeting of the same IRB. The IRB Office provides the IRB with the investigator's response, the revised protocol, and the previously submitted protocol. The item is placed on the agenda for re-review at the next meeting.
- For expedited, the investigator's response, the revised protocol, and the previously submitted protocol are given to the same reviewer(s) for re-review.

Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

The outcome of the IRB's deliberations is communicated to the investigator in writing. The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the IRB meeting or in the file for expedited review.

4. **Disapproved.** The IRB has determined that the research cannot be conducted at the MVAHS or by employees or agents of the MVAHS or otherwise under the auspices of the VA.
5. **Suspension/Termination.** The IRB may suspend or terminate approval of active research due to investigator non-compliance, unexpected problems, or serious harm to subjects. (See Section 1.24 for additional information.)
6. **Approval in Principle.** As per federal regulations, (38CFR16.118), there are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents.

One circumstance is if the study procedures are to be developed during the course of the research, but human subject approval is required by the sponsoring agency.

The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the as yet undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal Investigator must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any pilot studies or pre-tests.

Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects.

1.16 Reporting IRB Actions

All IRB actions are communicated to the Principal Investigator or designated primary contact person for the protocol, in writing within ten (10) working days via a template letter prepared by the IRB staff and signed by the IRB Chair. For an approval, along with written notification of approval, a copy of the approved consent form containing the stamped approval with the dates of the approval and expiration on each sheet will be sent to the investigator. For a deferral, the notification will include the modifications required for approval along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision.

All letters to investigators must be filed in the protocol files maintained by the IRB. The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB staff to the MVAHS Institutional Official and are stored permanently and securely in the IRB Office.

1.17 Responding to the IRB's Request for More Information

Initial Review

After the initial review, investigators have 90 days to submit the materials or information requested by the IRB. If the information for a new protocol submission is not received within 90 days, the IRB Coordinator may notify the IRB that the application has been administratively withdrawn. The new application packet is filed in the current year's terminated files and extra copies returned to the Principal Investigator.

Note: Failure to submit a response to IRB-stipulated changes or inquires related to deferred or tabled protocols within 90 days of the IRB date of determination will result in administrative closure of the IRB file. The PI will receive notification of the closure of the IRB file, including an explanation for this action. An extension beyond 90 days may be granted by the IRB if sufficient cause is provided by the PI.

Approved Research

The IRB may also request additional information after reviewing documents such as: continuing review applications, amendments, DSMB reports, AE reports, reports of audits, allegations of non-compliance, and other types of correspondence. Responses to requests for information about studies that have already been initiated should be submitted as soon as possible.

Depending on the nature of the research and type of information requested, additional materials submitted by the investigator are forwarded to a designated reviewer or placed on the IRB agenda. If the information for submissions other than new protocols is not submitted in a timely manner, the IRB may take any action necessary to protect subjects including suspension of the study. The Principal Investigator is notified in writing of the committee's actions.

1.18 Appeals

When an IRB protocol presented at a convened meeting is disapproved or deferred, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the

reasons for its decision and give the investigator an opportunity to respond in person or in writing.

In cases where there is disagreement between the IRB and the PI regarding the nature and extent of the requested changes and these disagreements cannot be resolved amicably in an informal manner, the PI and/or the IRB may make an appeal to the R&D Committee for a resolution of the matter. The R&D Committee may organize a meeting to help facilitate discussion between the IRB and the PI. While the R&D Committee may provide input and make recommendations to the IRB for expeditious resolution of the matter, final determinations for approval remain under the purview of the IRB.

Since the R&D Committee is responsible for policies and procedures followed by the IRB, the R&D Committee may review IRB decisions to ensure that the decision-making process is appropriate. If the R&D Committee has concerns regarding the process that the IRB has followed in making a decision, the Committee may require the IRB to reconsider the decision. However, the R&D Committee cannot overrule an IRB decision.

After careful evaluation of all materials available, the IRB provides the Principal Investigator with a written statement of its reasons for disapproving or requiring substantive modifications to the research and gives the PI an opportunity to respond in writing. IRB decisions may be appealed by submitting a detailed written rebuttal to the IRB Chair. This can be accomplished by providing documentation to substantiate the Principal Investigator's position or by indicating what modifications were made in order to address the concerns expressed in the communications from the IRB.

The appeal is placed on the agenda of the next IRB meeting. All appeals are approved or disapproved by a majority vote of the IRB. The R&D Committee must also review and approve all successful appeals. The R&D Committee may overrule an approval by the IRB; however, it may not (nor can any other body), overturn a disapproval by the IRB. If the IRB disapproves an appeal, the investigator is notified in writing. The memorandum provides explicit reasons for the decision.

1.19 Implementing the Study as Approved

The PI is responsible for ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable those for research involving investigational drugs or investigational devices.

The RCO is responsible for ensuring compliance with federal regulations, state law, VA policy and guidelines, and MVAHS policies and procedures for all research conducted at the MVAHS.

The RCO is expected to keep abreast of changes to laws and regulations, and interpretations of same, and to recommend revisions to local policies and procedures accordingly. The RCO monitors compliance with policies by the IRB, Administrative staff, and Principal Investigators, and takes immediate and appropriate actions where needed to avert non-compliance.

The functions of the RCO are as follows:

1. Providing leadership, expertise, and strategic direction for the facility's research compliance program.
2. Developing, implementing, and maintaining compliance oversight activities for all research activities conducted under the auspices of the MVAHS.
3. Conducting audits and reviews to ensure compliance with all VA and other federal requirements for the conduct of research, including:
 - a. Annual audits of all active studies to ensure that informed consent has been properly obtained and documented for each subject accrued since the previous audit, and
 - b. Regulatory compliance audits of all active studies at least every 3 years.
4. Serving as a local resource for regulations, policies, memoranda, alerts, and other VA and federal requirements related to research compliance.
5. Providing education to investigators and research staff regarding regulatory and policy requirements.
6. Ensuring prompt reporting in accordance with all applicable policies to the Office of Research Oversight (ORO).
7. Reporting any alleged serious and/or continuing non-compliance found during an informed consent or regulatory audit to the Facility Director, the ACOS/R, the R&D Committee, the IRB (if applicable), the IACUC (if applicable), the SRS (if applicable) as soon as possible but no later than 5 business days after becoming aware of the non-compliance.
8. Providing prompt written notification to the VA ORO, VHA CRADO, other relevant federal agencies (Office of Human Research Protections, the Food and Drug Administration, Office of Laboratory Animal Welfare, the United States Department of Agriculture), accrediting agencies, and funding agencies for all reportable research events.
9. Meeting, at least quarterly, with the Medical Center Director to discuss the status of the Research Compliance Office.
10. Assisting with the completion of the "Annual Facility Director's Certification of Research Oversight" checklist regarding research compliance auditing activities and findings.
11. Working collaboratively with the Research Service to ensure that the research program adheres to the laws, regulations, policies, procedures, and ethical standards governing all research activities conducted under the auspices of the MVAHS.
12. Completing all VA required research and Medical Center training.
13. In addition to formal responsibilities, the RCO performs duties as assigned, such as assistance with policy development, accreditation, and preparation of reports relevant to research compliance.

1.20 Just-In-Time Review Process

"Just-In-Time" procedures allow research projects to be submitted for funding consideration prior to receiving final R&D Committee approval to conduct the research. Research protocols that are to be submitted to VA, other Federal agencies, or other entities requiring a Medical Center Director's support letter for funding consideration must undergo a pre-submission review and receive concurrence from the R&D Committee prior to submission. For those projects that are funded, the PI must submit a local application directly to the subcommittees.

The subcommittees review the protocol and communicate committee decisions to the R&D Committee via the study approval letter signed by a voting member of the subcommittee. After all subcommittees have granted approval, the R&D Committee will conduct an activation review of the project and make a final determination (*VHA Handbook 1200.01 Research & Development Committee*). The R&D Committee Coordinator will not issue final approval documents until all other approvals have been obtained or verified. For research administered through the Foundation, the R&D Committee Coordinator verifies that a signed contract is on file prior to sending the R&D Committee approval letter. The R&D Committee approval letter, along with the IRB approval documents are sent to the PI in one complete package. The PI may begin the research project once he/she has obtained the complete approval of all appropriate non-research entities and R&D Committee subcommittees, and written notification from the ACOS/R prior to initiating a research project.

1.21 Investigator Hold

Investigators may request an administrative hold on a protocol when they wish to temporarily or permanently stop some or all approved research activities. An administrative hold is initiated by an investigator. Administrative holds are not suspensions or terminations.

Procedures

1. Investigators must notify the IRB in writing of the following:
 - a. They are voluntarily placing a study on administrative hold.
 - b. A description of the research activities that will be stopped.
 - c. The proposed actions to be taken to protect current participants.
 - d. The actions that will be taken, prior to IRB approval of proposed changes, in order to eliminate apparent immediate harm.
2. Upon receipt of this written notification, the IRB Administrator places the research on the agenda for review.
3. The IRB Chair and/or ACOS/R, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in “Protection of Currently Enrolled Participants” below.
4. The IRB Chair and/or ACOS/R in consultation with the investigator, determines how and when currently enrolled participants will be notified of the administrative hold.
5. The investigator may request a modification of the administrative hold by submitting a request for a modification to previously approved research.

Protection of Currently Enrolled Participants

Before an administrative hold, termination, or suspension, is put into effect the convened IRB or IRB designee considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring participants to another investigator.
- Making arrangements for clinical care outside the research.
- Allowing continuation of some research activities under the supervision of an independent monitor.
- Requiring or permitting follow-up of participants for safety reasons.
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor.

- Notification of current participants.
- Notification of former participants.

1.22 IRB Suspension or Termination of Research

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See Section 13.4 and 13.5 for a discussion of unexpected problems and 15.8 for a discussion of non-compliance.)

Suspension of IRB approval is a directive of the convened IRB or IRB Chair or the Director to temporarily stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspension directives made by the IRB Chair or Director must be reported to a meeting of the convened IRB. Suspended protocols remain open and require continuing review.

Termination of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review. Terminations of protocols approved under expedited review must be made by the convened IRB.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual ordering the suspension or termination will notify any subjects currently participating that the study has been suspended or terminated. The convened IRB or individual ordering the suspension or termination will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require that the subjects should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

The investigator **MUST** continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period.)

Note: Suspension or termination of protocols approved by the IRB can also be issued by Medical Center officials acting outside of and unrelated to the HRPP (i.e., not necessarily related to protecting the rights and welfare of study participants). Such Medical Center actions can be

made by the Medical Center Director, R&D Committee, ACOS/R, and the AO/R. Such Medical Center actions may be made for any reason in furtherance of the Institution's interest provided, however, that the PI is entitled to all rights and procedures afforded to him/her under the Medical Center Policies. The PI must report any suspension or termination of the conduct of research by Medical Center officials to the IRB. The IRB will then determine if suspension or termination of IRB approval is warranted.

The IRB may suspend or terminate research involving human subjects under certain conditions. Examples include:

- Failure to notify the IRB of any serious adverse events or unanticipated problems involving risks to subjects or others.
- A pattern of adverse events serious enough to warrant action by the IRB.
- Serious or continuing non-compliance - Employees should notify the IRB promptly if they discover any serious or continuing non-compliance with applicable regulatory requirements or with the determinations of the IRB.
- Failure to respond to the IRB's request for information.
- Immediate safety concerns discovered from information contained in protocol violation reports, audits or DSMB reports.

Notifying the R&D Committee and Institutional Officials:

If the IRB finds that suspension or termination is warranted, the IRB will do all of the following:

- a. Notify the investigator in writing of its findings, with copies to the investigator's service chief and the investigator's supervisor.
- b. Report directly (without intermediaries) to the Medical Center Director within 5 business days after the termination or suspension occurs. The report will include findings and recommendations. The Medical Center Director must promptly report the termination or suspension to the appropriate federal officials (OHRP, and FDA) and to the ORO RO within 5 business days after receiving such notification.
- c. Simultaneously distribute copies of the written report to the Medical Center Director, as applicable, to the ACOS/R, the R&D Committee, and any other relevant research review committee.

1.23 Research Exempt from IRB Review

All research using human subjects must be approved by the Institution. Certain categories of research (i.e., "exempt research") do not require convened IRB review and approval. Exempt research is subject to institutional review and as such the Chair must make the determination that the research qualifies for exemption from IRB review.

Children: Exemption for research involving survey or interview procedures or observations of public behavior does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.

Prisoners: VA does not conduct research with prisoners.

If the proposed research falls into at least one of the six categories listed below, the Principal Investigator may submit a *Request for Exempt Review* form along with the new research application and any other accompanying materials.

Research exempt from IRB consideration must still undergo scientific review, review from other subcommittees, as appropriate, and review and approval by the R&D Committee. If the application does not meet the criteria for an exemption, the IRB Chair may recommend the packet be considered through the expedited review procedures or forwarded to the IRB for full committee review. **Note:** applicable criteria for FDA-regulated research. With the above exceptions (i.e. children and prisoners), research activities not regulated by the FDA (see Section 11.8 for FDA Exemptions) in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review, but require institutional review, at MVAHS:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: (a) research on regular and special education instructional strategies, or (b) research on the effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (a) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (b) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, that is not exempt under paragraph (2) (b) of this section, if: (a) the human subjects are elected or appointed public officials or candidates for public office; or (b) federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subject.
Note: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs

or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies (a) if wholesome foods without additives are consumed, or (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR 56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

Procedures for Exemption Determination

The IRB Chair (or designee) reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The IRB Chair may designate an IRB member to review requests for exemptions submitted to the IRB. The Chair selects designees who are qualified to review this category of submission based on their expertise of the protocol content and knowledge of regulations pertaining to research conducted within the VA. If there is not a designated reviewer to consider requests for exemptions, the IRB Chair reviews the requests. Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers do not have any apparent conflict of interest.

To document the IRB reviewer's determination of the request for exempt research, he/she completes the *Reviewer Form for Exemption Requests* which is included along with the application packet. The IRB reviewer verifies on the form whether the submission meets the definition for "research" or "clinical investigation". If, at that point in the review process the reviewer is unsure, the form contains instructions that direct the reviewer to fill out the *Human Subject Determination* form.

The R&D Committee will be informed of the exempt status determination through the tracking sheet. Once the R&D Committee receives approval from the SRS (Chemical Hygiene and Biosafety Subcommittee) and the IRB exempt determination letter, the R&D Committee will conduct an activation review of the project and make a final determination (*VHA Handbook 1200.01 Research & Development Committee*). For research administered through the Foundation, the R&D Committee Coordinator verifies that a signed contract is on file prior to

sending the R&D Committee approval letter. The R&D Committee approval letter and the IRB exempt determination letter are sent to the PI in one complete package.

The PI may begin the research project once he/she has received a written IRB exemption determination letter and written confirmation of R&D Committee approval from the ACOS/R. Once approved by the R&D Committee, the project will be included in the R&D Committee's annual review of research projects.

The full IRB will be notified of all research that receives an exempt status in the IRB meeting agenda and minutes.

Please note that any individual involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research.

Additional Protections

Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

1.24 Expedited Review

An IRB may use the expedited review procedure to review either or both of the following:

1. Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk.
2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under certain conditions new and continuing review research applications may be considered without full IRB review through the expedited review process if the study meets the applicable criteria listed in this section.

Examples of the kinds of studies that might qualify for expedited review include:

- Surveys
- Chart reviews

The Principal Investigator may apply for expedited review of a new protocol by submitting a completed *Request for Expedited Review of New Protocol* form along with the forms required for a new human studies research project.

Note: The new application may qualify for a *Waiver of Informed Consent/HIPAA Waiver* or a *Request for Waiver of Documentation of IC*.

The new application packet will be forwarded to the IRB Chair (or designee) for review to determine: (1) whether the research meets the criteria for expedited review and (2) whether any requested changes to the protocol and/or informed consent document have been addressed, if applicable. The IRB Chair will refer new applications that do not meet the applicability criteria to the IRB for full committee review.

Continuing review applications previously approved by the expedited review process will be forwarded to the IRB Chair (or designee) for review (See Section 4 for information about submitting a continuing review application.)

All applications approved through the expedited review process must still undergo R&D Committee review.

Categories of Research Eligible for Expedited Review

The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

The categories in this list apply regardless of the age of subjects, except as noted.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may not be used for classified research involving human subjects.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

Research Categories eligible for expedited review one (1) through seven (7) pertain to both initial and continuing IRB review.

Research that meets the definition of “minimal risk” (See Section 1.7) and falls into at least one of the categories below is eligible for expedited review:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met. Research on drugs for which an investigational new drug application (IND) (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.) Research on medical devices for which (i) an investigational device exemption (IDE) application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or from other adults and children¹, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For

these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

[¹Children are defined in the DHHS regulations as "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."][45 CFR 46.402(a)]

3. Prospective collection of biological specimens for research purposes by noninvasive means. For example: hair and nail clippings in a nondisfiguring manner; deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; permanent teeth if routine patient care indicates a need for extraction; excreta and external secretions (including sweat); uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; placenta removed at delivery; amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) For example: physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; weighing or testing sensory acuity; magnetic resonance imaging; electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). [**Note:** Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [**Note:** Some research in this category may be exempt from the DHHS

regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

8. Continuing review of research previously approved by the convened IRB where:
the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or no subjects have been enrolled and no additional risks have been identified; or the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.]

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8) a., b., or c. are satisfied for that site. However, with respect to category 8 b., while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

[Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.]

Expedited Review Procedures

The Principal Investigator must submit to the IRB Office a *Request for Expedited Review of New Research Application* form along with the completed *Application for New Human Research Study* and all required documents.

The IRB Chair or designee or the Vice-Chair (s) will make a determination on whether or not a protocol may be reviewed using expedited procedures. The individual(s) making this determination cannot be involved in the proposed research.

The IRB Chair may designate a qualified designee to complete the review of the request and research project. The qualified designee to review the request and research project must be an experienced (having served on the IRB for at least one year) voting member of the IRB and have qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as

be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see Section 14) will not be selected.

The reviewer may exercise the authority of the IRB, but may not disapprove the research. If the IRB Chair or qualified designee does not approve the research through expedited procedures, then the research project will be reviewed by the convened IRB which may disapprove the research.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), should receive and review all documentation that would normally be submitted for a full-board review including the complete protocol, a continuing review form summarizing the research since the previous review (including modifications and unanticipated problems), notes from the pre-screening conducted by the IRB Office staff, the current consent documentation and determine the regulatory criteria for use of such a review procedure by using the *Expedited Review Checklist*.

The reviewer(s) conducting initial or continuing review completes the appropriate *Institutional Review Board - Protocol Review* checklist to determine whether the research meets the criteria allowing review using the expedited procedure and if so, whether the research meets the regulatory criteria for approval. If the research does not meet the criteria for expedited review, the reviewer will indicate that the research requires full review by the IRB and the protocol will be placed on the next agenda for an IRB meeting.

Reviewers will indicate approval, required modifications, or requirement for convened board review on the *Protocol Review/Initial Review* form and return it to the IRB Office. If modifications are required, the IRB Office staff will inform the investigator according to procedures in section 1.19 (“Reporting IRB Actions”).

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the IRB Chair may make a final determination. Upon the discretion of the IRB Chair the protocol will be submitted to the IRB for review.

If the IRB Chair (or designee) refers the request for expedited review for full committee review, the submission is placed on the agenda of the next IRB meeting. The Chair (or designee) notes this determination on the *Reviewer Form for Expedited Review* that is attached to the *Request for Expedited Review of New Research* form.

If the IRB concurs that it is expeditable, the continuing review can be expedited.

The full IRB will be notified of all research approved under expedited procedures in the IRB meeting agenda and minutes. All correspondence resulting from an expedited review will note the results of the review and be filed in the IRB study file in the IRB Office. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

The R&D Committee will be informed of the study approval through written notification signed by the IRB Chair or a voting member of the IRB. After all subcommittees have granted approval, the R&D Committee will conduct an activation review of the project and make a final

determination (*VHA Handbook 1200.01 Research & Development Committee*). For research administered through the Foundation, the R&D Committee Coordinator verifies that a signed contract is on file prior to sending the R&D Committee approval letter. The R&D Committee approval letter, along with the IRB approval documents are sent to the PI in one complete package. The PI may begin the research project once he/she has received written confirmation from the IRB, R&D Committee, and the ACOS/R.

SECTION 2 - NEW RESEARCH APPLICATIONS

2.1 Application for New Human Research Study

The *Application for Miami VA Research Project* packet contains all of the forms and instructions necessary to complete a new research submission. **Included in the packet is the *Application for New Human Research Study*. This document provides guidance about which forms and information to include in each new research application.** Although each type of research proposal has its own submission requirements, there are specific forms required for all studies. These are listed in Section 2.3 of the application. Section 2.4 lists forms and materials that might be required depending on the type of research to be conducted. Please read the application carefully to determine which documents must be submitted for review.

Sections of this manual also provide guidance about how to answer many of the questions on the *Application for New Human Research Study* form.

Research Protocol Outline

A research protocol outline is available on the Research Service website www.sfvafre.org. Investigators who develop their own protocols may find the outline helpful.

2.2 Types of New Research Proposals

IRB review is required for any of the following types of proposals:

- Clinical drug or device trials.
- Surveys/Questionnaires- may qualify for expedited review or exemption.
- Chart Reviews- may qualify for expedited review or exemption.
- Tissue/Data Repository - contact the IRB Administrator.
- Sponsor-Investigator Applications – these investigators both initiate and conduct an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- International research – contact the IRB Administrator.
- Engagement in international research requires approval from the CRADO as well as the IRB and R&D Committee prior to its initiation at the facility.

a. Definition of VA 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. **Note:** According to VHA Handbook 1200.05, research conducted at U.S. military bases, ships, or embassies is not considered international research.

b. Multi-Site Trials. 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.

2.3 List of Required Materials for all New Applications

For the convenience of the Principal Investigator, a table is provided of the forms and materials that must be submitted for all new research studies.

REQUIRED FORMS AND MATERIALS FOR ALL NEW RESEARCH STUDIES	
Name of Form or Item	Special Instructions
<i>Application for New Human Research Study</i>	When required information is missing in the protocol or not adequately explained, the PI must provide the information on this form. Other required materials and information are also indicated on the application.
Protocol	A research protocol outline is available on the Research Service website for investigators who develop their own protocols.
<i>VA Form 10-71 - Application for Miami VA Research Project</i>	Must have all applicable signatures Note: This form differs significantly from the <i>Application for New Human Research Study</i> form, which is only for human subject research.
<i>VA Form 10-1436 - Project Data Sheet</i>	Must have with all applicable signatures.
<i>Checklist for data security</i>	
<i>Location of Research Project/Research Sites memorandum</i>	The PI must describe where the study activities will take place. This form is also used for identifying research sites that are part of the Cooperative Studies program. Must have with all applicable signatures.
<i>VA Form 10-1086– Informed Consent Document and HIPAA Form</i> <u>or</u> <i>Request for Waiver or Alteration of Informed Consent/Waiver of HIPAA Authorization (combined on one form)</i> <u>or</u> <i>Request for Waiver of Documentation of Informed Consent</i>	The study must have either a consent form and HIPAA form or waivers.
<i>Report of Research Staff form.</i>	All study personnel must be listed on this form along with the dates of current Research required training.
<i>Scope of Practice – PI</i> <i>Scope of Practice – Research Staff</i>	Required for all research study personnel except M.D.'s and Ph.D.'s already credentialed

	through the VA system.
Conflict of Interest	
Certificates of human subject training, cybersecurity training, and subject privacy training.	Required for all research personnel. See Research website for list of required trainings and links.
Bio-sketches or CV's	Required for the Principal Investigator and any Co-Investigator(s).

2.4. List of Required Materials Specific to the Type of Study

Depending on the type of research to be conducted, other forms and materials may be required:

FORMS /MATERIALS REQUIRED DEPENDING ON THE TYPE OF RESEARCH TO BE CONDUCTED	
Name of Form or Item	Special Instructions
<i>Request for Expedited Review of New Protocol form</i>	If requesting expedited review, this form must be submitted with the new protocol application
<i>Request for Exempt Review form</i>	If requesting exempt review, this form must be submitted with the new protocol application
<i>Disclosure of Available Funds</i>	For sponsored studies
<i>FDA Form 1571-Investigational New Drug Application</i>	For studies where Investigator holds the IND
<i>Request for Waiver from the Requirement to Submit an IND Application to the FDA</i>	For sponsored studies
<i>FDA Form 1572 - Statement of Investigator (sponsored studies only)</i>	For sponsored studies
<i>VA Form 10-9012 - Investigational Drug Information Record</i>	For sponsored studies. Be sure to include all practitioners authorized to prescribe the study drug.
<i>Biohazard/Chemical Hazard Information Involving Research</i>	
<i>Biologic Sample Statement</i>	
<i>Application for the Use of Radioactive Materials</i>	
<i>Advertisements</i>	
<i>Notice of Privacy Practices</i>	
<i>Consent for Use of Picture and/or Voice VAF 10-3203</i>	
<i>Request for Access to Health Information for Research</i>	

2.5 Warnings or other Actions

The PI must disclose on the *Application for New Human Research Study* form whether he/she has been given a warning or received any other action from the FDA, another U.S. government agency or any global regulatory agency within the last five years regarding behavior by them or anyone else in a clinical study in which they participated.

2.6 Submission Reviewed by Other IRB

The Principal Investigators must indicate whether the protocol has been reviewed by any other IRB or whether the PI intends to submit it for review to another IRB. If the protocol has been reviewed by any other IRB, the PI is required to provide the IRB's determination (e.g. approved, disapproved, tabled, etc.) and any other pertinent documentation.

2.7 Required Documents before Initiation of Study Procedures

The Principal Investigator may initiate the study after receiving the following documentation:

- ✓ Approval memorandum signed by the ACOS/R.
- ✓ Signed *VA Form 10-1223 - Report of Subcommittee on Human Studies*.
- ✓ Signed *VA Form 10-9012 - Investigational Drug Information Record*, if applicable.
- ✓ *VA Form 10-1086 - Informed Consent Document* stamped by the IRB (if a waiver has not been granted) and *HIPAA Authorization Form*.

or

- ✓ Documentation of *Request for Waiver or Alteration of Informed Consent/Waiver of HIPAA Authorization* or *Waiver of Documentation of Informed Consent*, if applicable.
- ✓ Completion of *Pharmacy/ PI Review of Initial Study Drug Stock at Pharmacy Service*, if applicable. The PI completes this form with the Research Pharmacist.
- ✓ Interview with RCO (Sponsor-Investigators only).
- ✓ For a VA multi-site study, not only the PI, but also all LSIs, must obtain such approvals from the relevant local VA facilities' IRBs of record and all other local committees, subcommittees, and other approvals according to the respective applicable local, VA and other Federal requirements.

SECTION 3 - AMENDMENTS

3.1 Amendments and Proposed Changes to Approved Research

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes in approved research** - even though the changes are planned for the period for which IRB approval has already been given-unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once).

Principal Investigators or the sponsoring company may recommend a change based on the occurrence of an adverse event or other unforeseen circumstances. If the change is related to a biosafety or radiation safety issue, the appropriate subcommittee must first approve the modified plan.

No changes may be initiated without prior IRB approval, except where necessary to eliminate apparent hazards to subjects. When changes are made without IRB approval, the Principal Investigator must report the changes promptly to the IRB. The IRB will review whether the changes were consistent with ensuring the participants' continued welfare.

3.2 Definition - "Minor Change"

It is the policy of the IRB Office to refer amendments for expedited review whenever applicable. Amendments that meet the applicability criteria of "minor change" are eligible for expedited review.

Minor Change. A minor change is one that, in the judgment of the IRB reviewer, makes no substantial alteration in:

- The level of risks to subjects.
- The research design or methodology (adding procedures that are not eligible for expedited review would not be considered a minor change).
- The number of subjects enrolled in the research.
- The qualifications of the study staff.
- The facilities available to support safe conduct of the research.
- The likelihood of subjects' willingness to participate.
- Any other factor which would warrant review of the proposed changes by the convened IRB.

3.3 Submitting Forms and Materials

Amendment Materials

Investigators must submit documentation to inform the IRB about the changes in the status of the study, including, but not necessarily limited to:

- Completed *Request for Modification to Previously Approved Research* form (requires a complete description of the proposed changes).
- A tracked revised research protocol, with bolded text indicating any additions, and strikethrough text indicating any deletions and a clean (non-tracked) revised research protocol. Revisions, modifications, or amendments must be incorporated into the

research protocol. This practice ensures that there is only one complete protocol with the revision date noted on the first page of the protocol itself.

- A tracked revised informed consent form(s), with bolded text indicating any additions, and strikethrough text indicating any deletions and a clean (non-tracked) revised informed consent form(s).
- Complete protocol including any protocol modifications previously approved by the IRB.
- A revised sponsor protocol, grant, and/or funding application.
- Revised investigator's brochures, provided by study sponsors (if applicable).
- Revised or additional recruitment materials.
- Any other relevant documents.

1. Amendment to Protocol Only – Does Not Affect the Informed Consent Document

Note: Use this option when the changes affect only the research protocol (no changes to the informed consent document are required).

Seven sets of the following materials:

- ✓ A copy of the *Application for Miami VA Research Project* face sheet that was submitted at the time of initial review. This sheet should be marked "Amendment" in the section "Type of Application".
- ✓ A completed *Request for Amendment to Previously Approved Research* form.
- ✓ Documentation from the sponsoring company regarding the requested changes, if applicable. The documentation should include the following: (1) a description of the proposed changes and (2) justification for the changes.
- ✓ A revised copy of the protocol (if the protocol is more than 30 pages, provide only two copies).
- ✓ A copy of the currently approved informed consent document (bearing stamp).

One of the following:

- ✓ A clean copy of the current informed consent document which will be re-stamped and returned to the Principal Investigator along with the amendment approval letter.

2. Amendment to Protocol that Affects the Informed Consent Document

Note: Use this option when the changes to the protocol also affect the informed consent document.

Seven sets of the following materials:

- ✓ A copy of the *Application for Miami VA Research Project* face sheet that was submitted at the time of initial review. This sheet should be marked "Amendment" in the section "Type of Application".
- ✓ A completed *Request for Amendment to Previously Approved Research* form.
- ✓ Documentation from the sponsoring company regarding the requested changes, if applicable. The documentation should include the following: (1) a description of the proposed changes and (2) justification for the changes.
- ✓ A revised copy of the protocol (if the protocol is more than 30 pages, provide only two copies).
- ✓ Copy of the currently approved informed consent document (bearing stamp).
- ✓ Copy of revised informed consent document with the changes highlighted.

One of the following:

- ✓ A clean copy of the revised informed consent document (not highlighted) which will be re-stamped and returned to the Principal Investigator along with the amendment approval letter.

3. Amendment to Informed Consent Only

Note: Use this procedure to amend only the informed consent document (no changes to the protocol are required).

Seven sets of the following materials:

- ✓ A copy of the *Application for Miami VA Research Project* face sheet that was submitted at the time of initial review. The face sheet should be marked “Amendment” in the section “Type of Application”.
- ✓ A completed *Request for Amendment to Previously Approved Research* form.
- ✓ Supporting documentation from the sponsor, if applicable. The documentation should include the following: (1) a description of the proposed changes and (2) justification for the changes.
- ✓ Copy of currently approved informed consent document (bearing stamp).
- ✓ Copy of the revised informed consent document with the changes highlighted.

One of the following:

- ✓ A clean copy of the revised informed consent document (not highlighted) which will be re-stamped and returned to the Principal Investigator along with the amendment approval letter.

Amendments may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, an amendment request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. If, however, the researcher wishes to make substantial changes to the study procedures, he or she will need to submit a new application for human subject approval. Investigators must submit the required documentation to inform the IRB about the proposed changes in the protocol. Whenever possible, amendments and changes to research are expedited. A request for expedited review of the proposed changes may be requested by the PI on the IRB modification forms, and the IRB Administrative Staff will make the initial determination as to whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the amendment warrants full board review. The IRB reviews all materials received as listed under in the review of modifications to an approved protocol.

3.4 IRB Review Process: Expedited Review

Amendments are sent to the designated IRB amendment reviewer. The IRB Chair may designate an experienced IRB member to review the submission. Assignment of reviewers is based on the reviewers' expertise of the protocol content and knowledge of regulations pertaining to research conducted within the VA. If there is not a designated reviewer to consider the expedited submission, the IRB Chair reviews the request for expedited review.

The reviewer makes a recommendation regarding the suitability of the amendment for expedited review and provides a description of the proposed changes. For this type of expedited review request, a *Reviewer Documentation of Expedited Review of Minor Changes to Previously*
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Approved Protocol is included in the reviewer packet. The reviewer uses this form to determine whether the submission qualifies for expedited review (i.e. meets minimal risk criteria, and if so, the criteria under which it qualifies in this Section).

If the reviewer grants expedited review, he/she notes this determination on the *Reviewer Documentation of Expedited Review of Minor Changes to Previously Approved Protocol* and completes and signs *VA Form 10-1223 Report of Subcommittee on Human Studies*.

The IRB Chair reports all approved requests for expedited review to the IRB at its next meeting. If the reviewer determines that the change is not minor, then the protocol will be referred for full IRB review.

If the IRB reviewer refers the submission for full committee review, he/she notes the determination on the *Reviewer Documentation of Expedited Review of Minor Changes to Previously Approved Protocol* and the packet is placed on the next IRB agenda for full committee review.

The IRB Chair reports all amendments approved for expedited review at the next regularly scheduled IRB meeting. If the IRB expresses concern about a reviewer's decision to grant expedited review, the item is reviewed at the same meeting at which the determination was reported or placed on the agenda of the next meeting for full committee review. In either case, the reviewer would lead the discussion of the modification to the previously approved research.

3.5 IRB Review Process: Full Committee Review

When a proposed change in a research study is not minor, the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those amendments might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

3.6 R&D Committee Review

The R&D Committee is notified of all amendments or modifications to approved research by expedited review through the minutes of the IRB. Included in the minutes is a brief description of the amendment or reported modification to research. If any member of the R&D Committee raises concerns about the approval of the amendment or reported modification, the R&D Committee may vote to place the amendment on the agenda of the next R&D Committee meeting for full committee review. A decision is also rendered by the R&D Committee as to whether approval of the amendment should be revoked pending the Committee's further review.

3.7 Amendment Approval Documents

The Principal Investigator may proceed with the amended protocol or the proposed modifications to the research after receiving the following documents:

- ✓ An approval memorandum (original) – this document will describe any special instructions to the Principal Investigator (e.g. need for re-consent plan).

- ✓ A copy of the *VA Form 10-1223- Report of Subcommittee on Human Studies* signed by the IRB Chair.
- ✓ A newly stamped informed consent document (original) with a new approval date.

These documents are required whether the amendment/modifications were approved by expedited or full committee review.

SECTION 4 - CONTINUING REVIEW/ COMPLETION OF A STUDY

4.1 Continuing Review Form and Materials

The IRB is required to conduct continuing review for studies involving human subjects at least annually. The IRB may, at its discretion, increase the frequency of review during the continued approval process if there is evidence of increased risks to subjects.

Approximately 8 weeks before the IRB expiration date, IRB staff will send to the Principal Investigator a memorandum and a *Request for Continued Approval or Completion of Project Involving Human Subjects* form. This form and all accompanying documentation must be submitted to the IRB Office before the deadline listed on Page One of the form. If no response is received, reminders are sent out every two weeks prior to approval expiration. Because the following items are often overlooked, please be sure they are included in the continuing review application packet along with the other required documents:

- ✓ *Tracking Log for Non-Reportable Events.*
- ✓ Sponsor's periodic study monitoring report, if applicable.
- ✓ Copy of currently approved informed consent document, if applicable.

Note: To avoid a lapse in continuing review (see Section 4.2), it is extremely important to submit the completed continuing review packet as soon as possible.

4.2 Lapse in Continuing Review

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired, is research conducted without IRB approval. If the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (advertisements must be stopped or removed from public view), enrollment, consent, interventions, interactions, data collection, and data analysis unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions.

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval, the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects can only continue when the IRB or IRB Chair, in consultation with the COS, finds that it is in the best interest of the individual subjects to do so.

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 45 days and the PI has not provided the required continuing review information, the PI must submit a new application, through the R&D Committee, to the IRB for review and approval. If the study approval has lapsed 45 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

4.3 Continuing Review – Study Completion

The completion or termination of the study, whether premature or not, is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

To close the study, the PI must fill out the final report section of the *Request for Continued Approval or Study Closure of Project Involving Human Subjects* form before or at the time of continuing review. The study is not considered closed until all data analysis has been completed.

Completing Appropriate Actions at Research Project Completion

After completion of the research study, the PI is responsible for storing research records according to all applicable VA and Federal records retention requirements. If appropriate, the PI communicates the results to subjects or the community from which subjects were recruited.

Record Retention

In accordance with VA regulations at 38 CFR 16.115(b) and FDA regulations, research study records and IRB records (as described in Section 15.5) must be retained by the facility in accordance with the instructions set forth by the national Archives and Records Administration and published in the VHA's Records Control Schedule (RCS 10-1) (see *VHA Handbook 1200.05*). In addition, state laws or VAMC policy may exceed this requirement. In addition, IRB records are made available for inspection and copying by authorized representatives from outside agencies in a reasonable time and in a reasonable manner.

All research study records from Research Service are sent to Medical Administration Services (MAS) for archiving. Files archived by MAS include, but are not limited to the study files, including the study binder. Principal Investigators are responsible for obtaining the appropriate forms and assuring delivery of the materials to MAS.

Note: NO RESEARCH DATA IS TO BE DESTROYED.

4.4 Transferring of Records

If the PI leaves VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the investigator leaves one VA facility to go to another VA facility, the investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility's research office. The approval must be obtained from the first VA facility's research office, any other relevant individuals or offices according to VA and local requirements (e.g., compliance, privacy, or Information Security Officers (ISOs)) and the sponsor.

Note: The investigator is not the grantee, nor does the investigator own the data.

SECTION 5 - RISK/BENEFIT ASSESSMENT

5.1 Risk/ Benefit Information

Minimizing Risks -- The investigator is responsible for minimizing risks to the subjects or others. All new research applications must include a discussion of the potential risks and benefits of the study.

- Risks of the Study

Each of the following items must be addressed in the space provided on the *Application for New Human Research Study* form:

Potential Risks

1. Physical (e.g. minor pain, discomfort, injury from invasive procedures, drug side effects).
2. Psychological - undesired changes in thought processes and emotions (e.g. stress, guilt, embarrassment, invasion of privacy, breach of confidentiality).
3. Social (e.g. embarrassment in one's social group, stigmatization, standing in one's community, invasion of privacy, breach of confidentiality).
4. Legal (e.g. criminal prosecution for having engaged in illegal activities).
5. Economic. (e.g. loss of employment, loss of health insurance).

Identification of elements of the study design which are included to minimize risks.

Any departures from standard procedures or methods of care.

Information relative to the severity, likelihood, frequency, and reversibility of potential adverse actions.

- Benefits of the Study

Potential benefits to the individual should be indicated. Examples include: ameliorating the subject's disorder; providing the participant with better understanding of his/her disorder.

Potential benefits to society should be indicated. Examples include: increased knowledge about human physiology or behavior, improved safety, technological advances and better health.

- Explanation of How the Benefits Justify Risks

In addition to identifying the potential risks and benefits of the study, the Principal Investigator must also explain on the new protocol application how the benefits of the study justify the risks.

Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;

- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research - one of the major responsibilities of the IRB - involves a series of steps:

1. **Identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research.

Differentiating Usual Care from Research -- If the protocol involves “usual care,” the protocol must either include a narrative section or there must be a separate document in the IRB application that clearly differentiates the research intervention(s) from “usual care” (whether the “usual care” is limited to one “arm” of the study or is being delivered to all study subjects):

- When a study involves “usual care,” in the protocol or a separate document in the IRB application, the investigator must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject’s healthcare provider) responsible for relevant aspects of both the research and the usual care.
 - The subject needs to be able to identify which activity (e.g., treatment or service) is research, and which is usual care, and know who (the researcher or the subject’s healthcare provider) is responsible for:
 - ✓ Explaining potential risks and benefits of the treatment or service to the subject.
 - ✓ Providing the treatment or service.
 - ✓ Monitoring the treatment or service, as applicable.
 - ✓ Defining whether the adverse events result from usual care or research, as applicable.
 - ✓ Alerting the subject if there is a problem with the treatment or service (e.g., a newly discovered risk, a product recall).
 - Documenting the subject’s clinical course while receiving the treatment or service, as applicable.
2. **Determine whether the risks will be minimized** to the extent possible.
 3. **Identify the probable benefits** to be derived from the research.
 4. **Determine whether the risks are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained.
 5. **Ensure that potential subjects will be provided with an accurate and fair description** of the risks or discomforts and the anticipated benefits.

Risks to subjects are minimized:

1. By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
2. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

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

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

5.2 Changes to the Research that Affect the Risk/Benefit Information

If the risk/benefit information changes anytime during the study, the PI is required to notify the IRB in an amendment (see Section 3).

SECTION 6 - SUBJECT SELECTION (RECRUITMENT)

6.1 Recruitment Plan

The PI is responsible for providing a plan for just, fair, and equitable recruitment and selection of subjects.

NOTE: The requirement applies to both prospective and retrospective studies, including studies that use clinical or administrative databases or bio-specimens.

Recruitment procedures must be designed to assure informed consent is given freely and to avoid coercion or undue influence. MVAHS has a strict policy that does not allow any type of compensation for referring patients to a research study. During the recruitment phase, potential subjects are given a copy of the informed consent document to take home in the event that they need more time to read it or wish to consult with others (e.g. family members, personal physician). A telephone number to verify the validity of the study is included on the consent document. After recruitment and during the follow-up phase, researchers must begin calls to subjects by referring to previous contacts and the information provided on the informed consent document.

“Appendix A” of the *Application for New Human Research Study* form must be filled out for any study in which subjects will be recruited.

6.2 Recruitment Plan - Permissible Recruitment Methods

1. Principal Investigators and Co-Investigators may recruit their own patients to participate in their studies. The PI must submit a *Request for Waiver or Alteration of Informed Consent/Waiver of HIPAA Authorization* form before accessing patient files for research purposes and contacting potential subjects.
2. Advertisements - IRB approval is required for any advertisement used to recruit subjects. Advertisements should be limited to the information prospective subjects need to determine their eligibility and interest. (See Section 9.3 for more information about using advertisements).
3. The Principal Investigator (or designee) may approach subjects in VA clinics (appropriate specialty) to ask subjects about their interest in participating in the study.
4. VA practitioners not involved in the research may be asked to refer their own patients to the study. Practitioners are not permitted to disclose their patients' names directly to the Principal Investigator; however, VA practitioners may provide information to their own patients about the study. Interested patients may, in turn, initiate contact with the Principal Investigator.
5. Potential study participants will be identified / recruited from patient records or databases. This option is used when the study design and recruitment procedures require access to the patient's PHI before contacting them. The PI must submit a *Request for Waiver or Alteration of Informed Consent/Waiver of HIPAA Authorization* form before accessing the records and contacting potential subjects.

6. In order to recruit subjects for phone surveys, the Principal Investigator should first send a letter along with an informed consent document to the potential subject explaining the purpose of the study and any other information he/she may need to make a decision about whether or not to participate. Simply agreeing to participate during the initial phone contact does not constitute informed consent in and of itself. If the patient returns the signed consent form, the study may proceed. Similar procedures are applicable for studies employing centralized informed consent phone systems. However, an alternative to this informed consent process may be granted which would not require return of an informed consent document.
7. During the recruitment process, the investigator ensures that the research team makes initial contact with the prospective subject in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research (e.g., if the prospective subject has diabetes, the subject may indicate a desire to be notified of any diabetes-related research studies). The initial contact must provide a telephone number or other means that the prospective subject can use to verify the study constitutes VA research.
8. Investigators ensure that in later contact, the research team begins telephone calls to the subject by referring to previous contacts and, when applicable, the information provided in the consent document, and ensuring that the scope of telephone contacts with the subject is limited to topics outlined in IRB-approved protocols and consent documents.
9. Potential study participants will be recruited in a manner other than the methods listed above. The Principal Investigator must describe the recruitment methods in the *Application for New Human Research Study* and submit any other required documents.
10. Investigators are required to make every reasonable effort to make available the informational brochure, “Volunteering in Research – Here Are Some Things You Need To Know,” to prospective research subjects in settings where investigators may recruit subjects (e.g., clinic waiting areas), and to prospective subjects, and their surrogates where applicable, when the individuals are approached to take part in a study.

6.3 Advertisements

In “Appendix A” of the *Application for New Human Research Study* form, the PI must explain how advertisements will be used to recruit subjects.

The IRB must approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of the MVAHS IRB. The IRB will review:

1. The information contained in the advertisement.
2. The mode of its communication.
3. The final copy of printed advertisements.
4. The final audio/video taped advertisements.

This information should be submitted to the IRB with the initial application or as an amendment to the protocol.

The IRB reviews the material to assure that it is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. During its review the IRB considers the following:

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol.
2. Claims, either explicitly or implicitly, that the drug, biologic or device was safe or effective for the purposes under investigation.
3. Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device.
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational.
5. Promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation.
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
7. The inclusion of exculpatory language.

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

1. The name and address of the clinical investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (e.g. no cost of health exam).
8. Advertisements will not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Once approved by the IRB, an advertisement cannot be altered or manipulated in any way without prior IRB approval. Posted advertising materials must have an IRB stamp and date.

Adding Advertisements to the Study Procedures after the Study Begins

To use advertising after the study has been approved, the PI must submit the following items to the IRB:

- ✓ Amendment package (see for instructions about how to submit an amendment) – Select option #1 – “Amendment to Protocol Only”.
- ✓ *Change in Recruitment* form.
- ✓ Advertising materials.

6.4 Vulnerable Populations

The recruitment plan must stipulate whether vulnerable populations (Mentally Disabled Persons, Economically or Educationally Disadvantaged Persons, Pregnant Women, Prisoners, Children) will be recruited. Students and employees may also be considered vulnerable populations.

Note: the PI should promptly inform the IRB and R&D Committee when a subject becomes incarcerated while participating in the study. If the PI wishes to have the prisoner subject continue to participate in the research, the R&D Office will request a waiver from the CRADO.

Note: VA policy stipulates that children cannot be included in VA-approved research without a waiver from the Chief Research and Development Officer.

If vulnerable populations are to be recruited, the Principal Investigator must provide the following information on the *Application for New Human Research Study form*:

- ✓ Inclusion of vulnerable populations must be justified.
- ✓ Describe what measures will be taken to assure that the rights of vulnerable populations are adequately protected.
- ✓ Describe additional safeguards that will be implemented to protect vulnerable populations. Examples include but are not limited to:
 - Someone from the IRB may oversee the consent process.
 - A waiting period between initial contact and enrollment to allow time for family discussion and questions.
 - Consultation with subject matter expert.
 - Verification from sources other than the principal investigator that no material changes have occurred in the protocol.
 - Patient record flag.
 - Certificate of Confidentiality (COC).
 - Use of audio-visual aids during the IC process.
 - Tests of comprehension.
 - Someone not involved in the research to obtain the consent.
 - The inclusion of a consent monitor or a subject advocate.
 - Interpreter for hearing-impaired subjects.
 - Translation of informed consent forms into languages subjects understand.
 - Reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.

6.4.1 Recruiting Decisionally Impaired Subjects

In “Appendix A” of the *Application for New Human Research Study form*, the Principal Investigator must provide the following information when decisionally impaired subjects will be recruited:

- Justification for including persons with impaired decision making capacity. VA regulations stipulate that there must be compelling reason to include subjects with impaired decision making capacity.
- Whether the study is minimal risk.
- A description of the informed consent process - including those potential subjects whose capacity might fluctuate during the course of the study.

- Plan for documenting impaired decision-making capacity.
- Plans for assessing capacity and ensuring subjects' capacity, understanding, and informed consent or assent throughout the study.
- Procedures for ensuring subjects representatives are well informed regarding their roles and obligations to protect individuals with impaired decision-making capacity.
- Procedures for ensuring that participants will not be forced or coerced to participate in the research study.

In "Appendix A" of the *Application for New Human Subject Research Study*, the PI must provide the following information when pregnant women are recruited.

- Plan to monitor risk of the participant and fetus.
- Procedure to select potential participants.
- Background and for the study must indicate if information is available on animals and non-pregnant individuals and provide data for assessing potential risk for pregnant women and fetuses.

6.5 Recruitment of Non-Veteran Patients

Non-Veteran patients may be recruited only when there are not sufficient Veteran subjects available to conduct the study. The Principal Investigator must justify the inclusion of non-Veteran subjects in "Appendix A" of the *Application for New Human Research Study* form. All regulations pertaining to Veteran patients are also applicable to non-Veteran subjects.

When a non-Veteran subject is enrolled in a research study, the Principal Investigator is responsible for submitting *VA Form 10-10 EZ - Applications for Health Benefits* to the IRB Office. (This form is used to create a new medical record for non-Veteran research subjects). If a non-Veteran subject is already enrolled in the VA system, this step is not required.

A \$384 fee will be charged to the Principal Investigator's research project account to establish a new medical chart for any non-VA subject not already enrolled in the VA system.

6.6 Payment or Compensation to Research Subjects

If subjects are to be compensated for their participation in the study, the compensation plan must be described in "Appendix A" of the *Application for New Human Research Study* form. VA has specific regulations and guidance regarding payment or compensation (e.g. coupons) to subjects who participate in research. These include:

- Per federal regulations, (VHA Handbook 1200.05), at the time of initial application, the IRB reviews any financial or other form of payment to research subjects to assure that the amount is not coercive given the nature of the research or creates an undue influence on the subject to participate. The information is provided in the protocol and the consent form. Additional information may be required on an "as needed" basis.
- Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation. Payment may not be withheld as a condition of the subject completing the research. Any amount paid as bonus for completion of the entire study should not be so great that it becomes coercive. If the subject withdraws early, payment must be prorated to reflect the time and

inconvenience of the subject's participation up to that point. The schedule, amount, and conditions of payment must be stated in the informed consent form.

- Payment does not include finders' fee.
- VA policy prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care.
- Compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing is prohibited.

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

1. No direct subject benefit. When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this same or similar situation.
2. Others being paid. In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same proposed rate, the IRB may find that payment is appropriate.
3. Comparable situations. In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers 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 reimbursed by another mechanism.

Investigators who wish to pay research subjects must indicate in their research project application the justification for such payment. They may include consideration of the criteria listed above and address the following:

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

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

For specific procedures for paying research volunteers see Medical Research Service policies *HSP-008A “Paying Human Subject Volunteers with VA Appropriated Funds”* and *HSP-008B “Paying Human Subject Volunteers with Research Foundation Administered Funds.”*

6.7 Enrolling Patients in More Than One Study at a Time

As a general rule, subjects participating in research at this facility may not enroll in more than one active study at a time without a waiver from the IRB. However, a request for a waiver may be considered on a case-by-case basis if there will be no overlap between the studies, and enrollment in two concurrent studies will not have a confounding effect on the data. If the request involves patients enrolled in a CSP study, the Principal Investigator must obtain approval from the Cooperative Studies Coordinating Center.

Waivers are requested by submitting a memorandum to the IRB Office that includes the following information:

- ✓ Number and title of the specific studies for which a waiver is requested.
- ✓ Names of Principal Investigators.
- ✓ A brief description of the study and the patient’s participation in the research.
- ✓ Concerns about any overlap between the studies and/or confounding effects on the data.
- ✓ Signatures of any other Principal Investigators acknowledging the request (when more than one Principal Investigator is involved).
- ✓ Specify request is for a single patient or for potentially recruitable populations.

6.8 Changes to the Recruitment Plan

The PI must submit a completed amendment application for IRB review and approval before implementing the changes to the recruitment plan.

SECTION 7 - INFORMED CONSENT

7.1 Informed Consent Document

Unless a waiver has been granted by the IRB, investigators must obtain informed consent using *VA Form 10-1086-VA Research Consent Form* before implementing any study procedures. It is essential that the document contain all relevant information and that it is stamped with an IRB approval and expiration date. The most current IRB-approved version of *VA Form 10-1086, Research Consent Form*, for each study (or the most current IRB-approved electronic version of VA Form 10-1086) must be used as the informed consent form

EXPIRED INFORMED CONSENT DOCUMENTS MUST NOT BE USED.

A sample informed consent document is available at: www.sfvafre.org.

7.2 Informed Consent Investigator Checklist

A form entitled *Investigator Checklist for Preparation of Informed Consent Documents* has been developed to assist investigators in preparing *VA Form 10-1086 - VA Research Consent Form*. This checklist describes the content that should appear in the consent document, including the basic elements and additional elements required by other federal regulations. The checklist is available at: www.sfvafre.org.

Note: The PI is responsible for ensuring that the language in the informed consent form is consistent with that in the protocol, in the application and, when applicable, in the HIPAA authorization.

7.3 Description of the Informed Consent Process

In addition to developing a consent form that meets regulatory requirements, Principal Investigators must also describe how the informed consent conference will be conducted. The *Application for New Human Research Study* form provides space in the “Informed Consent” section for answering specific questions about the informed consent process. Specifically the following items should be adequately described on the form:

- ✓ Describe how the required information will be presented to subjects (consent form, orally, information sheet, etc.).
- ✓ Describe the circumstances under which consent will be obtained
 1. When will informed consent be obtained (e.g. Informed consent must be obtained before study participants begin).
 2. Where will the informed consent meeting be conducted (e.g. Describe setting; how will privacy protected).
 3. Describe the plans for on-going consent.
- ✓ Who will obtain consent? Describe their experience in obtaining consent from subjects. (Only research personnel listed on *Report of Research Staff* form are authorized to consent subjects.)
- ✓ How will it be determined that the subjects or the subjects’ authorized representatives understand the information presented?
- ✓ Are patients who do not read or understand English being recruited?
- ✓ The informed consent will be *documented* by obtaining a written consent form that is *signed and dated* using VA Form 10-1086?
- ✓ Does the sponsor require a witness during the consenting process?

- ✓ What steps will be taken to minimize the possibility of coercion or undue influence?
- ✓ What is the mechanism for reporting new information to the IRB between reviews?
- ✓ Describe how the informed consent meeting will be documented in CPRS. Standard language is provided in the *Investigator Checklist for Preparation of Informed Consent Documents*.

7.4 Conducting the Informed Consent Conference

Informed consent is not just a written document, but also a process that starts with initial presentation of the concept of the research activity to a prospective study participant (or legally authorized representative /surrogate). The same process for informed consent for subjects who have decision-making capacity also apply for the surrogate. Disclosures required by Handbook 1200.05 that must be made to the subject by the investigator must be made to the subject's surrogate. On the *Application for New Human Research Study* form, the Principal Investigator must describe the informed consent process for (1) decisionally impaired individuals and/ (2) subjects whose decisional capacity fluctuates. If it is determined that the subject lacks decision-making capacity and has a surrogate, that surrogate generally assumes the same authority and responsibilities as the subject in the informed consent process.

Minimizing the possibility of coercion or undue influence is central to the informed consent process. All elements of the consent form are to be discussed with the study subject, allowing the subject sufficient time to decide whether or not he/she wants to participate in the study. The consent form may be mailed to subject prior to the first study visit. The PI and/or designee must discuss the consent form with the subject and address all questions within his/her scope of responsibility.

- Provide information that the subject in similar circumstances would reasonably want to know.
- The investigator, or designee, must ensure the informed consent process clearly defines for the subject which potential risks are related to the research and, therefore, must be discussed with the research team, versus those associated solely with usual care provided by the subject's healthcare provider. The informed consent process must include language advising subjects to review the risks of the latter with their healthcare providers.
- Read the consent document or give the subject adequate time to read it before it is signed. Give the subject the opportunity to take the consent form home or consult with others before agreeing to participate.
- Ensure that the patient indicates understanding of all information provided. For example, the investigator may ask the subject to describe the study goals or procedures in the subject's own words.
- Encourage subject to ask questions; discuss answers in detail.
- Identify by name and profession the investigator who has primary responsibility for the subject's care. The names and professions of any other individuals responsible for performing the research procedures under consideration must also be disclosed.
 - Advise the subject of personnel associated with the study who will be in contact with him/her.
- Give a copy of the pamphlet entitled "Volunteering in Research – Here are Some Things You Need to Know", which contains two contact numbers (Facility Patient Advocate and IRB Office) independent of the research team who can provide relevant information of the research study.

7.5 Instructions for Documenting the Informed Consent Process

The Principal Investigator is required to document the informed consent conference in the CPRS Template: *T- Research Study: Documentation of Consent Discussion*. Documenting the informed consent conference activates the medical record flag for studies requiring such flags. Instructions for using the template are listed below.

Instructions for Documenting the Consent Conference in CPRS

To add this template to your Documents List:

- 1) Open a CPRS session.
- 2) Go to "Tools", select "Options".
- 3) Click on the "Notes" tab, and click on the "Document Titles" button.
- 4) In the "Document Class" field, select "Progress Notes"
- 5) In the "Documents Titled" field, type "T-Research Study..." You will see the document listed in the space below the "Document Titles" field. Click on the template and then click on the "Add" button.
- 6) Click on "Save Changes", then click on "Okay" to exit and click "Okay" again to return to the main CPRS screen.

NOW you are ready to use the template.

Select a New Note and associate it with the patient involved.

(If you did not see the patient in a scheduled Outpatient clinic visit, then select "Historical Visit".)

From your Documents List, select the new template (if you did the process above, it should be listed at the top of your list).

PLEASE NOTE: You cannot minimize the template once you begin to fill it out. If you click on the "X" at the top right hand corner, you will LOSE everything you've typed. All the fields marked with an asterisk have to be included in the progress note.

Once you have completed the template and have clicked "Okay" you will be back in the CPRS editing screen. Verify that the information entered is correct, then sign the note electronically.

Documenting Surrogate Informed Consent Process in the Medical Chart

In addition to the requirements for documenting the informed consent process in the medical chart, documentation for subjects who lack decision-making capacity and have a surrogate, must also include:

- The surrogate's name;
- Relationship to the patient;
- Authority to act as surrogate (whether DHCP, legal guardian or next-of-kin); and
- How the consent was obtained (in person, telephone, by mail, or facsimile(fax)).

A copy of a legally recognized document may also be included in the medical record.

7.6 Medical Record Flags

Flags are pop-up windows used in the electronic medical record (CPRS) to indicate a patient's participation in a research study. Flagging is required for all projects that include an intervention that is not part of normal clinical treatment, where investigational drugs are being dispensed as part of the research protocol, or other such interventional studies. Flags should include pertinent information regarding procedures, special complications, medications, etc. that should not be used while the patient is enrolled in a research protocol. If there are no such special considerations of concern, then the flag would simply be for informational purposes. The flag will be triggered each time the medical record is accessed. Most studies require a flag. Examples of studies that would not require a flag are:

1. The subject's participation in the study involves:
 - a. Only one encounter,
 - b. Only the use of a questionnaire, or
 - c. The use of previously collected biological specimens.

OR

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.

The determination of whether a flag is needed for a study can occur in two ways:

- a. Based on the specifics of an individual research protocol, the Principal Investigator may recommend that a flag be used.
- b. During initial review of a new research application, the IRB may recommend that a flag be used. If the IRB independently determines that a flag is necessary, the Principal Investigator will be notified in writing.

Before initiating the study, the Principal Investigator must provide the IRB Office with a "flag" statement regarding any warnings or information that other healthcare workers, who are providing concurrent medical to these patients need to know (e.g. procedures or medications to avoid). In cases where the flag would simply be for informational purposes, then only the basic information needs to be provided. After review and approval by the IRB Chair, this statement will be used as the actual pop-up flag in CPRS. Once the study begins, it is the responsibility of the Principal Investigator to deliver the informed consent documents to the IRB Office before a patient begins the study intervention. The delivery of the informed consent will be logged and sent to MAS, and this will initiate the setting of the flag by the IRB staff in the study participant's medical record.

7.7 Documenting Termination of Participation in a Study

When a subject terminates his or her participation in a study, the Principal Investigator is responsible for: (1) documenting the termination in the CPRS template: *T- -Research Study: Termination of Study Participation*. The procedure for documenting a patient's termination in a study in CPRS is similar to that of documenting participation in a study (see instructions in Section 10.5). After completing the CPRS template, the Principal Investigator must provide to the IRB Office a copy of the termination record. Upon receipt of the termination record and any other required documentation, IRB staff will release the flag.

7.8 Assent from Children

VA policy stipulates that children cannot be included in VA-approved research unless the Chief Research and Development Officer grants a waiver. Proposed research must not involve greater than minimal risk.

In the rare instances where children are included in a research study, the IRB may require assent from the child. The IRB considers the age, maturity, and psychological state of the child involved.

The Assent Form

Researchers should draft a form that is age appropriate and study specific, takes into account the typical child's experience and level of understanding, and that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it's up to the child to participate and that it's okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions from the child.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

It is a rare occasion when children are used in VA research; therefore additional information about parental permission and the consent process can be found in the HRPP SOP.

7.9 Waiver or Alteration of Informed Consent/Waiver of HIPAA Authorization

Under certain circumstances, the IRB may approve consent procedures that do not include or alter some or all of the required elements of informed consent and HIPAA regulations. To request these types of waivers, the Principal Investigator must include a completed *Request for Waiver or Alteration of Informed Consent/Waiver of HIPAA Authorization* form along with the new application materials. To be eligible for the waivers, the research must meet all of the criteria listed on the form.

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research involves no more than minimal tangible or intangible risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- (a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
 1. Public benefit or service programs
 2. Procedures for obtaining benefits or services under those programs
 3. Possible changes in or alternatives to those programs or procedures; or
 4. Possible changes in methods or levels of payment for benefits or services under those programs.
- (b) The research could not practicably be carried out without the waiver or alteration.

FDA regulations do not provide for waivers of informed consent except in emergency situations (See Section 11.12).

To request this type of waiver, the Principal Investigator is required to submit a completed *Request for Waiver or Alteration of Informed Consent/ Waiver of HIPAA Authorization* form along with the *Application for New Human Research Study* form.

Note: MVAHS procedures include the HIPAA authorization criteria in the *Request for Waiver or Alteration of Informed Consent/HIPAA Waiver of Authorization* form.

7.10 Waiver of Documentation of Informed Consent

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

1. The only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality; or
Note 1: Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)
Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.
2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers.

In these cases, the Principal Investigator must submit a *Waiver of Documentation of Informed Consent* form. The waiver form, which contains a "Letter of Introduction" /summary (a written description of the information that will be provided to participants regarding the research) is included in the new research submission.

7.11 Research Personnel Authorized to Consent Research Subjects

A *Report of Research Staff Member* form, which lists staff members authorized to carry out the informed consent conference, must be included in any new research application. Only research personnel listed on this report are permitted to conduct the informed consent conference.

Any person designated to obtain informed consent must receive appropriate training and be knowledgeable enough about the protocol to answer the questions of prospective subjects.

7.12 Translators and Translated IC Documents

A translator may be used to explain the informed consent information; however, the consent document must be written in the language understandable to the subject. IRB approval is required before implementing a translated informed consent document. Expedited review procedures may be used to approve translated consent forms if the English language consent document has already been approved. A Spanish translation of the *VA Research Consent Form* template is available on the website.

7.13 Advocates

Subjects who are competent to give informed consent may elect an advocate to assist them during the decision-making process of the informed consent conference; however, advocates are not legally authorized representatives (i.e. surrogates) and may not make decisions on behalf of the patient.

7.14 Surrogate (Legally Authorized Representative) Informed Consent

VA's General Counsel has determined that the "applicable law" to be used in determining the appropriate surrogate is VA's Informed Consent statute (38 U.S.C. 7331) and its Informed Consent Regulation (38 CFR 17.32). [VAOPGCADV 7-2005].

If it has been verified that the potential research participant is unable to give informed consent for him/herself, his/her legally authorized representative may consent on behalf of him/her to participate in the procedure(s). A legally authorized representative is defined as an individual, or judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research in the following descending order of priority:

- Person appointed as healthcare agents under DPAHC
- Court appointed guardian of the person
- Spouse
- Adult child (18 years of age or older)
- Parent
- Adult siblings (18 years of age or older)
- Grandparent
- Adult grandchild (18 years of age or older)

Please Note: The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes. Refusal to consent by a person who is a higher priority surrogate shall not be superseded by the consent of a person who is a lower priority surrogate. Additionally, if there are two or more individuals in the same class and the decision is not unanimous among all available members of the class, then no person under this section may provide informed consent. Surrogates may not receive financial compensation for providing the consent.

Surrogate consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements in listed below (a-c), or as established by a legal determination.

1. The practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
2. Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.

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

A surrogate must be fully informed of the study and have sufficient opportunity to consider what the wishes of the potential subject would be and whether or not to consent on behalf of the subject. The surrogate must receive all of the information a regular enrollee would receive in language that is understandable to the surrogate. Surrogate consent will be accepted in the order identified in the SOP and consistent with Florida state law. If the potential subject indicates that he/she does not wish to participate then the surrogate consent cannot be honored.

When surrogate consent is used, the investigator must document in writing the name of the surrogate and that he/she: 1) is aware of his/her responsibility, 2) has been informed about risks/benefits of the study, 3) is aware that the subject had consented to participate, if applicable, 4) is aware of his/her rights to withdraw his/her consent, 5) may contact the PI or Research Service for questions/problems, 6) is aware that the subject, if possible, has given his/her assent to participate in the study, 7) will be informed of future information that is needed to be an informed participant. Progress notes during the period of surrogate consent should note that subject him/herself demonstrates no dissent from participation in the study.

7. 15 Informed Consent by Mail, Fax or Telephone

When it is impractical to obtain informed consent in person, consent may be obtained by fax or mail. Informed consent obtained by fax or mail must also include a telephone conference as part of the informed consent process. The use of faxed or mailed documentation of informed consent should not be used as a matter of convenience. Its use should be limited to situations in which geographical barriers or other conditions prohibit obtaining informed consent in person from the subject's legally authorized representative. All requirements for obtaining informed consent as specified VA guidance documents apply to informed consent using mailed or faxed documentation of signature for informed consent. In addition, the requirements for the use of surrogate consent must be fulfilled.

Original Signed Consent Form

The original signed and dated informed consent form must be filed in the investigator's research file for that subject so that it is readily accessible for auditing. If the subject submits the signed and dated informed consent form to the investigator or designee by facsimile, the person who obtains informed consent must sign and date the facsimile, and then the facsimile can serve as the original informed consent document.

Procedures for Obtaining Surrogate Consent By Mail or Fax:

- Following confirmation that the mailed or faxed informed consent document has been received by the subject or the subject's legally authorized representative, the consent conference will be conducted by telephone between a member of the study team authorized to obtain consent and the surrogate.
- The subject or surrogate must have an individual witness the informed consent conference, if recommended by the IRB. The identity of the surrogate and witness will be documented before the conference.

- If the subject or surrogate agrees to the subject's participation in the study, he/she will sign and date the informed consent document on the subject's signature line.
- The witness must also sign and date the form, if recommended by the IRB.
- The consent document will then be returned to the investigator by mail or fax. The original mailed or faxed consent form must be filed in the subject's research file.
- The Principal Investigator is also responsible for submitting additional materials to the IRB and documenting the informed consent process in CPRS.

Consent by E-mail: Signature consent by e-mail is not permitted.

7.16 Informed Consent Approval Period

Informed consent documents are approved for a limited time (one year or less from the date of the IRB meeting at which the protocol was approved or approved contingent upon minor modifications).

The new informed consent document supplants any previously approved consent form(s). Newly enrolled subjects must sign the most recently approved informed consent document.

EXPIRED INFORMED CONSENT DOCUMENTS MUST NOT BE USED.

Note: There may be circumstances in which all subjects need to be re-consented. (See Section 7.9)

7.17 Signatures and Dates.

The informed consent form must be signed and dated by:

1. The subject or the subject's LAR.
2. The person obtaining the informed consent, and
3. A witness, if required by IRB (e.g., the IRB may require a witness if the study involves an invasive intervention or an investigational drug or device).
 - a. The witness is required to witness only the subject's or subject's LAR's signature, not the informed consent process (e.g., if the subject does not want the witness to know the nature of the research study), unless the sponsor or IRB requires the witness to witness the informed consent process.
 - b. The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member.

7.18 Signing and Dating the Informed Consent Document/Witnesses

- Prior to engaging in any study activities, subjects or the subject's legally authorized representative will sign and date the consent document. The consent document signed by the subject must have the IRB approval stamp on it.
- The sponsor or IRB can require that the informed consent process be witnessed. In this case, a witness must sign and date the consent. The requirement of a witness name and signature signifies that the witness has observed the subject signing the consent form.

The witness must be someone other than the person who obtains informed consent. Persons at least 18 years of age may serve as a witness.

All pages of the informed consent document are to be initialed by the participant (or authorized representative). The following individuals sign and date the informed consent document:

- Subject or surrogate (LAR).
- If the research is FDA regulated, the subject or surrogate will date the consent document.
- Witness. If the witness serves in the both capacities (i.e. witnesses signature and witnesses consent process, a note to that effect is placed under the witness' signature line).
- Advocate, if applicable.
- Translator, if applicable. Translators who take part in the informed consent conference may serve as the witnesses if they are not part of the research team.

7.19 Re-Consenting Subjects

Current and previous subjects may need to be re-consented if changes to the research protocol result in an amended informed consent document. Such changes may result in the need to re-consent subjects already enrolled in the study by means of a new informed consent conference and an amended consent form.

When re-consenting subjects, the Principal Investigator is responsible for:

- ✓ Submitting a re-consent plan to the IRB for active patients and patients who have completed the study.
- ✓ Submitting a monthly progress note to the IRB regarding the status of the plan.
- ✓ Forwarding a copy of the newly signed informed consent document to the Pharmacy Service.

7.19.1 Clarification of Informed Consent Expiration Date and Policy of Reconsenting of Subjects

The purpose of the IRB approval date and expiration date at the bottom of each page of the informed consent document is to indicate that version of the consent document has been reviewed and approved for the purpose of subject recruitment during the time period indicated on that form. A new consent document is provided on continuing review with an updated IRB Approval and Expiration date to be used in the next period of IRB approval. This is not intended to require patients who were already enrolled in the study to have to sign new informed consents every year.

Amendment procedures require the issuance of a new IRB-stamped consent form regardless of whether there has been a change to the consent form or not. It is not necessary for subjects to sign every version of a consent form. Subjects enrolled in a research study should only be asked to re-sign an informed consent document if there is new information which may affect their decision to continue being in the study.

7.20 One Subject, One Informed Consent

Research studies are often reviewed and approved by more than one IRB (e.g. MVAHS and University of Miami). No patient should sign informed consent documents from more than one institution for the same study, except under special circumstances which must be discussed with

the IRB Chair. For any questions regarding this policy, please contact the MVAHS Research IRB Office.

7.21 Maintaining a Master List of All Subjects

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

1. Investigators must not add a subject's name to the master list of all subjects until after:
 - a. Informed consent has been obtained from that subject, and
 - b. When appropriate, informed consent has been documented using an IRB-approved informed consent form.
2. The IRB may waive the requirement for the investigator to maintain a master list for a given study if both of the following conditions are met:
 - a. There is a waiver of documentation of informed consent, and
 - b. The IRB determined that including the subject on such a master list poses a potential risk to the subjects from a breach of confidentiality.
3. If the IRB waives the requirement to maintain such a master list, the IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.
4. 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.

7.22 Executed Informed Consent Documents

After the informed consent document is signed, the Principal Investigator is responsible for:

- ✓ Sending a copy to the IRB Office. IRB staff will forward the consent document to the Medical Administration Service (MAS) where it will be scanned into the subject's medical record. The IRB staff will set the flag in the study participant's medical record, if applicable.
- ✓ For studies involving investigational drugs, a copy of the VA Form 10-9012 must be submitted to the IRB Office along with the consent document.
- ✓ Forwarding a copy to the Pharmacy Service along with a prescription, if applicable
- ✓ The informed consent process must be documented in the *CPRS Template for Documentation of Informed Consent Discussion for Research Study* that is contained in the subject's medical chart.
- ✓ A copy of the completed informed consent discussion template must be submitted to the IRB Office.
- ✓ The date a patient begins the study procedures must be documented in his/her medical chart (e.g. date subject begins to receive study drug).
- ✓ Providing a copy to the research subject or surrogate.
- ✓ Maintaining the original under conditions of confidentiality in the research study records.

SECTION 8 - SAFETY MONITORING PLAN

8.1 Data and Safety Monitoring Plan

All studies, including minimal risk, require a safety monitoring plan. The IRB reviews the protocol-specific plan for monitoring the data collected to assure the safety of subjects. The plan may include establishing a Data Safety Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) as required by DHHS or FDA regulations. In addition, for studies that do not have a DSMB and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, a general description of the data and safety-monitoring plan is reviewed by the IRB as part of the proposed work.

Where appropriate, a research plan should make adequate provisions for monitoring data collected to provide for the safety of participants. The initial research plan submitted to the IRB should describe the procedures for data safety monitoring and reporting of adverse events and unanticipated problems involving risks to subjects or others. Provisions for a DSMB or any independent safety monitoring board and the procedures planned for transmitting the results to the IRB are reviewed at initial review. Otherwise, an explanation as to why it is not necessary must be approved by the IRB.

If not included in the protocol, the PI must describe the safety monitoring plan on the *Application for New Human Research Study* form. The plan must address all of the applicable criteria listed below:

- ✓ The plan to monitor research progress and subject reactions, including who will do the monitoring and how monitoring will be accomplished.
- ✓ The plan must include:
 1. The frequency of data collection including when safety data collection starts; and
 2. The frequency or periodicity of review of cumulative safety data.
- ✓ Identification of a Data Safety Monitor or Data Safety Monitoring Board, where applicable.
- ✓ The plan for dealing with adverse events and unanticipated problems involving risk to subjects or others. The plan must address all potential adverse events and unanticipated problems. These include: physical, psychological, economic, social, and legal.
- ✓ The plan to assure compliance with reporting of adverse events and/or unanticipated problems involving risks to participants or others.
- ✓ The plan to assure data accuracy and protocol compliance.
- ✓ If not using a Data Monitoring Committee (DMC), and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring.
- ✓ Conditions that trigger an immediate suspension of the research, if applicable.

Note: The data and safety monitoring plan may vary depending on the potential risks,

complexity, and nature of the study. The use of an independent DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are high-risk, vulnerable populations are included, or when required by the funding organization, FDA, sponsor, or other relevant entity.

8.2 Describing Data and Safety Monitoring Plan for Retrospective Studies

The DSMP is required for retrospective studies, including studies involving pre-existing data and biological specimens. When applicable, the plan needs to include, but is not limited to, the following:

1. A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being;
and
2. A procedure to determine when and how to notify individual subjects or their healthcare providers of findings that may affect the subjects' health.

8.3 Submitting Data Safety Monitoring Board Reports

Data Safety Monitoring Board (DSMB) reports must be submitted to the IRB within 5 days of receipt along with a memorandum that contains the following information:

- ✓ Name of Study.
- ✓ Name of Principal Investigator.
- ✓ Brief description of what is being submitted.

8.4 Unanticipated Problems to Previously Approved Research

Prompt reporting of unanticipated problems or risks to subjects to the IRB is crucial whenever they occur during the study. The PI is responsible for submitting an *Unanticipated Problem Reporting* form to the IRB when reportable events occur.

Reportable Event: Any event, problem, or new information that may represent an unanticipated problem involving risks to participants or others and requires prompt reporting. Examples of Reportable Events are listed in Section 13.5.

See the Human Research Protection Program Standard Operating Procedures (Section 8) for more information concerning unanticipated problems and/or serious adverse events.

8.5 Reporting

Within 5 business days of becoming aware of any unanticipated problem involving risks to subjects or others in VA research, members of the VA research community are required to ensure that the problem has been reported in writing to the IRB.

Unanticipated problems involving risks to subjects or others include:

1. Serious unanticipated problems involving risks to subjects or others, these include:
 - a. 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.
 - b. 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.

- c. 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.
 - d. Any DMC, DSMB, or DSMC report describing a safety problem.
 - e. Any sponsor analysis describing a safety problem for which action at the facility level may be warranted.
 - f. 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.
 - g. Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs.
2. Local Unanticipated SAEs Investigators must promptly report within five (5) business days of becoming aware of any local unanticipated SAE's.

Investigators must report the following events immediately to the MVAHS Privacy Officer or MVAHS ISO, as appropriate, upon discovery of the event(s):

- 1. Unauthorized use, loss, or disclosure of individually identifiable patient information.
- 2. Violations of information security requirements.

8.6 Submission of Reports

Investigators must report possible unanticipated problems to the IRB promptly. Investigators and/or study staff must report any event, problem, or new information that may represent unanticipated problems involving risks to participants and others to the IRB Office in writing using the *Unanticipated Event Reporting Form*. The written report should contain the following:

- If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) days of receiving notice of the event.
- Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (5) business days from the date of the event or from the date the investigator is notified of the event.

Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.

Investigators or the study team must report possible unanticipated problems to the IRB Office in writing using the *Unanticipated Problem Reporting Form*. The written report should contain the following:

- 1. Detailed information about the possible unanticipated problems, including relevant dates.
- 2. Any corrective action, planned or already taken, to ensure that the possible unanticipated problems is corrected and will not occur again.

3. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.
4. Any other relevant information.
5. Any other information requested by the IRB Office.

A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded by the IRB Office staff to the IRB Chair if the IRB Office staff believes that immediate intervention may be required to protect participants or others from serious harm. Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the IRB Chair will notify the PI on the study, when appropriate.

8.6.1 Type of Problem or Event

Adverse Event: An AE is defined as 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. Some adverse events are expected and can be anticipated.

Unexpected AE: An unexpected adverse event 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 to Research: If in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants.

Serious Adverse Event: A SAE is one that results in death, a life-threatening experience, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unanticipated Problem: An Unanticipated Problem results in risk to subjects or others that is not discussed in the protocol and informed consent document.

Protocol Deviation: A protocol deviation is defined as a violation that is unanticipated and happens without any prior agreement (protocol visit scheduled outside protocol window, blood work drawn outside protocol window, etc.). The IRB will review these reports for frequency and may audit any protocol reporting frequent deviations.

Deviations

It is the responsibility of the Principal Investigator not to deviate from the protocol approved by the IRB, except to avoid an immediate hazard to the participant. The Principal Investigator must submit an amendment request along with the *Unanticipated Problem Reporting* form to the IRB and receive written approval prior to implementation of any change to the protocol.

Deviations that increase risk have potential to recur or undertaken to eliminate an immediate hazard would be considered an Unanticipated Problem and should be reported as described in according to Section 8.5.

When a sponsor requests that the IRB be notified of a deviation, the completed form will be forwarded to the IRB Chair or designee for review of the *Unanticipated Problem Reporting* form submitted by the investigator.

Repetitive deviations may be ruled by the IRB to constitute non-compliance resulting in suspension of IRB approval.

Protocol Exceptions: Protocol exceptions are defined as circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient/subject (Example: patient/subject is allergic to one of the medications provided as supportive care). Usually it is a violation that is anticipated and happens with prior agreement from the sponsor.

It is the responsibility of the Principal Investigator to report to the IRB, exceptions made to the protocol. The IRB will perform an expedited review of the *Unanticipated Problem Reporting* form submitted by the Principal Investigator along with documentation of sponsor justification and approval.

These exceptions must be approved by the sponsor and IRB before being implemented. Exceptions may not increase risk or decrease benefit, affect the participant's rights, safety, welfare, or affects the integrity of the resultant data.

On the *Unanticipated Problem Reporting Form*, the PI will be required to indicate the type of problem, event or new information and provide a description of problem.

8.7 IRB Review

The primary reviewer will be given the protocol file, the currently approved consent document, previous reports of unanticipated problems involving risks to participants or others, the investigator's brochure (if one exists), the event report, and recommendations from the IRB Chair or designee, when appropriate. All IRB members will receive the event report.

After review of the protocol and event report, the full IRB will make findings and recommendations based on the following considerations:

- Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
 - What action in response to the report is appropriate.
 - Whether suspension or termination of approval is warranted.
 - Whether further reporting to institutional and/or federal officials is required.
1. If the IRB finds that the event is not an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:
 - a. No action

- b. Requiring modifications to the protocol
 - c. Revising the continuing review timetable
 - d. Modifying the consent process
 - e. Modifying the consent document
 - f. Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
 - g. Providing additional information to past participants
 - h. Requiring additional training of the investigator and/or study staff
 - i. Other actions appropriate for the local context
2. If the IRB finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:
- a. Requiring modifications to the protocol
 - b. Revising the continuing review timetable
 - c. Modifying the consent process
 - d. Modifying the consent document
 - 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
 - l. Referral to other Medical Central entities (e.g., legal counsel, risk management, institutional official)
 - m. Suspending the research
 - n. Terminating the research
 - o. Other actions appropriate for the local context
3. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination must follow the reporting requirements in VHA Handbook 1058.01.
4. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will do all of the following:
- a. Notify the investigator in writing of its findings, with copies to the investigator's service chief and the investigator's supervisor.

- b. Report directly (without intermediaries) to the facility Director within 5 business days after the termination or suspension occurs. The report will include findings and recommendations. The facility Director must promptly report the termination or suspension to the appropriate federal officials (OHRP and FDA) and to the ORO RO within 5 business days after receiving such notification.
- c. Simultaneously distribute copies of the written report to the Medical Center Director, as applicable, to the ACOS/R, the R&D Committee, and any other relevant research review committee.

8.8 Reconsideration of the IRB Decision

The notice to the investigator of the IRB determination will inform the investigator that he or she has ten (10) business days from receipt of the notice to request reconsideration of the IRB decision by sending the IRB a written request for reconsideration including the basis of the investigator's request.

1. If a n investigator requests reconsideration, the investigator's written request is considered at the next IRB meeting and the IRB makes a determination whether to uphold, reverse or modify its decision. The IRB notifies the investigator of the final outcome.
2. If the IRB receives a request for reconsideration from the investigator, the IRB should notify the R&D Committee and the medical center Director of the request and of the final outcome.

8.9 Non-Reportable Events

All events, problems, and new information that do not meet the above reporting requirements must be reported to the IRB in *Tracking Log for Reportable and Non-Reportable Events* form at the time of the next continuing review.

The IRB recognizes that sponsors may require that the PI report all off-site serious adverse events and IND safety reports to the IRB. The IRB complies with this request in an efficient manner to acknowledge receipt of these reports.

PIs should report adverse events and IND safety reports that do not meet the above reporting requirements by using the *Tracking Log for Reportable and Non-Reportable Events* form. Upon receipt, the IRB Administrative Staff will review the *Tracking Log for Reportable and Non-Reportable Events* and check the form for completeness. The form will be returned to the investigator if it is incomplete.

If the investigator answered "yes" to all three of the reportable criteria listed below for a local event, the IRB staff will contact the investigator to request that the investigator complete an *Unanticipated Event Reporting* form. The IRB Office staff will track such requests by placing a copy of the request in the study file.

1. Did the event, problem, or new information harm one or more participants or others, or place one or more participants or others at increased risk of harm?

2. Was the event, problem, or new information unexpected (in terms of nature, severity, or frequency) given the procedures described in the protocol related documents and the characteristics of the population being studied?
3. Was it more likely than not that the event was caused by the research procedures or affects the rights and welfare of current participants?

Otherwise, the IRB Administrative staff will stamp the form “received”, sign and date the form, and return a copy of the form to the PI.

8.10 Notifying the Research Office of Audits, Site Visits and Monitoring Visits

Research Service must be notified of any site visits conducted by entities external to the MVAHS or its affiliates (e.g. pharmaceutical companies, Contract Research Organizations). Principal Investigators are required to forward any correspondence from monitors to the IRB as soon as it is received. During each visit, the Principal Investigator is responsible for the following:

- ✓ Immediately notifying the ACOS/R (or A/O R) of the visit. If the visit is unscheduled, the ACOS/R must be notified as soon as the Principal Investigator becomes aware of the visit.
- ✓ Assuring the study monitor signs in as a visitor with the ACOS/R.
- ✓ Meeting the study monitor before the monitor begins his/her work. The role of the monitor should be reviewed.
- ✓ Discussing with the monitor the results of the visit before the monitor leaves the facility.
- ✓ Scheduling an exit interview with ACOS/R (or AO/R) if the monitor records any potential or actual serious findings. (Findings that require an exit interview include but are not limited to: (1) any suspicions or concerns of serious non-compliance and (2) any serious non-compliance with the study protocol, IRB requirements or applicable regulations and policies.)
- ✓ Immediately notifying the IRB Office in writing that the monitor recorded no significant findings, if none were found.

SECTION 9 - INVESTIGATIONAL DRUGS AND DEVICES

9.1 Investigational Drugs and Devices in Research

The FDA has explicit regulations regarding the use of investigational drugs and devices.

Under certain conditions, Principal Investigators must have an investigational new drug (IND) application before drugs can be shipped. Additionally, use of an “off-label” marketed product in research requires an IND when the research is used to support: (1) a new indication for use; (2) a change in labeling; or (3) a change in advertising. An IND may be required for “off-label” use when the route of administration, dosage level, use in a patient population or other factor significantly increases risks. Use of “off-label” products requires informed consent and IRB approval.

Depending on the risk assessment of a device that a sponsor provides (significant risk or non-significant risk), an investigational device exemption (IDE) may be required. In cases where the sponsor does not make a risk assessment, the IRB makes the risk determination. The IRB may also override a sponsor’s non-significant assessment and determine that the device falls under the category of significant risk.

The sponsor or sponsor/investigator is responsible for procuring the IND or IDE. Unless a waiver has been granted, the Principal Investigator must submit documentation along with the new research application indicating that an IND has been procured.

Note: Principal Investigators should contact the IRB Office if they are unsure about whether an IND or IDE is required.

9.2 Waiver of IND Application

All studies that utilize products regulated by the Food and Drug Administration (FDA) need to have either an approved IND application from the FDA, or a waiver from the requirement to secure an IND approved by the IRB. To request a waiver, the Principal Investigator must submit a completed *Request for Waiver from the Requirement to Submit an IND Application to the FDA* form along with the new research application.

To be eligible for a waiver, the study must meet the following five criteria:

1. The investigation is not intended to be reported to the FDA as a well-controlled study of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
2. 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.
3. 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.
4. The investigation is conducted in compliance with the requirements for institutional review set forth in 21CFR Part 56 and with the requirements for informed consent set forth in 21 CFR Part 50.
5. The investigation is conducted in compliance with the requirements of Part 312.7.

9.3 Changes to the Investigator Drug Brochure

The Principal Investigator is responsible for reporting changes to the Investigator Brochure. The notification or amendment may be expedited. When reporting changes to the Investigator Brochure, the Principal Investigator is responsible for reviewing it to determine if changes are needed to the informed consent document. Depending on whether or not changes are required, the Principal Investigator must do one of the following:

1. If changes to the informed consent document are not required, the following items must be submitted to the IRB Office:
 - ✓ A memorandum that: (a) indicates the study for which the Investigator Brochure is being submitted; and (b) provides an explanation as to why changes to the informed consent document are not needed.
 - ✓ One copy of the current informed consent document (bearing stamp).
 - ✓ Two copies of the Investigator Brochure.
2. If changes to the informed consent document are required, the following items must be submitted to the IRB Office:
 - ✓ An amendment packet (see Section 3: - Option #2 - Amendment to Informed Consent Only.)
 - ✓ Two copies of the Investigator Brochure.

9.4 Submitting FDA Form 10-9012 *Investigational Drug Information Record* to the IRB Office

The Principal Investigator is responsible for submitting *FDA Form 10-9012 Investigational Drug Information Record* along with the new research application.

1. The form must include the names of all practitioners authorized to prescribe the study drug.
2. When a subject is entered into the study the Principal Investigator is responsible for submitting the 10-9012 along with executed informed consent to the IRB Office for scanning into the medical record.

9.5 Investigational Drug or Device: Humanitarian Use and Emergency Use Emergency Use:

An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval. The first three of the following conditions must be met for this type of emergency use:

1. A human subject is in a life-threatening situation.
2. No standard acceptable treatment is available.
3. There is insufficient time to obtain IRB approval.
4. The emergency use must be reported to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB.
5. Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below (see “Emergency Use of an Investigational Drug without Informed Consent”).

Note: Any subsequent use of the test article at this institution is not permitted without prior IRB and R&D Committee review and approval.

Emergency Use of an Investigational Drug without Informed Consent:

There are two circumstances under which FDA regulations at 21 CFR 50.23 permits the emergency use of a test article without informed consent.

1. When the human subject is confronted by a life-threatening situation necessitating the use of the drug, when a legally effective informed consent cannot be obtained from the subject, when time is not sufficient to obtain consent from the subject's legally-authorized representative, and when there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject (21 CFR. § 50.23(a)).
2. If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject and time is not sufficient to obtain the independent determination required in 21 CFR § 50.23(a) in advance of using the drug (21 CFR § 50.23(b)).

Note: This use without prospective IRB approval is not research, but medical treatment, and cannot be counted as research data.

9.6 Policy

FDA regulations apply to any research that involves a *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56, as well as, where appropriate, 38 CFR 16.

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research conducted under the auspices of MVAHS.

9.7 Definitions

Investigational Drug. According to VHA Handbook 1108.04, an investigational drug is a chemical or biological drug that is used in a clinical investigation. An investigational drug can be:

- (1) A new chemical compound, which has not been released by the FDA for general use;
or
- (2) An approved drug that is being studied for an approved or unapproved use, dose, dosage form, administration schedule, or under an Investigational New Drug (IND) application, in a controlled, randomized, or blinded study (see VHA Handbook 1108.04).

Note: Concurrent medications, comparators, or rescue medications used in the investigational trial that are not the drug(s) being studied are not defined as investigational drugs unless they are not commercially approved or not available through commercial channels. Prescription drugs, over-the-counter drugs, nutritional supplements, herbal preparations, and legend items used for

diagnosis or treatment and meeting the definition of “investigational drug” (see sub pars. 3pp(1) and 3pp(2)) are considered investigational drugs.

Investigational Device. A medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

Emergency Use. Emergency use is defined as the use of an investigational drug or biological product with 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.

Planned Emergency Research. “Planned emergency research” differs from “emergency use” situations because planned emergency use involves IRB approval of a research study before the emergency arises (21 CFR 50.24). Planned emergency research cannot be conducted by the VA.

Significant Risk (SR). Significant risk device means 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; or
- (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; or
- (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.

Non-Significant Risk (NSR). A non-significant risk device is an investigational device other than a significant risk device.

Humanitarian Use Devices (HUD)

As defined in 21 CFR 814.3(n), a HUD is a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4, 000 individuals in the United States per year.” An HUD requires a Humanitarian Device Exemption (HDE), Title 21 CFR 814.3(n), which is an application that is similar to a premarket approval (PMA) application, but exempt from the effectiveness requirements of sections 514 and 515 of the act. FDA approval of the HDE authorizes the marketing of the Humanitarian Use Device (HUD). **NOTE:** If a physician uses a HUD as defined and described in FDA regulations, the physician must follow FDA regulations (VHA Handbook 1200.05).

FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

9.8 Procedures

- a. At initial submission, the PI must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The PI may use the *Human Subjects Research/Exemption Determination Form- FDA* and *Human Subjects Research/Exemption Determination Form- Non-FDA* to assist in making this determination.
- b. During the pre-review process, the IRB Chair or designee will confirm whether FDA regulations are applicable using the *Human Subjects Research/Exemption Determination Form- FDA*. If FDA regulations apply and the research is not exempt, the IRB Administrator will indicate on the agenda that the protocol is an FDA-regulated study.
- c. If required by the **sponsor (see Section 1.5)**, the PI will indicate on the application form that ICH-CGP compliance is required and will affirm compliance. If the study involves investigational drugs and is industry sponsored and the PI does not indicate ICH-GCP compliance, the **IRB Administrator** will confirm with the Office of Sponsored whether ICH-GCP compliance is required and obtain PI affirmation of compliance.

9.9 Investigational Drugs and Devices in Research

IND/IDE Requirements

The PI must indicate on the *Application for New Human Research Study* whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations.

Documentation of the IND/IDE could be a

1. Industry sponsored protocol with IND/IDE.
2. Letter from FDA.
3. Letter from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA (21 CFR 812.2(b)). If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided. If the research involves drugs or devices and there is no IND/IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

1. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
2. If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

IND Exemption

For drugs, an IND is not necessary if the research falls in one of the following categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
 - a. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug

- b. The research is not intended to support a significant change in the advertising for the product;
 - c. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
 - d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]
 - e. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]
 - f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].
2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
 3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:
 - a. It involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
 - b. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
 - c. It is shipped in compliance with 312.160.

Note: The following are also exempt from the IND requirements : (a) a clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND; and (b) a drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

Exempted IDE Investigations

For devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time ;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - 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;

4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

9.10 Responsibilities

PI

1. The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines and MVAHS policies and procedures.
2. The PI must obtain approval from the IRB and R&D Committee before initiating any research activities.
3. The PI proposing the drug/device research will be required to provide a plan – to be evaluated by the IRB and R&D Committee - that includes storage, security, and dispensing of the drug/biologics/device.
 - a. The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.
 - b. The PI will delegate the responsibility for drugs/biologics accountability to the Pharmacy Service and follow pharmacy policies as described in HSPM 119-09-07.
 - c. All devices received for a study must be stored in a locked environment under secure control. Access to the devices shall be limited to personnel designated by the PI. Proper instructions on the use of the device must be provided to the subjects. A device inventory log must be kept on all investigational device studies. The log will include information concerning the equipment that is investigational or shipped specifically for the study. The log will include the following information:
 - i. study name
 - ii. IRB number
 - iii. Sponsor name or funding agency
 - iv. PI name
 - v. Type of device
 - vi. Device model number
 - vii. Device serial number
 - viii. Lot number (if applicable.)
 - ix. Person receiving the device from storage (if applicable)
 - x. Date device was received
 - xi. Date device was implanted or used
 - xii. Patient name
 - xiii. Patient medical record number

- xiv. Date device returned to sponsor or disposition (if product is returned to the sponsor or destroyed, documentation of why, when and person involved).

These records shall be maintained in the project files or in the project's regulatory binder, and for the same period of time as indicated by the sponsor regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

- 4. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 13.5 and 13.6.
- 5. For research involving investigational new drugs:
 - a. The PI is required to inform Pharmacy Service that R&D Committee and IRB have approved the protocol through submission of the R&D Committee and IRB approval letters, the signed *VA Form 10-1223 - Report of Subcommittee on Human Studies*; the signed *VA For 10-9012, Investigational Drug Information Record*, and the approved protocol. MVAHS has relinquished this responsibility to the R&D Committee Coordinator. The R&D Committee Coordinator will forward all of the above named documents to the Pharmacy Service.

- b. The PI must inform the IRB and Pharmacy Service when a study involving investigational drugs has been terminated by the sponsor.

The PI must send a signed copy of *VA Form 10-1086 Informed Consent Form* to the Pharmacy Service to document each subject's consent to participate in the study.

When a research patient is admitted to the hospital, the principal investigator or study coordinator is responsible for providing an in-service to treating providers to include providers, nurses (head nurses, charge nurses, and staff nurses), and clinical pharmacists] informing them on general study-related information. A memorandum with the study name, the in-service presenter, and all attendees at the in-service will be forwarded to the research pharmacist for filing in the study file.

- c. The PI will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.
 - d. The PI will maintain the following:
 - i. Current curriculum vitae (CV).
 - ii. Protocol.
 - iii. Records of receipt and disposition of drugs.
 - iv. List of any co-investigators with their curriculum vitae.

- v. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation.
- vi. Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to Pharmacy Service and the IRB in the manner defined by the protocol.
- vii. IRB and R&D Committee letters of approval.
- viii. Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.

6. For research involving investigational devices:

- a) If a device is considered NSR by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
- b) If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining.
- c) The PI will maintain the following:
 - i. Current curriculum vitae (CV).
 - ii. Protocol of the study.
 - iii. Records of animal study reports.
 - iv. Records of receipt and disposition of devices.
 - v. List of any Co-investigators with their curriculum vitae.
 - vi. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation.
 - vii. Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All adverse device effects are reportable; even if the investigator considers that the event is not related to the device. All unexpected adverse effects shall be reported immediately to the IRB in the manner defined by the protocol.
 - viii. IRB and R&D Committee letters of approval and the EOC Committee approval letter if applicable.
 - ix. Device training.
 - x. Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.
- d) Following completion of the study the termination procedure for investigational drugs must be applied if pharmacy control, or if the devices are kept by the investigator

the log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

e) If, after use, the PI keeps the devices, he/she must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

f) The PI will submit to the sponsor and to the IRB a report of any unanticipated adverse device effect 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.

7. When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Research Application asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the “Guidance Document on Requirements of the Sponsor and the Investigator as a Sponsor” and will comply with the regulatory responsibilities of a sponsor. The Research Service will conduct education programs for investigators holding an IND or IDE on the sponsor regulations and periodically conduct random audits of PIs holding an IND or IDE as per the Research Quality Improvement Program. The RCO also reviews the information with the PI when the PI receives the initial application packet.

IRB

1. The IRB will review the research in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).
2. For research involving investigational devices:
 - a. The IRB will review the control plan and determine whether it is adequate. If the Chair determines that the IRB does not have the necessary expertise to evaluate the plan, outside consultation will be used (e.g., Biomechanical Engineering).
 - b. Unless the FDA has already made a risk determination for the study, the IRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. [21 CFR 812.2(b)]. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If the study that has been submitted as NSR is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.
 - c. The IRB will not review protocols involving significant risk devices under expedited review.
 - d. The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR/SR.

- e. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.

9.11 Emergency Use

Emergency Exemption from Prospective IRB Approval

Emergency Medical Care

Nothing in the HRPP SOP nor the Common Rule are intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable local, state, VA and other Federal requirements (38 CFR 16.116(f)). **Note:** Emergency medical care is not research and does not need to be approved by an IRB.

FDA defines emergency use as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is no sufficient time to obtain IRB approval. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized.

Informed consent must be obtained in accordance with and to the extent required by 21 CFR 50. Informed consent must be documented in writing in accordance with and to the extent required by 21 CFR 50.27.

The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review. This notification must not be construed as an approval for the emergency use by the IRB. The IRB Chair or designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations.

Emergency Waiver of Informed Consent

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- a. The subject is confronted by a life-threatening situation necessitating the use of the test article;
- b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- c. Time is not sufficient to obtain consent from the subject's legally authorized representative;
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5-6 working days. The IRB must be notified within 5 working days when an emergency waiver is used. This notification must not be construed as an approval for

the emergency waiver by the IRB. The IRB Director or designee will review the report to verify that circumstances of the emergency waiver conformed to FDA regulations.

Expanded Access of Investigational Drugs

FDA regulations allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods:

1. **Compassionate Use:** The term “compassionate use” is erroneously used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term “compassionate use” does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.
2. **Group C Treatment Investigational New Drug (IND):** A means for the distribution of investigational drugs, agents, or biologics to oncologists for the treatment of cancer under protocols outside controlled clinical trials. Group C drugs, agents, or biologics usually have shown evidence of relative and reproducible efficacy in a specific tumor type. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, MVAHS IRB requires prospective IRB review and approval.
3. **Open – Label Protocol:** A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.
4. **Parallel Track:** A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that “parallel” the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the Department of Health and Human Services may, on a protocol-by-protocol basis, waive the provisions of 45 CFR Part 46 where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the MVAHS IRB.
5. **Treatment IND or Biologics:** A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Prospective IRB review and approval is required.
 - a. There are four requirements that must be met before a treatment IND can be issued:
 - i. The drug is intended to treat a serious or immediately life-threatening disease;

- ii. There is no satisfactory alternative treatment available;
 - iii. The drug is already under investigation or trials have been completed; and
 - iv. The trial sponsor is actively pursuing marketing approval.
- b. The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:
- i. **Informed Consent.** Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, the IRB should ensure that potential subjects are fully aware of the risks involved in participation.
 - ii. **Charging for Treatment INDs.** The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB Committee should pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB should balance this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.
6. **Single-Patient Use:** The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval is required (See 5 above).
7. **Emergency IND:** The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or biologics.

Emergency Waiver of IND

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in

advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

Expanded Access of Investigational Devices

1. **Compassionate Use (or Single Patient/Small Group Access).** The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group. It must be a serious disease or condition and no alternative treatment available. Prior FDA approval is needed before compassionate use occurs.
2. **Treatment Use.** An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases. The criteria include:
 - a. Life-threatening or serious disease
 - b. No alternative
 - c. Controlled clinical trial
 - d. Sponsor pursuing marketing approval
3. **Continued Access.** FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA. There must be a public health need or preliminary evidence that the device will be effective and there are no significant safety concerns.

Humanitarian Use Devices (HUD) Humanitarian Use Devices (HUD)

As defined in 21 CFR 814.3(n), a HUD is a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.” An HUD requires a Humanitarian Device Exemption (HDE), Title 21 CFR 814.3(n), which is an application that is similar to a premarket approval (PMA) application, but exempt from the effectiveness requirements of sections 514 and 515 of the act. FDA approval of the HDE authorizes the marketing of the Humanitarian Use Device (HUD).

In accordance with 21 CFR 814.124, the IRB is required to perform a full board review for the initial review of a HUD. At the time of review, the IRB will determine if written consent from participants for use of the HUD is necessary. However, neither the act nor the regulations require informed consent for use of a HUD. Because a HDE provides for marketing approval, use of the HUD does not constitute research or an investigation, which would normally require informed consent. Although informed consent is not required, there is nothing in the statute or regulation that preempts a state or institution from requiring prospective informed consent. Most HDE holders, however, develop patient labeling that incorporates information to assist a patient in making an informed decision about the use of the HUD. That is, the patient labeling generally

contains a discussion of the potential risks and benefits of the HUD and any procedures associated with its use. Patient labeling also should state that the device is a humanitarian use device and effectiveness for the labeled indication has not been demonstrated.

Procedures for Submitting a Humanitarian Use Device Exemption:

- ✓ Obtain approval from Chief of Staff
- ✓ Submit to the Research Office five packets of the following:
 1. Project Summary
 2. Summary of Safety and Probable Benefit
 3. FDA HDE application approval letter
 4. Patient Information Booklet
 5. Device Package Insert
 6. Any other pertinent information
 7. CV for clinician requesting approval for use of the device
 8. 10 additional packets of only items a-d

Note: If any of these three situations should arise, please contact the Research IRB Office for guidance on how to proceed. If it is an emergency, please follow the steps outlined above.

These materials will be placed on the next agenda of the Human Studies Subcommittee for full IRB review.

Specific instructions will be given with regards to clinical consent process (either the need for a research-like consent form or approval to use the sponsor provided patient information brochure) and CPRS documentation.

IRB will determine continuing review approval, if applicable.

IRB will evaluate the risks and benefits but is not required to make a Significant/Non-Significant Risk determination.

If approved by the IRB, the Principal Investigator will receive documentation that includes specific information about continuing review requirements, reporting of adverse events that occur at this facility, documenting consent requirements and any other requirements deemed necessary by the IRB.

Reporting (MDRs) and a Summary Update

If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, approval must be obtained from the COS, and the PI is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use.

It is the responsibility of the PI to notify the FDA within five days if the IRB withdraws approval for use of a HUD. The PIs are reminded that HUDs are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application.

Using HUDs in Emergency and Compassionate Use Situations

Off-label use of HUD

In an emergency situation, a HUD may be used off-label (outside of its approved indication for use), but FDA recommends you follow certain patient protection measures before use. Because IRB review and approval is required before a HUD is used within its approved labeling, FDA believes similar procedures should apply if you use a HUD outside of its approved labeling. That is, in an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient; however, in this situation, FDA recommends that the physician and HDE holder follow the same emergency use procedures that govern the use of unapproved devices.

Emergency Use of Unapproved Devices

According to this policy, before the device is used, if possible, the physician should obtain the IRB Chair's concurrence, informed consent from the patient or his/her legal representative, an independent assessment by a uninformed (i.e., not the referring) physician, and institutional clearance. In addition, the physician should obtain authorization from the HDE holder before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder, who would then submit this information as a HDE report to the FDA.

If a HUD is used in an emergency situation, the physician should devise a schedule for monitoring the patient, taking into account the specific needs of the patient and the limited information available about the risks and benefits of the device. See Guidance on IDE Policies and Procedures for further discussion of the post-treatment procedures for emergency use cases, including the submission of a follow-up report to FDA.

Compassionate Use of an HUD

Compassionate use of an HUD is a non-emergency situation, where a physician determines there is no alternative device for the patient's condition. FDA recommends that the physician ensure that patient protection measures discussed above are addressed before the device is used. In addition, the FDA recommends first obtaining FDA approval for compassionate use. FDA believes that a physician who wishes to use a HDE-approved device for compassionate use should provide the HDE holder with:

- a description of the patient's condition and
- the circumstances necessitating use of the device,
- a discussion of why alternative therapies or diagnostics are unsatisfactory
- information to address the patient protection measures.

FDA also recommends the HDE holder submit the above information in a HDE report for FDA approval before the use occurs to help ensure adequate patient protection. FDA will review the information in the most expeditious manner possible and issue a letter to the HDE holder. If the physician undertakes a compassionate use, he or she should devise a schedule for monitoring the patient, taking into consideration the specific needs of the patient and the limited information available regarding the risks¹²⁵ of 176 HRPP-SOP, 11-19-09 and benefits of the device for this unapproved use. See Guidance on IDE Policies and Procedures for further discussion of the post-approval procedures for compassionate use cases, including the submission of a follow-up report to FDA.

Waiver of Informed Consent for Planned Emergency Research

“Planned emergency research” differs from “emergency use” situations because planned emergency use involves IRB approval of a research study before the emergency arises (21 CFR 50.24). Planned emergency research cannot be conducted by the VA.

9.12 Gene Transfer Research

Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by both the FDA and the NIH Office of Biotechnology Activities. FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.

DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).

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

SECTION 10 - BIOLOGICS AND RADIOACTIVE MATERIALS

10.1 Use of Biologics

If biologic materials will be used in the research, the PI is responsible for submitting the following forms along with the new research application:

- ✓ *Biohazard and Chemical Hazard Information Involving Research*
- ✓ *Biological Sample Statement*

10.2 Use of Radioactive Materials

If radioactive materials will be used in the research, the PI is responsible for submitting a completed *Application for the Use of Radioactive Materials* form.

If the protocol does not clearly describe how radioisotopes will be used, the Principal Investigator must provide the information on the *Application for New Human Research Study* form.

SECTION 11 - STUDY PROTOCOL ELEMENTS

11.1 Ensuring Complete Information in Research Protocol

Research protocols must contain specific information to ensure adequate review. Certain elements are required for all protocols (see Section 11.2) and others are study-specific (11.3, 11.4).

11.2 Required Elements

All protocols must contain the elements listed below:

- ✓ Research objectives, specific aims and hypotheses.
- ✓ Background and significance section state the problem to be investigated, the rationale for the proposed research, current state of knowledge relevant to the proposal and potential contribution of this research to the problem(s) addressed.
- ✓ Literature references.
- ✓ Research methods.
- ✓ Projected start and completion times.
- ✓ Target population(s).
- ✓ Inclusion and exclusion criteria listed.
- ✓ If appropriate, is the sample size justified to show that the proposed number of subjects is at least the minimum needed to achieve the research objectives.
- ✓ Data analysis plan is consistent with the study objectives.
- ✓ Provisions to maintain human subject privacy and the confidentiality of data.
- ✓ List of all facilities and study locations provided.
- ✓ Section to differentiate research intervention from usual care, if applicable.

11.3 Study Specific Elements

If the protocol contains any of the optional study elements listed below, a clear explanation must be provided in the protocol or on the *Application for New Human Research Study* form:

- Use of deception or incomplete disclosure.
If yes, are briefing procedures described in the new research application?
- Subjects' behavior will be recorded unknowingly.
- Double-blinding.
If yes, is there a provision for (1) trending and (2) for unlocking the code?
Note: To unlock the code for a blind study, the IRB or the PI have the ability to un-blind a study patient if the need arises. The IRB or PI must contact the sponsor to do so. The PI must inform the IRB of this situation.
- Randomization.
- Washout period.
- Radiation exposure.
- Deviation from standard care.
- Whether the submission is a challenge study.

11.4 Surveys/Questionnaires

If the study includes the use of any surveys/questionnaires they must be included along with the *Application for New Human Research Study* form.

SECTION 12 - SUBJECT PRIVACY AND CONFIDENTIALITY OF DATA

12.1 Privacy and Confidentiality

VA personnel upon receiving approval from the IRB may obtain and use medical, technical, and administrative records from this or other VA facilities for research purposes. Principal Investigators must follow VA policy to gain access to national databases.

General Considerations for Protecting Patient Privacy

In developing strategies for the protection of subjects' privacy, consideration is given to:

1. Methods used to identify and contact potential participants.
2. Settings in which an individual will be interacting with an investigator.
3. Appropriateness of all personnel present for research activities.
2. Methods used to obtain information about participants and the nature of the requested information.
3. Information that is obtained about individuals other than the "target participants," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey).
4. How to access the minimum amount of information necessary to complete the study.

The PI will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA forms, research protocol, and/or other submitted, applicable materials.

Investigators can obtain and use real Social Security numbers only when real Social Security numbers are required to meet the specific aims of the research protocol or to enter information into the subjects' health records.

The collection and use of real Social Security numbers must be approved by the IRB, and the investigators must follow all applicable VA and other Federal requirements for obtaining and using real Social Security numbers.

- The policies and procedures regarding privacy/confidentiality apply to all methods of data collection - review of medical records, interviews, questionnaires, and mailed surveys. The method of data collection may not be altered during a study unless the IRB has approved changes to the protocol.
- Collecting additional data not expressly described in the IRB approved protocol is prohibited. In addition, contact with Veterans is limited to those clinically essential or as outlined in IRB approved protocols. Contacts do not solicit sensitive information (e.g., SSNs).
- VHA investigators use the requested data only in a manner consistent with the approved research protocol for which the information was requested.
- Data collection instruments such as questionnaires must not be constructed in such a way that the identity of the respondent can be easily determined. Removing or coding names,

particularly for small data sets, may not be sufficient when other identifiable information is collected such as age, gender, job title, etc.

- The IRB expedited review process is not used when identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability; or be damaging to the subject's financial standing, employability, or insurability.
- Principal Investigators must arrange for sponsors and other authorized personnel from regulatory agencies to access electronic medical records by contacting the MVAHS IDM Service. In order to protect patient privacy, Principal Investigators are responsible for limiting sponsors' access to data collected during the time the patient participated in the study by either (1) provide sponsors the requested information or (2) sitting with them at a computer terminal while the sponsor views the data. Unauthorized use, loss, disclosure, of individually-identifiable patient information are reported to the MVAHS Privacy Officer. Violations of VA security are reported to the MVAHS Information Security Officer.
- Providing for Reuse of Data -- The investigator, if the data may be reused in other studies, describes the research data repository in which the data is to be stored. There must be a research informed consent and a HIPAA authorization associated with the protocol unless these requirements are waived by the IRB. If the IRB does not waive the requirements then the informed consent and HIPAA authorization content must include language on the uses and disclosures of the data as defined in the protocol as well as information on how privacy and confidentiality will be maintained and how the data will be secured. If the creation and operation of the data repository is not included in the data collection protocol, there must be a separate IRB-approved protocol for the creation and operation of the data repository. Contact the IRB Office for more information.

12.2 Definitions

Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the subjects from the data, then the research is not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

Identifiable information – information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Privacy. As part of the review process the IRB also considers how patient privacy will be protected.

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are getting access to subjects or subjects' private, identifiable information and the subjects' expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

Private Information - 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).

12.3 How to Submit a Patient Privacy and Data Security Plan

As part of the review process the IRB also considers how patient privacy and confidentiality of data will be protected. On the *Checklist for Reviewing Privacy Confidentiality and Information Security in Research* form, the Principal Investigator must indicate the methods that will be used to protect patient privacy and ensure data security. If any of the elements are missing from the protocol, they should be included in the space provided in *the Privacy and Confidentiality and Information Security Checklist*.

12.4 HIPAA

Ensuring HIPAA Authorization is Obtained

No human being is involved as a subject in research unless the investigator or a designee has obtained legally effective HIPAA authorization for the use and disclosure of the subject's PHI, or has obtained Privacy Board or IRB-approved waiver of HIPAA authorization. The necessity to obtain subjects' PHI must be formally and prospectively designated in writing in the protocol.

Unless an exception has been approved by the IRB individuals must authorize the use and disclosure of their Personal Health Information (PHI) for research purposes.

The authorization elements - outlined in the *Investigator Checklist for Preparation of the Informed Consent Document* - must be contained in consent forms submitted along with any new research applications.

Key concepts of HIPPA Privacy Rule (45 CFR 164.508) include the following:

- Covered Entity: The VHA is a single covered entity for the purpose of complying with the Privacy Rule. This covered entity includes all VHA hospitals and healthcare systems.
- Use and Disclosure of Information: According to the definitions in the Privacy Rule, information is "used" when it remains within the entity holding the information and is "disclosed" when it is released outside the entity that holds this information.
- "Protected Health Information" (PHI): is individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded in the Privacy Rule.
- Minimum Necessary: The Privacy Rule restricts use and disclosure of PHI. However, it does contain exceptions granting access in certain circumstances. Underlying all the exceptions, however, is the principle that any access should be limited to the minimum amount of information necessary to accomplish the intended purpose of the use or disclosure. For VHA research purposes, this standard requires a VHA researcher to evaluate the needs of his or her study and to request access only to those pieces of information that are necessary for the complete and accurate development of the research. This is advisable even if a research subject permits more information to be used or disclosed.

12.5 HIPAA Authorization

When completing the *HIPAA Authorization Form*, the PI must ensure that the document contains the following elements:

Consistency: The HIPAA authorization contains similar language as the application, protocol and informed consent with regard to the protected health information to be used or disclosed, entities to whom information will be disclosed, expiration of authorization, and purpose.

Subject Identity: The HIPAA authorization has a place for the subject's identity, i.e. name.

Description of Information: The protected health information to be used or disclosed is specifically listed on the HIPAA authorization. **Note:** If HIV, sickle cell anemia, drug and/or alcohol abuse treatment information will be disclosed, it must be specifically stated in the HIPAA Authorization.

Authorization to Use or Disclose: The HIPAA authorization identifies the people and organizations authorized to make the requested use or disclosure.

Recipient Identification: The HIPAA authorization identifies to whom the information will be disclosed or released for use.

Description of Purpose: The HIPAA authorization includes a description of each purpose for which the information will be used or disclosed. A statement such as "for research purposes" is sufficient, though a more thorough description is preferred. If the study will eventually close, but the data will remain in a repository, the authorization should cover both events.

Expiration: The HIPAA authorization includes a date or event that explains when the authorization expires.

Signature and Date: The HIPAA authorization contains the signature line of the subject as well as the date signed. If subjects who are incompetent or lack decision making capacity will be included, a signature line for the person legally authorized in writing by the individual (or the individual's legal guardian) to act on behalf of the individual, (i.e. power of attorney) is listed.

Right to Revoke: The HIPAA authorization includes a statement that the subject has the right to revoke the authorization in writing, except to the extent that the entity has acted in reliance on it.

How to Revoke: The HIPAA revocation statement includes a description of how the subject may revoke the authorization, i.e. to whom it should be submitted.

A research subject has the right to revoke, in writing, his or her authorization at any time by completing a *Miami VA Healthcare System Revocation of Authorization* form. The individual's revocation is effective, except to the extent that the researcher has taken action in reliance upon the authorization prior to the revocation. The reliance exception permits the continued use and disclosure of PHI already obtained with an authorization to the extent necessary to protect the integrity of the research (e.g., to account for a subject's withdrawal from a study, to conduct investigations of scientific misconduct or to report adverse events).

Conditioning: The HIPAA authorization includes a statement that treatment, payment, enrollment, or eligibility for benefits cannot be conditioned on the subject completing the authorization, but participation in the study may be conditioned on the subject signing the authorization.

Data Protection and Re-disclosure: The HIPAA authorization includes a statement that individually identifiable health information disclosed pursuant to the authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

12.6 Waiver of HIPAA Authorization

If the investigator requires a waiver or alteration of the HIPAA authorization, the investigator must provide the Privacy Board or IRB with information sufficient for the Privacy Board or IRB to find that such waiver or alteration is necessary.

To request a waiver the PI must submit a *Request for Waiver of IC/HIPAA Authorization*. The form must contain all of the elements listed below as applicable.

Minimal Risk Justification: The waiver of HIPAA authorization is justified because the use of information includes no more than minimal risk to the privacy of the subjects.

Written Assurance of Protection: The request for waiver of HIPAA authorization provides adequate written assurance that the requested information will be protected from improper use and disclosure and will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule.

Protection of Identifiers: The request for waiver of HIPAA authorization provides an adequate plan to protect the identifiers from improper use and disclosure.

1. Limiting access to data – only authorized personnel may access data. Only VA personnel access VA-owned equipment used to process VA information or access VA processing services.
2. Removal of identifying information.
3. Coding identifiable information.
4. Employees follow VA procedures when handling viral or malicious code infection: Employees must immediately stop using any computer or software suspected of malicious infection or malfunction. In all such cases, the machine must be immediately isolated from any VA network connections. Do not reboot (turn off/on) the system, as many viruses are triggered to propagate upon system reboot, which can cause further damage. If it appears that a negative activity is occurring (such as the deletion of files) then the system must be shut off and left off until a clean Antivirus boot media is used to clean the system. Employees not authorized to attempt recovery and restoration must not remove the suspected software themselves, but must contact a qualified IT Specialist via their respective help desks to attempt recovery. Recovery must be attempted only by an authorized IT Specialist. If a non-VA technician is called to service non-VA OE, the employee must exercise caution to protect VA data, including information that facilitates access to VA private networks. An employee must never surrender or swap hard drives or other storage to an outside party if he or she was storing VAPI at the time of the system problem. Only VA-approved software and tools may be used to attempt recovery from virus or other malicious code infection.

5. Employees do not simultaneously connect to VA and one or more non-VA networks while using VAGFE.
6. Passwords or other authentication information are not stored on remote systems unless encrypted.
7. Employees do not simultaneously connect to VA and one or more non-VA networks while using VAGFE.
8. For all VAGFE and non-VA OE used to transmit, transport, access, process or store VA data, employees do not take equipment, information, or software off-site without authorization by supervisor.
9. Portable computers that have VAPI on their storage device(s) or have software that provides access to VA private networks are secured under lock and key when not in the immediate vicinity of the responsible employee.
10. Employees use physical locks to secure portable computers to immovable objects when the computers must be left in a meeting room, or other semi-public area to which individuals other than the authorized employee have access.
11. When traveling, employees keep portable computers or storage devices in their possession, not in check-in baggage.
12. Obtaining a Certificate of Confidentiality. Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. The CoC was developed to protect against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. Regardless of funding source, CoC's can be obtained from NIH. See <http://grants.nih.gov/grants/policy/coc/index.htm>
13. All removable media must have appropriate encryption software, be password protected, and ensure sensitive data removed or secured.
14. Only VA-owned Government Furnished Equipment (VAGFE), including laptops and handheld computers, are used when accessing the VA intranet remotely, and all required security software is installed and updated to connect to the VA Virtual Private Network; access to the VA Intranet using non-VA owned Other Equipment (OE) is provided via approved VA VPN access protocols, which offer access to a limited set of VA applications and services; employees are required to use only computers and electronic storage media configured to conform to all VA security and configuration policies to store, transport, transmit, use and access VA Protected Information and use of VAGFE and OE meets all requirements listed in VA Directive 6504 §2e.
15. VAGFE and OE that contain VAPI are equipped with, and use, a VA-approved antivirus (AV) software and a personal ("host-based") firewall that is configured with a VA-approved configuration; in the event that the computer/device connecting remotely is simultaneously attached to a second network (such as an in-home LAN), the secondary network computers/devices are provided with similar AV and host-based/personal firewall protection; all VAGFE devices attempting to access the VA intranet remotely via the One-VA VPN client have the AV and Host-based Intrusion Prevention System (HIPS) software installed and current, including all critical updates and patches, in order to be granted access; employees using non-VA OE devices to access the VA intranet remotely comply with the policy set forth in "Anti-Virus/Firewall accepted for use on non-government owned equipment attached to the One-VA VPN" (May 5, 2005).

16. Employees using VAGFE and OE ensure equipment is connected to a firewall and they understand they must comply with VA policy pertaining to firewalls.
17. Sensitive data is not transmitted by remote access unless VA-approved protection mechanisms are used (e.g. encryption).
18. Wireless routers and access points, even if not used at the enclave perimeter, are configured in accordance with the “VA Wireless and Handheld Device Security Guideline”.
19. Passwords or other authentication information are not stored on remote systems unless encrypted.
20. Supervisors must confirm and notify the ISO that employees have returned all VAGFE related to remote access when their access has terminated.

Note: Investigators are encouraged to contact the MVAHS IRM service or the facility ISO to verify whether the methods they use to protect patient privacy and ensure data security meet VA requirements.

Destruction of Identifiers: The request for waiver of HIPAA authorization provides an adequate written plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

For further information contact the IRB Office and the Information Security Officer.

Need for Information: The request for waiver of HIPAA authorization explains why the research could not practicably be conducted without access to and use of the requested information.

Need for Waiver: The request for waiver of HIPAA authorization explains why the research could not practicably be conducted without the waiver.

Description of PHI: The request for waiver of HIPAA authorization includes a brief description of the protected health information. Protected Health Information is individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded in the Privacy Rule. Below is the list of identifiers:

1. Name
2. All geographic subdivisions smaller than a state, including street address, city, county and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people and (2) the initial three digits of a zip code for all such geographic units containing 20,000 is changes to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages older than 89 and all elements of date (including year) indicative of such age, except such ages and elements may be aggregated into a single category of age 90 or older.
4. Telephone numbers
5. Fax numbers

6. Electronic mail addresses
7. Social Security Number
8. Medical record number
9. Health plan beneficiary number
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plates
13. Device identifiers and serial numbers
14. Web Universal Research Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints.
17. Full-face photographic images and any comparable images.
18. Any other unique identifiers.

USC 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), there is assurance in writing that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner.

Specimens: The study states whether specimens will be labeled with identifiable or de-identified information.

De-Identification of Data: The research protocol indicates that data will be de-identified and the method described truly de-identifies the data according to VHA Handbook 1605.1, Appendix B, Paragraph 2a (document statistical determination) or Paragraph 2b (removal of all 18 individually-identifiable information). (Ref: VHA Handbook 1200.05, ¶37b) *Request for Access to Health Information to Research*).

1. De-identified information is provided to PI by the research team who has access to IIIHI per a HIPAA authorization or waiver of authorization.
2. De-identified information is provided by PI who has access to IIIHI to his/her research team.
3. De-identified information is to be sent to non-VA research team member (i.e. statistician).
4. De-identified information will be disclosed to a non-VA party.

Data is considered to be “de-identified” when the following identifiers are removed:

1. Name
2. All geographic subdivisions smaller than a state, including street address, city, county and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people and (2) the initial three digits of a zip code for all such geographic units containing 20,000 is changes to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages older

than 89 and all elements of date (including year) indicative of such age, except such ages and elements may be aggregated into a single category of age 90 or older.

4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security Number
8. Medical record number
9. Health plan beneficiary number
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plates
13. Device identifiers and serial numbers
14. Web Universal Research Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints.
17. Full-face photographic images and any comparable images.
18. Any other unique identifiers.

12.7 Other Exceptions to the Requirement of Authorization Preparatory to Research

PIs may access PHI in order to prepare a protocol without an individual's authorization, a waiver of authorization or a data use agreement. The PI must submit to the Privacy Officer, in writing, certification that:

- a. The use or disclosure is requested solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research;
- b. The PHI will not be removed from the MVAHS in the course of the review; and
- c. The PHI for which use or access is requested is necessary for the research.
- d. Appropriate IRB and R&D Committee documents must be provided before data can be released.

Note: The contacting of potential research subjects or conducting pilot studies are not activities Preparatory to Research.

Note: When authorization to access PHI under the Preparatory to Research option has been granted, the Principal Investigator is responsible for:

1. *Writing a progress note in all medical charts reviewed for the study that includes:* (a) purpose/reason for accessing record; (b) date(s) record was accessed; (c) name of person who accessed record and contact information; (d) description of data recorded; (e); and
2. *Maintaining an accurate log of each record reviewed for that research protocol.* The log must include the complete name and social security number of each subject.

Research on Protected Health Information of Decedents

The protections of the Common Rule apply only to living human beings; by contrast, the Privacy Rule also protects the identifiable health information of deceased persons ("decedents"). The Privacy Rule contains an exception to the authorization requirement for research that involves the protected health information of decedents. A covered entity may use or disclose decedents' protected health information for research if the entity obtains representations from the researcher that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about

whom information is being sought. Researchers should submit the applicable IRB form for IRB approval when they intend to conduct research involving decedents' protected health information.

Note: When authorization to access PHI under the Decedent Research option has been granted, the Principal Investigator is responsible for:

- (1) Writing a progress note in all medical charts reviewed for the study that includes: (a) purpose/reason for accessing record; (b) date(s) record was accessed; (c) name of person who accessed record and contact information; (d) description of data recorded; (e); and
- (2) Maintaining an accurate log of each record reviewed for that research protocol. The log must include the complete name and social security number of each subject.

Limited Data Sets with a Data Use Agreement

A PI may use and/or disclose PHI included in a limited data set, pursuant to a data use agreement.

- a. A limited data set excludes all direct identifiers listed in section 8.6 under description of PHI of this policy, with the exception of city, state and Zip Code, all elements of dates and other numbers, characteristics, or codes not listed as direct identifiers.
- b. The use of a limited data set requires a data use agreement. This document is intended to provide assurance of the limited use or disclosure of the information in the limited data set. The data use agreement must contain the following:
 - i. Permitted uses and disclosures of the limited data set by the recipient, consistent with the purpose for which it was used or disclosed.
 - ii. Identification of who is permitted to use or receive the limited data set.
 - iii. Stipulations that the recipient will:
 - Not use or disclose the information other than permitted by the agreement or otherwise required by law;
 - Use appropriate safeguards to prevent the use or disclosure of the information, except as provided for in the agreement, and require the recipient to report to the covered entity any uses or disclosures in violation of the agreement of which the recipient becomes aware;
 - Hold any agent of the recipient to the standards, restrictions and conditions stated in the data use agreement with respect to the information; and
 - Not identify the information or contact the individuals.
- c. The PI completes and submits the form *Investigator Representation for Research on Limited Data Sets of Protected Health Information* and a copy of an executed data use agreement to the ISO IRB for review. The ISO will review the request and the data use agreement and determine whether the criteria set forth in subparagraph section 16.10 (a) and (b) are met.

- d. VHA Data Use Forms are available on VHA Forms Intranet at <http://vawww.va.gov/vaforms/> (Department of Veterans Affairs Form 10-0403, Responsible Requestor and Project Information Sheet; VA Form 10-0403a, Data Use Agreement; VA Form 10-0403b, Data Access List).

12.8 Additional Requirements for Protecting Patient Privacy and Confidentiality of Data

The following requirements can be found on the *Checklist for Reviewing Privacy Confidentiality and Information Security in Research*:

Software: The study identifies specially obtained software that will be used, the source of the software, whether a license will be required, who will fund the license as well as any data that will be stored in temporary files on the computer's hard drive.

Web Applications: The study identifies any web application, as well as its security features, that will be used for such purposes as recruiting subjects, completing questionnaires or processing data.

Data Flow: The study includes a description of the data collection, data flow and/or data management process that will be used during the course of the study.

Data Security Plan: Study describes how electronic data as well as paper records will be secured. See Protection of Identifiers for examples.

Data on a Hard Drive: The study identifies whether VA research data will be stored on the hard drive of a PC. If so, it is considered VA best practice to encrypt the PC.

Contact IRMS for additional information.

Mobile Devices: The study states that all mobile devices will be encrypted and that the encryption is FIPS 140-2 validated. **Note:** All mobile/portable devices and media and any information transmitted to and from a wireless device must be protected with VA approved encryption technology that is FIPS 140-2 validated.

Contact IRMS for additional information.

Storage Location: The study identifies precisely where data and specimens will be stored, i.e. physical site, network location/server name (e.g. vhaacbarsch), type of mobile storage device, building and room, etc.

Removal of VA Sensitive Information from the VA Protected Environment: The study states whether or not research data is intended to be removed from the VA protected environment.

Protection of Media Stored at Alternate Site: If the study team plans to store VA sensitive information outside the VA protected environment, the study indicates by what method it will be protected.

Data Transmission: The study states how sensitive electronic information will be securely transmitted. **Note:** VA sensitive data or information may only be transmitted using VA-approved solutions such as FIPS 140-2 validated encryption.

Data Backup: The study indicates that mobile storage devices do not contain the only copy of research information. Original electronic VA research data stored on a mobile device or outside the VA protected environment will be backed up regularly and stored securely within VA's protected environment.

Employees should make redundant copies ("backups") of essential business data and software on remote or mobile computers at regular intervals, and store multiple sets of backup data in protected locations other than the location of the device containing the data.

Shipping Data: Study indicates whether sensitive research data that must be sent via common carrier will be encrypted with FIPS 140-2 validated encryption if it is electronic and will be sent via delivery service with a chain of custody.

Contact the ISO for further information.

Data Return: The study includes a statement regarding what VA information will be returned to the VA, how the information will be returned to the VA, or plans for its destruction. **Note:** VA research data and information must be retained in accordance with the applicable VA Records Control Schedule (RCS), which is a set of rules established by the Federal government that states when Federal agencies are allowed to dispose of records. Prior to destruction of research records, the PI should contact the Records Management Officer for current policy.

Data Destruction: The study includes a description of the methods that will be used to destroy data at the end of its life cycle. **Note:** If the protocol states information will not be returned to the VA, the protocol must state how and when the information will be destroyed.

Maintaining and Destroying Sensitive Data. When no longer needed, VA sensitive information maintained electronically is destroyed by a method rendering it unreadable, undecipherable, and irretrievable as prescribed in the most current version of "Fixed Media Sanitization"- (Office of Cyber Security VA Memo, April 20, 2004).

Investigators are advised to contact the MVAHS IRM service and ISO for additional information about destroying sensitive data.

Record Retention. The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). (VHA Handbook 1200.05)

Termination of Data Access: The study states that removal of access to research study data will be accomplished for study personnel when they are no longer part of the research team.

The PI must ensure that access previously granted has been revoked in a memo to the IRB.

Incident Reporting: In accordance with VA policy, procedures are in place for reporting incidents, i.e. theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls.

Release of PHI

- Requests to access data by persons not employed by VA must be submitted to the CRADO in VA Central Office at least 60 days before access is desired. Requests for information filed pursuant to the Freedom of Information Act (FOIA) ordinarily requires a response within 10 working days. VA guidelines and policy must be followed when making such requests to allow for a timely reply.

This does not apply to those individuals having access for the purpose of monitoring the research. Obtaining and using the records must be in compliance with all VA regulation and with the Standards for Privacy of Individually-Identifiable Health Information (45 CFR Parts 160 and 164).

- Information from Research Subjects who are not VHA Employees
 - a. VHA may disclose the individually-identifiable health information of research subjects who are not VHA employees to non-VHA Investigators for research purposes provided there is a prior written authorization. A prior written authorization may be incorporated into an Informed Authorization Notice or an Informed Consent Document.
 - b. If there is not prior written authorization, VHA may disclose individually-identifiable health information, excluding 38 U.S.C. 7332-protected information to Federal investigators (e.g. Department of Defense) if the Undersecretary for Health (or designee) has approved the research, and an IRB or Privacy Board has waived the authorization requirement in accordance with 45 CFR 164.512 (i) prior to the request of PHI.
 - c. If there is no prior written authorization, VHA may disclose:
 1. Individually-identifiable health information, excluding 38 USC §7332-protected information and names and addresses of the individual subjects, to non-Federal investigators if there is VHA approval both by the Under Secretary for Health or designee; and IRB or Privacy Board waiver of authorization.
 2. Individually-identifiable health information, including names and addresses of the individual subjects, but excluding 38 USC §7332-protected information of the individual subjects, to non-Federal investigators if the non-federal investigators provide the name and addresses of the individual subjects; there is VHA approval by both the Undersecretary for Health (designee); and there an IRB or Privacy Board waiver of authorization.
- Information from Research Subjects in their Capacity as VHA Employees
 - a. VHA may disclose the individually-identifiable information of research subjects in their capacity as VHA employees, excluding health information, to non-VHA Investigators for research purposes without written authorization, and only in accordance with the Privacy Act and applicable VA privacy policy.
 - b. VHA employee health information is to be disclosed using the same privacy processes as veteran health information. (*VHA Handbook 1605.1 Privacy and Release of Information*)

13(a) (2) contains information about the information that can be disclosed about VA employees participating as research subjects).

SECTION 13 - CONFLICT OF INTEREST

13.1 Conflict of Interest

As one method of preventing, monitoring, managing, and resolving conflicts of interest (COI), MVAHS requires full disclosure of conflicts of interest by investigators.

13.2 Definitions

Conflict of Interest. A COI occurs when any financial arrangement, situation, or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. It includes any situation in which financial or personal obligations may compromise, or present the appearance of compromising, an individual's or group's professional judgment in conducting or reporting research.

Dually-Appointed Personnel (DAP). A DAP is an individual holding both a MVAHS and an academic affiliate position.

Financial Interest Related to the Research. Financial interest related to the research means financial interest in the sponsor, product or service being tested.

1. Any financial arrangement whereby compensation to the investigator could influence, or be influenced by, the outcome of the study.
2. Salary and other payments for services (e.g., consulting fees, honoraria, etc.).
3. Payments of other sorts from the sponsor of the research (e.g., a grant to fund other ongoing or additional research, compensation in the form of equipment, retainer for on-going consultation, etc.).
4. Equity interests (e.g., stocks, stock options, or other ownership interests).
5. Proprietary interests or intellectual property rights (e.g., patents, trademarks, copyrights, licensing agreements, royalties, etc.).
6. Non-cash items such as travel expenses or business gifts.
7. Ownership interest (equity or stock options) related to the research of any amount when the value of the interest would be affected by the outcome of the research.
8. Compensation related to the research of any amount when the values of the interest would be affected by the outcome of the research.

Significant Financial Interest. Significant Financial Interest includes:

- Ownership interest, stock options, or other financial interest related to the research unless it meets four tests:
 - Less than \$10,000 when aggregated for the immediate family.
 - Publicly traded on a stock exchange.
 - Value will not be affected by the outcome of the research.
 - Less than 5% interest in any one single entity.
- Compensation related to the research unless it meets two tests:
 - Less than \$10,000 in the past year when aggregated for the immediate family.

- Amount will not be affected by the outcome of the research.
- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement.
- Board or executive relationship related to the research, regardless of compensation.

Non-Financial Conflict of Interest. Non-financial conflict of interest situations include but are not limited to:

- ✓ Serving dual roles, such as healthcare provider and investigator.
- ✓ Publication.
- ✓ Promotion or tenure.
- ✓ Membership in oversight committees such as the R&D Committee and IRB.
- ✓ Position of authority.
- ✓ Position that includes responsibilities for the review and approval of research projects or contracts other than his/her own that may potentially affect the design of, decisions made, and/or action taken surrounding a specific study.
- ✓ Personal/relational (e.g. spouse works for sponsor).

Investigator. Investigator is the PI and any other person who is responsible for the design, conduct, or reporting of research.

Compensation. Compensation resulting from a favorable outcome of clinical studies in the form of equity interest in the sponsor of a covered study or in the form of compensation tied to sales of a product, such as royalty interest.

Proprietary interest. Proprietary interest in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright, or licensing agreement.

Covered clinical study. Covered clinical study is any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include Phase I tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute “covered clinical studies” for purposes of complying with financial disclosure requirements.

Significant payments. Significant payments of other sorts means payments, that have a monetary value of more than \$25,000, exclusive of the costs of conducting the clinical study or other clinical studies, made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the investigator is carrying out the study and for one year following the completion of the study.

Applicant. Applicant means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

Sponsor. Sponsor of the covered clinical study means the party supporting a particular study at the time it was carried out.

Immediate Family Member(s). Immediate family member(s): having a relationship to a person (whether by blood, law, or marriage) as a spouse, parent, child, grandparent, grandchild, stepchild, or sibling.

Disclosure. Disclosure is the formal written process of documenting all aspects relating to the development of potential intellectual property for the purpose of determining and assigning ownership.

Equity. The money value of a property or of an interest in a property in excess of claims or liens against it.

Institutional conflict of interest. An institutional conflict of interest may occur when the institution, or any of its senior management, or an affiliate foundation or organization has an external relationship or financial interest in a company or organization that itself has a financial interest in a VA investigator's research project.

Institutional officials. These are individuals in a position to make decisions with institution-wide implications. These include the medical center Director/Institutional Official (IO), COS, ACOS/R, and other senior officers and management officials.

Intellectual Property (Invention). Intellectual property is any art, machine, manufacture, design, or composition of matter, or any variety of plant, which is or may be patentable under the patent laws of the United States.

Inventor. The inventor is the individual responsible for the conception or reduction to practice of a device or process.

Patent. A patent is an official written document securing to an inventor for a term of years the exclusive right to make, use, or sell an invention.

Re-disclosure. Re-disclosure is the formal written process of documenting all aspects relating to any improvement of a previously disclosed invention for the purpose of issuing a new determination on the improved invention.

Royalty. A royalty is compensation for an invention.

13.3 Reporting Financial and Non-Financial Conflict of Interest

The Principal Investigator is responsible for reporting financial and non-financial interests for themselves and any research staff members on the *Application for New Human Research Study* form. When a potential conflict of interest situation is identified, the individual for whom the

conflict has been identified must fill out the *Disclosure of Available Funds and Financial Interest* form.

13.3.1 Investigator/Staff Disclosure of COI

Investigators and study staff are required to disclose potential COIs (financial and non-financial) that may appear to bias any research under their influence through the following procedures:

- At the time of initial review of a protocol, disclosures are made by completing the “Conflict of Interest” section of the application form.
- If a conflict of interest is identified, the PI and must submit a *Disclosure of Financial Interest form*. If the PI reports a potential COI for a staff member, the staff member will be required to fill out the *Disclosure of Financial Interest form*.

This applies to all proposals submitted to MVAHS for local review, and to proposals submitted to VACO and other agencies for funding consideration.

Disclosures are also completed at the time of initial review. On continuing review investigators are asked to report any changes in financial status.

The IRB Administrative staff review the COI disclosures submitted at initial and continuing review or if a there is a change in COI disclosure. If an investigator or study staff responds affirmatively to the existence of a potential conflict, the IRB Administrative staff notifies the COI Administrator.

13.4 Conflict of Interest Administrator and Committee

The *Disclosure of Available Funds and Financial Interest* form and any other applicable materials will be forwarded the Conflict of Interest Administrator. If the COI Administrator determines a potential conflict of interest exists, the packet will be forwarded to the COI Committee. The IRB and R&D Committee will be notified of the Committee’s determination and recommendations. The IRB and R&D Committee may make additional recommendations to reduce or eliminate the COI.

COI Administrator Evaluation of COI for PIs and Study Staff

1. If the PI or any study staff responds affirmatively to the existence of a potential conflict, the COI Administrator will request additional information from the PI or study staff, as necessary. He/she will review the materials and determine whether the proposed project could reasonably appear to be directly and significantly affected by the related COI of the PI or study staff. Although not exhaustive of all COI situations, a direct impact could occur when:
 - a. The project results would be directly relevant to the development, manufacture or improvement of the products or services of an organization in which the PI or study staff has a financial COI.
 - b. The organization in which the PI or study staff has a financial COI is a proposed subcontractor in the project.
 - c. There is a relationship between the project sponsor and the PI or study staff outside the project that has the potential to affect performance in the project.

- d. Any member of the research team serves on an oversight committee (e.g. IRB, R&D Committee).
 - e. Any member of the research team has a close family member that works for the sponsor.
2. If the COI Administrator determines there is no reasonable basis to conclude that the design, conduct or reporting of the project could be directly and significantly affected by the potential COI, he/she will inform the PI (and members of the study staff, when applicable), the R&D Chair, and IRB Chair in writing that the project has been cleared of any COI. A copy of the notification will be reviewed by the IRB and placed in the study file.
 3. If the COIA determines that the design, conduct or reporting of the project could be directly and significantly affected by the potential COI reported by the PI or study staff, then he/she will call a meeting of the COI Committee.
 4. The COI Committee will make a recommendation as to whether the project should proceed and under what conditions or restrictions that might occur. These recommendations will be made in writing to the PI (and member of the study staff, when applicable), R&D Chair, and IRB Chair. The COI Administrator will record the minutes from the meeting and maintain the documentation used in deliberations. This information will be strictly confidential and will be kept in a secure file maintained by the COI Administrator.
 5. If during the conduct of a project any new or related potential COI described above should arise, the PI must disclose this to the R&D and IRB through the Research IRB Office. A review will be conducted as with the original disclosure.
 6. Disclosure must be made at least annually. For human subject research this will be done in conjunction with the application for continuing review.
 7. Determinations made by the COI administrators and COI Committee are recorded on the *Conflict of Interest Reviewer Form*.

13.5 Management of COI

The IRB will determine if the rights and welfare of human research participants will be better protected by any or a combination of the following:

1. The PI or the study staff will divest significant financial interests.
2. The PI will disclose the relationship with the sponsor on all publications, in the consent form provided to human subjects, and in other appropriate public forum (including manuscripts, abstracts and lectures).
3. The PI will separate the research from consulting, providing an acceptable detailed written plan for achieving this.
4. The PI will substitute someone else to serve as project PI and is appropriately distanced from the conduct of the research.
5. The PI will secure an independent reviewer for monitoring of the research and analysis of the data.
6. The PI will modify the protocol or safety monitoring plan.
7. The PI will be disqualified from participating in all or a portion of the research.
8. The PI or the study staff will sever relationships creating the conflict.
9. See Section 14.3.4 for managing IRB member conflict of interest disclosed at a convened IRB meeting.

13.6 R&D Committee Evaluation of COI

The R&D Committee will review the actions taken by the IRB. The Committee will determine what actions, in addition to those required by the IRB, should be taken by the institution or the investigator to manage, reduce or eliminate the COI. The IRB must review any changes made by the R&D Committee prior to final approval of the study. Points to consider are:

- How is the research supported or financed?
- Who designed the study?
- Will the institution receive any compensation?
- Is the institution an appropriate site for the research?

13.7 Appeals

The PI or the study staff may appeal the COI Committee's decisions through the COS, who will determine whether the matter should go back to the COI Committee or be referred to VA general counsel for further consideration. This appeal may be made within 15 working days of the date of the COI Committee's correspondence.

13.8 Changes in Disclosure Information after the Study Begins

If the PI believes a potential COI situation develops after the study begins for any member of the research team, he/she must inform the IRB.

13.9 Failure to Comply with the COI Policy

Failure to comply with conflict of interest policies and procedures and/or committee determinations constitutes research non-compliance and will be investigated accordingly.

SECTION 14 - RESEARCH PERSONNEL

14.1 Requirements for Conducting Human Subject Research at MVAHS

Under the authority of Title 38 U.S.C. Section 7304 all VHA employees involved in human subject research, regardless of appointment mechanism, (Title 38, Title 5, or WOC), must possess adequate credentials and training to ensure their understanding of the protection of human subjects and the ethical conduct of research.

Investigators who maintain an appointment at this facility may submit a new research application.

Responsibilities

PI is responsible for ensuring that all individuals involved in the research activity are in compliance with credentialing and training requirements in accordance with this policy. All employees under his/her supervision involved in human subject research must 1) complete the required credentialing process, 2) have designated functions described in the research scope of practice statement that are consistent with the employee's qualifications, 3) ensure that employees are working within their research scope of practice, and 4) have appropriate VA appointments. The Research Scope of Practice statements must be reviewed and approved by the AO and the ACOS/R.

PIs involved in human subject research are responsible for ensuring that all employees under their supervision, working on approved human subject research, have completed required training in the ethical principles and acceptable human subject research practices every two years.

Study staff involved in human subject research are responsible for completing required training in the ethical principles and acceptable human subject research practices every two years as defined at MVAHS as within 730 days after the previous training. They must also complete the required VA research training as well as the annual VA facility training. New staff will complete the courses PRIOR to performing any duties related to the research study.

IRB Coordinator is responsible for providing management of the documentation and verification of individual's human subject protection education requirements.

Definitions

Human Subject Protection (HSP) Credentialing. HSP credentialing is the formal systematic process of verifying, screening, and evaluating qualifications and other credentials that include formal (required) education, licensure, registration, certification, relevant training and experience, and current competence.

Human Subject Protection (HSP) Education. HSP education requirements include two components: general protection of human research subjects and good clinical practices.

Study Staff: Study staff include: PIs, Co-I, Study Coordinators and other study staff who interact with subjects in person and/or on the telephone and those who collect and analyze individually identifiable data. This applies regardless of pay status, appointment type, and length of time in the VA facility and includes research staff with a WOC appointment. Study staff

(performing research duties at MVAHS) who do not have a VA paid appointment must receive a VA Without Compensation (WOC) appointment.

Research Scope of Practice or Functional Statement

Each member of the research team must have a research scope of practice statement or functional statement that has been approved by the individual's immediate supervisor, ACOS/R, and A/O that defines the duties the person is allowed to perform for research purposes. A research scope of practice statement or functional statement must be developed for all research personnel (clinical and non-clinical) who are not privileged for all the duties the person is allowed to perform for research purposes. The research scope of practice statement or functional statement must be consistent with the occupational category under which the individual was hired, and it must not include any duties for which the individual is not qualified. Current scopes of practice for all non-privileged research personnel must be retained by the Research Office.

Note: A duty (e.g., a procedure) cannot be added to a scope of practice statement or functional statement, unless the individual meets all criteria to perform the duty in the clinical setting (e.g., the individual must be privileged for a procedure if privileging is required for that procedure in the local clinical setting).

- a. A research scope of practice statement or functional statement, which is required for each study, may be written to cover multiple studies (i.e., personnel need a research scope of practice statement for each protocol). These scopes of practice are maintained in the IRB project folder.
- b. If an employee's clinical privileges, clinical scope of practice statement, or clinical functional statement includes all of the duties necessary for a specific research study (e.g., taking a medical history, drawing blood, performing a muscle biopsy, ordering and interpreting laboratory tests), a separate research scope of practice statement or functional statement does not need to be developed. However, if there are additional duties, these need to be included in the research scope of practice statement along with a copy of the clinical privileges, clinical scope of practice statement, or clinical functional statement.

License, Registration, and Certification. The employee must have all required licenses, registrations, or certifications to perform a given procedure, intervention, or other activity in the research setting and practice only within the scope allowed by such licenses, registrations, or certifications.

VetPro. VetPro is an internet enabled data bank for the credentialing of VHA Healthcare providers that facilitates completion of a uniform, accurate, and complete credentials file.

Licensed Independent Practitioners (LIP) A LIP is any individual 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. Only licensed independent practitioners may be granted clinical privileges. All such individuals will be credentialed through VetPro – Federal Credentialing Program.

The List of Excluded Individuals and Entities (LEIE). The LEIE, the sanctions list, or the exclusionary list, is a list of persons and organizations that have been excluded from

participation in federal healthcare programs, e.g., Medicare, Medicaid, VA healthcare. It is maintained by the DHHS Office of Inspector General (OIG). Individuals are placed on the LEIE for such things as conviction for defrauding Medicare or Medicaid, patient abuse, licensing board actions, or default on government-sponsored student loans.

The Debarment List. The Debarment List is maintained by the FDA and includes individuals or firms barred from participating in the drug industry because they have been convicted of crimes related to FDA's regulation of drugs.

The Disqualified/ Restricted/Assurances List for Clinical Investigators. This list identifies clinical investigators who have, or have agreed to, certain restrictions on their conduct in future studies.

The Public Health Service Administrative Actions. The Public Health Service Administrative Actions maintains a list of researchers who have had administrative actions imposed against them by the Office of Research Integrity (ORI).

14.2 Mandatory Training

This training requirement applies to all individuals involved in the conduct of VA human subject research regardless of pay status, appointment type (Title 38, Title 5, IPA, or WOC), and length of time at MVAHS, including but not limited to:

- a. Investigators;
- b. Study coordinators;
- c. Research assistants;
- d. Other members of the research team who see VA subjects, VA PHI, or;
- e. Trainees, such as house officers and students.

All research staff involved in or who have direct contact with (staff listed on a human subject research study) must complete, prior to initiating a research activity, the following:

- CITI/GCP Course in the Protection of Human Research Subjects.
- Privacy Training.
- Information Security Training.

Exceptions to Mandatory Training

These training requirements do not apply to:

- a. Secretarial support staff.
- b. Research office staff whose responsibilities do not involve human research (e.g., those who deal only with research involving animals).

Submitting Certificates of Training

Certificates for the training activities described above are attached to the *Report of Research Staff Members* form, and submitted for each new research application and, when applicable, upon continuing review. IRB staff members verify the information on the form and contact the

PI when the training record is incomplete. Training records are tracked in a database maintained by the IRB Office. The IRB considers the information during its review of the submission.

14.3 Qualifications to Conduct Research

As part of the review process, the IRB considers the qualifications of the PI from the applicable forms provided in this manual (e.g. CV's, Scopes of Practice, etc.).

All VA research staff (clinical and non-clinical) conducting human research (exempt or nonexempt) must be credentialed and privileged (if applicable) through VetPro as required by current local, VA, VHA (see VHA Handbook 1100.19), and ORD requirements. Research staff (including volunteers) may only perform those activities in a research study for which they have the relevant:

- a. Credentials. Each member of the research staff must be appropriately credentialed, except individuals providing secretarial support who should undergo the Human Resource Management Service (HRMS) process for administrative personnel.
- b. Privileges.
 - (1) MVAHS requires privileging to perform a given duty (e.g., a procedure) in the clinical setting the individual must be privileged at that facility to perform the duty before the individual can perform that duty in the research setting.
 - (2) MVAHS requires privileging to perform a given procedure, it is not sufficient for only the supervisor of the person performing the research procedure to be privileged for that procedure. The person actually performing the research procedure must be privileged for the procedure.

Verification of Education, Certifications and Licenses

All education that leads to a degree or certification, and any education or training that is relevant to the activities performed by the employee (such as survey methods, interview skills, etc.) must be documented and verified. This is accomplished through the HRMS at the time of initial appointment. All new employees must also be verified against the Exclusionary Lists and the Debarment Lists.

All current certifications and licenses should be updated and verified at the time of expiration or annually. Any new educational degrees, licenses or certifications, obtained since the last verification should also be confirmed during the next annual/continuing review.

Verification of credentialing may be obtained through the Medical Staff Office and/or through a Resident Credentialing Verification Letter (RCVL) for medical students and residents.

Students and other trainees (including residents and fellows), including VA employees, from schools with an academic affiliation agreement consistent with current VHA policy, may serve as investigator within a VA facility, or use data, or human biological specimens that have been collected within VA for clinical, administrative, or research purposes.

An investigator sufficiently experienced in the area of the trainee's research interest must serve as principal investigator or co-principal investigator and is responsible for oversight of the research and the trainee.

14.4 Identification Badges

Copies of VA ID badges for all personnel listed on the *Report of Staff Members* form must be submitted along with the new research application.

14.5 Qualified Healthcare Provider for Study-Related Healthcare Decisions

If the investigator is not a clinician, and when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not be limited to:

- (1) Reviewing the data, adverse events, and new study findings.
- (2) Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's healthcare provider of information that may affect the health of the subject).

14.6 Alternate Principal Investigator

For every approved clinical study, the Principal Investigator must designate an Alternate Principal Investigator to act in place of the Principal Investigator in case of disability or unavailability of the Principal Investigator. The name of the Alternate PI must be filled in on the *Report of Research Staff* form.

If circumstances are such that the Alternate PI is required to assume the responsibilities of the PI, the following documentation is required:

- ✓ Memorandum describing the reason for the change.
- ✓ Two copies of the Alternate Principal Investigator's current CV.

The memorandum is placed on the agenda of the next IRB meeting.

14.7 Transferring a Study to a New Principal Investigator

Principal Investigators planning to leave the MVAHS must make arrangements to close or transfer their studies to another Principal Investigator.

PIs who wish to transfer their studies to a new PI are required to submit the following materials to the IRB for full committee review:

- ✓ Amendment packet (see Section 3). The new informed consent must have the proposed investigator's name on it and all required signatures.
- ✓ Memorandum requesting that the Principal Investigator be released from his/her duties and a recommendation of a new Principal Investigator for the study.
- ✓ Memorandum signed by the proposed Principal Investigator accepting responsibility for conducting the study.
- ✓ New Principal Investigator's current CV or bio-sketch.
- ✓ A revised *FDA Form 1572 - Statement of Investigator* (for sponsored studies only).
- ✓ Revised *Report of Research Staff Members* form.
- ✓ Copies of certificates for human subject, cyber security, and privacy trainings.

- ✓ *VA Form 10-5386-Research and Development Information System Investigator Data* (“Page 18”).
- ✓ *Scope of Practice* forms (reviewed and co-signed by proposed Principal Investigator).
- ✓ Revised *VA Form 10-9012 - Investigational Drug Information Record*, if applicable.
- ✓ Copy of work identification.
- ✓ A new *Disclosure of Available Funds* form.
- ✓ Questions 2 and 3 in Section 10 of the *Application for New Human Research Study* form that address conflict of interest.

14.8 Co-Investigators: Adding/Removing/Changing Duties

To report any of the following changes for Co-Investigator(s), the PI must submit the following materials to the IRB for full committee review:

1. Adding a Co-Investigator to a study:
 - ✓ Amendment packet (see Section 3).
 - ✓ Memorandum listing the name of the study to which the Co-investigator will be added. Include a description of his/her study related duties.
 - ✓ New Co-Investigator’s current CV.
 - ✓ Revised *FDA Form 1572 - Statement of Investigator* (for sponsored studies only).
 - ✓ Revised *Report of Research Staff* form.
 - ✓ Copies of certificates for human subject, cyber security, and privacy trainings.
 - ✓ *Revised Scope of Practice* form.
 - ✓ Revised *VA Form 10-9012 - Investigational Drug Information Record* (if Co-investigator is authorized to prescribe study drugs).
 - ✓ Copy of work identification.
 - ✓ Updated *Disclosure of Financial Interests-Conflicts of Interest* form, if applicable.

2. Change in duties of a Co-Investigator:
 - ✓ Amendment packet (see Section 3).
 - ✓ A memorandum listing the name of the study. Include a description of the Co-investigator’s new study-related duties.
 - ✓ Revised *Report of Research Staff* form.
 - ✓ Revised *FDA Form 1572 - Statement of Investigator* (for sponsored studies only).
 - ✓ Revised *Scope of Practice*.

3. Removing a Co-Investigator from a study:
 - ✓ Amendment packet (see Section 3).
 - ✓ A memorandum listing the name of the study. Include the name of the Co-Investigator to be removed from the study, and indicate whether another Co-Investigator will assume his/her responsibilities.
 - ✓ Revised *Report of Research Staff* form.
 - ✓ Revised *FDA Form 1572 - Statement of Investigator* (for sponsored studies only).

14.9 Adding/Removing/Changing the Duties of Study Personnel

Under specific circumstances, the IRB must be notified when changes in study staff occur. The notification may be expedited.

- If a study team member is identified by name in the IRB-approved protocol, a replacement or termination of their role constitutes a change in the protocol. Such a change requires IRB approval.
- If a study team member is replaced by another individual and the IRB-approved protocol identifies the person by title and not name, a replacement by another individual with the same title is not a protocol change. No IRB approval is required.
- IRB may also require a specific individual(s) by name to be part of the study team as a condition for IRB approval of the research. In that case, a proposed change in that specific individual would require IRB approval.

Listed below are instructions for submitting changes in study staff that require IRB review:

1. Adding research personnel to a study:
 - ✓ Memorandum listing the name of the study to which the staff member will be added. Include a description of his/her study related duties.
 - ✓ Current CV for professionals (RN, ARNP, etc.).
 - ✓ Copies of certificates for human subject, cyber security, and privacy trainings for each staff member added.
 - ✓ Updated *Scope of Practice* form for each staff member added, if applicable.
 - ✓ Revised *Report of Research Staff* form.
 - ✓ Copy of work identification.
2. Change in duties of study personnel:
 - ✓ A memorandum listing the name of the study. Include a description of the staff member's new study-related duties.
 - ✓ Updated *Scope of Practice* form for each staff member added, if applicable.
 - ✓ Revised *Report of Research Staff* form.
3. Removing research personnel from a study:
 - ✓ A memorandum listing the name of the study. Include the name of the staff member to be removed from the study and indicate whether another staff member will assume his/her duties. (See above: #1 Adding research personnel to a study and #2 Change in duties of study personnel).
 - ✓ Revised *Report of Research Staff* form.
 - ✓ The PI must ensure that access previously granted has been revoked in a memo to the IRB.

SECTION 15 - INVESTIGATOR RESPONSIBILITIES

15.1 Investigator Responsibilities

The principal investigator, local site investigator, and investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other federal requirements, including the local VA facility's standard operating procedures, regarding the conduct of research and the protection of human subjects.

The PI is the ultimate protector of the human subjects who participate in research and is responsible for the conduct of the research. A PI may delegate research responsibilities; however, he/she must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

As per VHA Handbook 1200.05 the IRB recognizes one PI for each project. If the PI: 1) has a WOC appointment; 2) is a student, resident, or fellow; 3) is not credentialed to perform and/or supervise the study procedures; and/or 4) is not qualified to be responsible for study related healthcare decisions, a Responsible Investigator (RI) is named in the protocol. The PI is an investigator who assumes ultimate responsibility for the conduct of the research and must adhere to all PI responsibilities. A PI must have a VA appointment.

The PI must maintain credentials and privileges at the MVAHS appropriate for performing all procedures proposed in all research protocols involving human subjects submitted by the PI. If the PI lacks the requisite credentials and privileges, a Co-PI must be listed on the application. The PI assumes responsibility for the specific procedures in question. This individual is then responsible for all study-related healthcare decisions.

Responsibilities include: Reviewing the data, adverse events, and new study findings. Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's healthcare provider of information that may affect the health of the subject).

In order to satisfy the requirements of this policy, PIs who conduct research involving human subjects must:

1. Develop and/or conduct research that is in accordance with the ethical principles outlined in the Belmont Report.
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects. In the event that the PI did not design the research study, the PI determines that design is sound to carry out the research.
3. Have sufficient resources necessary to protect human subjects, including:
 - a. Access to a population that would allow recruitment of the required number of subjects.
 - b. Sufficient time to conduct and complete the research.
 - c. Adequate numbers of qualified staff.

- d. Adequate facilities.
 - e. A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.
 - f. Availability of medical or psychological resources that subjects might require as a consequence of the research.
4. Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Florida and the policies of MVAHS.
 5. Assure that all key personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principals upon which they are based.
 6. Protect the rights and welfare of prospective subjects.
 7. Ensure that risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
 8. Recruit subjects in a fair and equitable manner.
 9. Obtain and document informed consent as required by the IRB and ensuring that no human subject is involved in the research prior to obtaining their consent.
 10. Have plans to monitor the data collected for the safety of research subjects.
 11. Protect the privacy of subjects and maintain the confidentiality of data.
 12. 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, include additional safeguards in the study to protect the rights and welfare of these subjects.
 13. Have a procedure to receive complaints or requests for additional information from subjects and respond appropriately.
 14. Ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating investigators and research staff.
 15. Comply with all IRB decisions, conditions, and requirements.
 16. Ensure that protocols receive timely continuing IRB review and approval.
 17. Report unanticipated problems involving risk to subjects or other and any other reportable events to the IRB including protocol deviations and complaints.
 18. Obtain IRB review and approval in writing before changes are made to approved protocols or consent forms.
 19. Seek IRB assistance when in doubt about whether proposed research requires IRB review.
 20. Create a progress note in CPRS documenting the informed consent process with the patient, when the subject is actually entered into the study and when the human subject's participation is terminated.

21. Ensure research compliance - Ensuring that research is in compliance with all applicable local, VA, and other Federal requirements.
22. Promptly report changes in PI or LSI.
23. Implement the study as approved.
24. Ensure consistency of the informed consent form, protocol, and HIPAA Authorization.
25. Ensure HIPAA Authorization is obtained.
26. Perform subject outreach.
27. Complete appropriate actions at research project completion.
28. Maintain a master list of all subjects.
29. Ensure appropriate research laboratory test reporting.
30. Ensure requirements of multi-site studies.

15.2 Investigational Drugs and Devices in Research: Investigator Responsibilities

Investigators conducting research projects involving investigational drugs are responsible for:

- ✓ Completing and filing *FDA Form 1572-Statement of Investigator*.
- ✓ Completing *VA Form 10-9012-Investigational Drug Information Record*. The original is sent to the IRB Office where it is maintained. IRB staff will forward a copy to the Pharmacy Service along with a copy of the protocol and approval documentation when the study begins.
- ✓ Forwarding a copy of each signed informed consent document to the Pharmacy Service.
- ✓ Retaining a copy of *VA Form 10-1223-Report of Subcommittee on Human Studies*.
- ✓ Obtaining the investigational drug from the manufacturer and its delivery to the custody of the Pharmacy Service.
- ✓ Completing the *Pharmacy/PI Review of Initial Study Drug Stock* form. The Research Pharmacist will contact the Principal Investigator when the study drugs have been delivered to the Pharmacy Service. The study may not be initiated until this form is completed.
- ✓ Providing signed authorization each time the investigational drug is issued.
- ✓ Adhering to the data safety monitoring plan.
- ✓ Informing the Pharmacy Service, IRB and R&D Committee when a study involving investigational drugs has been terminated.
- ✓ Providing written disposition of any remaining drug upon termination.

15.3 Research Staff Responsibilities

Every member of the research team is responsible for protecting human subjects by:

- ✓ Complying with all IRB determinations and procedures.
- ✓ Adhering rigorously to all protocol requirements and informing investigators of all adverse subject reactions or unanticipated problems.
- ✓ Ensuring adequacy of the informed consent process.
- ✓ Taking measures to ensure adequate protection for subjects and minimizing risks.
- ✓ Notifying the IRB promptly of any serious or continuing non-compliance with applicable regulatory requirements, or determinations of the IRB, of which they become aware, whether or not they themselves are involved in the research.

- ✓ Knowing and adhering to the scope of practice or clinical privileges that have been approved for them on the *Scope of Practice* form.
- ✓ Knowing and adhering to applicable statutes, regulations and policies related to conducting human studies research.
- ✓ Completing and updating human subject (CITI/GCP) and protection of patient privacy/data security training.
- ✓ Engaging only in human subject research activities that have been approved, as required by VA regulations and policies.
- ✓ Understanding shared responsibility. All staff members have a responsibility to conduct research ethically and according to regulatory guidelines.

15.4 Medical Chart Documentation

The following items must be maintained in the subject's medical chart:

- ✓ Progress notes for any subject visit or contact including the informed consent process, enrollment, date patient begins study procedures, visits, and terminations.
- ✓ Progress notes describing serious/unexpected adverse events.
- ✓ Note indicating PHI was accessed or disclosed under a waiver of authorization, when applicable.
- ✓ Note describing that PHI was accessed while conducting decedent or preparatory research, when applicable.
- ✓ Copy of informed consent document, when applicable.
- ✓ Copy of *VA Form 10-9012-Investigational Drug Information Record*, when applicable.
- ✓ Documentation of the informed consent process.
- ✓ Termination of a subject's participation in a study when applicable.
- ✓ Documentation of legally authorized representative status (surrogate status) must be noted in the CPRS template.
- ✓ A copy of a legally recognized document indicating surrogate status may also be included in the medical record.

15.5 Record Keeping and Self Assessment Tools

1. Case record forms, copies of informed consent documents, all correspondence, and regulatory documents must be maintained in locked file cabinets.
 - a. Copies of all IRB-approved versions of the protocol and amendments.
 - b. Case report forms and supporting data, including, but not limited to, signed and dated informed consent forms and HIPAA.
 - c. Documentation on each subject including, but not limited to:
 - Informed consent.
 - Interactions with subjects by telephone or in person.
 - Observations.
 - Interventions.
 - Other data relevant to the research study, including, but not limited to: progress notes; research study forms; surveys and questionnaires; reports of adverse events; data analyses; reports including, but not limited to, abstracts and other publications; all correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D Committee, ORO; and a master list of all subjects for whom informed consent has been obtained in the study.

2. Documents must be maintained so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements.
3. Accounting of Disclosure must be maintained for each disclosure of information from the study to a non-VA entity. (The facility Privacy Officer can assist in providing a mechanism to account for this disclosure.)
4. Only authorized team members may access research records.
5. Record Retention. The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). (VHA Handbook 1200.05)
6. It is good clinical practice to maintain all regulatory documents and study correspondence in a binder/folder. See www.va.gov/chrr/regulatory for a complete list of frequently audited documents.
7. Principal Investigators may use the following self-assessment tool as guidance in determining which documents to maintain in their files:
 - Regulatory Documents and Study Correspondence (see Appendix A)
8. Principal Investigators may use the following self-assessment tool as guidance in determining compliance with IRB regulations:
 - Informed Consent Compliance Checklist (see Appendix B)

The “Study Binder” must contain the following documentation, where applicable:

1. Protocol
2. IRB Correspondence
3. Consent Forms
4. HIPAA Authorizations
5. Study staff information
6. FDA
7. NIH
8. Sponsor
9. Monitoring/DSMB
10. Product Information
11. Laboratory Information
12. Drug/Device Accountability
13. Data Collection
14. Study Logs

15.5.1 Transferring of Records

If the investigator leaves VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the investigator leaves one VA facility to go to another VA facility, the investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility's research office. The approval must be obtained from the first VA facility's research office, any other relevant individuals or offices according to VA and local requirements (e.g., compliance, privacy, or Information Security Officers (ISOs)) and the sponsor. **Note:** The investigator is not the grantee, nor does the investigator own the data.

15.6 Reporting Requirements and Communications with the IRB

After the research project has been initiated, the Principal Investigator is responsible for notifying the IRB of any communications from sponsors and regulatory agencies including:

1. Information from sponsors:
 - ✓ Adverse events occurring at other sites.
 - ✓ Data Safety Monitoring Board Reports.
 - ✓ Audits, site visits, monitoring visits.
 - ✓ Other reports and information as required.

2. Information from regulatory agencies (FDA, OPRR, ORO):
 - ✓ Policy changes and directives.
 - ✓ Audits, site visits, monitoring visits.

15.7 Research Misconduct

Research Misconduct is defined as “fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results”.

Allegations of misconduct are forwarded to the MVAHS Research Compliance Officer for processing according to the guidelines set forth in *VHA Handbook 1058.2 (May 4, 2005)*.

Within seven days of receiving the final Investigation Report, as outline in the handbook, the Medical Center Director is required to transmit the report to the VISN Director. Copies of the final Investigation Report and the Medical Center Director’s recommendations must be provided to the Respondent, ORO Central Office, and the head of the agency or entity that has joint jurisdiction. When the VISN Director has made a final decision on the merits of the case, that decision is transmitted to ORO Central Office along with the Investigation Report.

15.8 Non-Compliance

15.8.1 Definitions

Non-Compliance. Non-compliance is defined as failure to comply with any of the regulations and policies described in this document and failure to follow the determinations of the IRB and/or failure to follow VA requirements. Non-compliance may be minor or sporadic or it may be serious or continuing.

Serious Non-Compliance. Serious non-compliance is defined as failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB, and/or failure to follow VA requirements, which, in the judgment of either the IRB Chair or the convened IRB, increases risks to participants, decreases potential benefits, or compromises the integrity of the human research protection program. Research being conducted without prior IRB approval or participation of subjects in research activities without their prior consent (in studies where consent was not specifically waived by the IRB) is considered serious non-compliance.

Continuing Non-Compliance. Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, suggests a likelihood that instances of non-compliance will continue without intervention. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

15.8.2 Non-Compliance

Investigators and their study staff are required to report instances of possible non-compliance. The Principal Investigator is responsible for reporting any possible non-compliance by study personnel to the IRB. Common reports to the IRB that are not serious or continuing are typically protocol violations. However, any individual or employee may report observed or apparent instances of non-compliance to the MVAHS IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and cooperating with any IRB and/or institutional review of these reports.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report non-compliance, he or she may contact the IRB Chair directly to discuss the situation informally.

Examples of cases of non-compliance that should be reported include but are not limited to:

- Failure to obtain IRB approval.
- Failure to obtain informed consent before enrolling subjects in research.
- Use of a consent form not approved by the IRB.
- Enrollment of an ineligible subject; consenting an incompetent subject.
- Failure to report serious/unexpected adverse events.
- Failure to withdraw a subject from a protocol that resulted in an injury.
- Use of an unapproved, coercive, and misleading advertisement.
- Coercion of a research subject to remain on study.

Reports of non-compliance must be submitted to the IRB Office within 5 working days of discovery of this non-compliance. The report must include a complete description of the non-compliance, the personnel involved and a description of the non-compliance. Complainants may choose to remain anonymous.

15.8.3 Review of Findings of Non-Compliance

Non-Compliance is Not Serious or Continuing

When the IRB Chair determines that the non-compliance occurred, but the non-compliance does not meet definition of serious or continuing non-compliance, the determination is reported in writing to the PI and if applicable the reporting party. The IRB Chair will work with the PI to develop a corrective action plan to prevent future non-compliance. The report of non-compliance and corrective action is reported to the IRB through the “expedited review report”. If however, the PI refuses to cooperate with the corrective action plan, the matter is referred to a convened meeting of the IRB with notification to the IO, ACOS/R, and R&D Committee.

Serious or Continuing Non-Compliance

When the IRB Chair determines that non-compliance has occurred and that the non-compliance meets the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next convened available meeting. However, the IRB Chair may use discretion and call an emergency IRB meeting should the circumstances warrant such an urgent meeting.

All findings of serious or continuing non-compliance referred to the IRB will be reviewed at a convened meeting. At this stage, the IRB may:

1. Find that there is no issue of non-compliance;
2. Find that there is non-compliance that is neither serious nor continuing and an adequate corrective action plan is in place;
3. Find that there is serious or continuing non-compliance and approve any changes proposed by the Chair and/or ad hoc committee or take any possible actions listed in section 10.4.4;
4. Find that there may be serious or continuing non-compliance and direct that a formal inquiry (described below) be held; or
5. Request additional information.

Final Review

When the IRB determines that there is serious or continuing non-compliance, either on its own accord or after a formal inquiry, the IRB's possible actions could include, but are not limited to:

1. Advising the Principal Investigator about the rules and regulations involving human subject research;
2. Providing a verbal or written reprimand;
3. Request a correction action plan from the investigator;
4. Verification that participant selection is appropriate and observation of the actual informed consent;
5. An increase in data and safety monitoring of the research activity;
6. Request a directed audit of targeted areas of concern;
7. Request a status report after each participant receives intervention;
8. Modify the continuing review cycle;
9. Request additional Investigator and staff education;
10. Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation;
11. Require modification of the protocol;
12. Require modification of the information disclosed during the consent process;
13. Require current participants to re-consent to participation;
14. Suspend the study (See below); or
15. Terminate the study (See below).

In cases where the IRB determines that the event of non-compliance also meets the definition of unanticipated problem involving risks to subjects or others, the policy and procedure for review of such events will also be followed, as described in Section 8.5.

The investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below.

If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below (VHA Handbook 1058.01):

- (1) Should the IRB determine that the reported incident constitutes serious non-compliance or continuing non-compliance, the IRB Chair, or designee must report the determination directly (without intermediaries) to the facility Director within 5 business days after the determination.
- (2) The IRB Chair's report must be made in writing, with a simultaneous copy to the ACOS for Research, the R&D Committee, and any other relevant research review committee.
- (3) The facility Director must promptly report the determination to the appropriate federal agencies (e.g. OHRP and FDA) and within 5 business days to ORO RO, with a simultaneous copy to the VISN Director and the ORD, after receiving such notification.
- (4) An initial report of an IRB determination that serious non-compliance or continuing non-compliance occurred is required, even where the determination is preliminary or disposition of the matter has not been resolved at the time of the report.

Note:

If the IRB determines that the non-compliance was serious or continuing, the IRB may immediately suspend or terminate the research. Any suspension or termination must follow the reporting requirements in VHA Handbook 1058.01 as outlined below. If, after reviewing a report, the IRB finds that suspension or termination is warranted, the IRB will do all of the following:

- a. Notify the investigator in writing of its findings, with copies to the investigator's service chief the investigator's supervisor.
- b. Reported directly (without intermediaries) to the facility Director within 5 business days after the termination or suspension occurs. The report will include findings and recommendations. The facility Director must promptly report the termination or suspension to the appropriate federal officials (OHRP, and FDA) and to the ORO RO within 5 business days after receiving such notification.
- c. Simultaneously distribute copies of the written report to the Director, as applicable, to the ACOS for Research, the R&D Committee, and any other relevant research review committee.

APPENDIX A

Regulatory Documents and Study Correspondence

Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
1.1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
1.2	Signed protocol and Amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/Amendment(s) and CRF	X	X
1.3	Information given to trial subject -Informed consent form (Including all applicable translations)	To document the informed consent	X	X
	-Any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	X	
1.4	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
1.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
1.6	Signed agreement between involved parties, e.g.:	To document agreements		
	-Investigator/institution and sponsor		X	X
	-Investigator/institution and Clinical Research Organizations (CROs)		X	X (where required)
	-Sponsor and CRO			X
	-Investigator/institution and authority(ies) (Where required)		X	X

	Title of Document (Cont.)	Purpose (Cont.)	Located in Files of	
			Investigator/ Institution	Sponsor
1.7	Dated, documented approval/favorable opinion of institutional review board (IRB) of the following: -Protocol and any Amendments -CRF (if applicable) -Informed consent form(s) -Any other written information to be provided to the subject(s) -Advertisement for subject recruitment (if used) -Subject compensation (if any) -Any other documents given approval/favorable opinion	To document that the trial has been subject to IRB review and given approval/favorable opinion. To identify the version number and date of the document(s).	X	X
1.8	IRB composition (roster)	To document that the IRB is constituted in agreement with GCP	X	X (where required)
1.9	Regulatory authority(ies) authorization/approval/ notification of protocol (where required)	To document appropriate authorization/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
1.10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
1.11	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
1.12	Medical/laboratory/technical procedures/tests -Certification <u>or</u> -Accreditation <u>or</u> -Established quality control and/or external quality assessment <u>or</u> - Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
1.13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects		X

	Title of Document (Cont.)	Purpose (Cont.)	Located in Files of	
			Investigator/	Sponsor Institution
1.14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
1.15	Shipping records for investigational Product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
1.16	Certificate(s) of analysis of Investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial.		X
1.17	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
1.18	Master randomization list	To document method for randomization of trial population		X (third party if applicable)
1.19	Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with 2.20 below)		X
1.20	Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with 2.19 below)	X	X

During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
2.1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
2.2	Any revisions to: -Protocol/amendment(s) and CRF -Informed consent form -Any other written information provided to subjects -Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents that take effect during trial	X	X
2.3	Dated, documented approval/favorable opinion of institutional review board (IRB) of the following: -Protocol amendment(s) -Revision(s) of: -Informed consent form -Any other written information to be provided to the subject -Advertisement for subject recruitment (if used) -Any other documents given approval/favorable opinion -Continuing review of trial as set by IRB, but at least once every year	To document that the amendment(s) and/or revision(s) have been subject to IRB review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X
2.4	Regulatory authority(ies) authorizations/ approvals/notifications where required for: -Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
2.5	Curriculum vitae for new investigator(s) and/or subinvestigators	(See section 1.10)	X	X
2.6	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see section 1.11)	X	X

2.0 During the Clinical Conduct of the Trial (Cont.)

	Title of Document (Cont.)	Purpose (Cont.)	Located in Files of	
			Investigator/ Institution	Sponsor
2.7	Updates of medical/ laboratory/technical procedures/tests -Certification or -Accreditation or -Established quality control and/or external quality assessment or - Other validation (where required)	To document that tests remain adequate throughout the trial period (see section 1.12)	X (where required)	X
2.8	Documentation of investigational product(s) and trial-related materials shipment	(See section 1.15)	X	X
2.9	Certificate(s) of analysis for new batches of investigational products	(See section 1.16)		X
2.10	Monitoring visit reports	To document site visits by, and findings of, the monitor		X
2.11	Relevant communications other than site Visits -Letters -Meeting notes -Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
2.12	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see section 1.3)	X	
2.13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
2.14	Signed, dated, and completed case report forms (CRFs)	To document that the investigator or Authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
2.15	Documentation of CRF corrections	To document all changes/ additions or Corrections made to CRF after initial data were recorded	X (copy)	X (original)
2.16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports as soon as they are discovered	X	X

2.0 During the Clinical Conduct of the Trial (Cont.)

	Title of Document (Cont.)	Purpose (Cont.)	Located in Files of	
			Investigator/ Institution	Sponsor
2.17	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s) of unexpected serious adverse drug reactions in accordance with their respective guidelines	X (where required)	X
2.18	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information which affects the safety of the participants, impacts on conduct of the research, or alter the IRB's approval/favorable opinion to continue the trial	X	X
2.19	Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB by the investigator as set by the IRB and, by the sponsor, to other regulatory authority(ies), as required	X	X (where required)
2.20	Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
2.21	Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
2.22	Subject enrollment log	To document chronological enrollment of subjects by trial number	X	
2.23	Investigational product(s) accountability at the site	To document that investigational products(s) have been used according to the protocol	X	X
2.24	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
2.25	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

After Completion or Termination of the Trial.

After completion or termination of the trial, all of the documents identified in sections 1.2 and 2.0 should be in the file together with the following:

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
3.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
3.2	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
3.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
3.4	Audit certificate (if required)	To document that audit was performed (if required, also, the auditing entity should provide an audit certificate)		X
3.5	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
3.6	Treatment allocation and decoding Documentation	Returned to sponsor to document any decoding that may have occurred		X
3.7	Final report by investigator/institution to IRB where required, and, by the sponsor, where applicable, to the regulatory authority(ies)	To document completion of the trial	X	
3.8	Clinical study report – Sponsor and/or investigator must provide IRB with a summary of trial's outcome and applicable regulatory agencies with any reports they require	To document results and interpretation of trial	X (if applicable)	X

APPENDIX B

Informed Consent Compliance Checklist

ITEM		✓	CORRECTIVE ACTION
1.	Was informed consent obtained from each subject?		Report this violation to the IRB.
2.	For each subject consented, is an original consent form in the Principal Investigator's research file?		<ul style="list-style-type: none"> • Report this violation to the IRB. • Write a signed and dated note to file explaining when and who obtained consent. • Write a signed and dated note to file; explaining why only a photocopy is available.
3	Are all pages of the consent form on file for each subject signed and initialed on each page?		<ul style="list-style-type: none"> • Report this violation to the IRB. Write a signed and dated note to file confirming that all information was presented to the subject, and if possible, explain why pages are missing.
4.	Is subject identification (written or imprinted with hospital card) on all pages of the consent form?		<ul style="list-style-type: none"> • Ensure that identification is on all pages of consent form for future subjects. If possible, add subject's identification to all existing consent forms.
5.	Was consent obtained from each subject prior to performing any screening procedures to determine eligibility?		<ul style="list-style-type: none"> • Report this violation to the IRB.
6.	Did all subjects receive a copy of the signed and dated consent form?		<ul style="list-style-type: none"> • Report this violation to the IRB.
7.	Is there documentation to support that the subject received a copy of the signed and dated consent form?		<ul style="list-style-type: none"> • Complete the CPRS template entitled "T—Research Study: Documentation of Informed Consent Discussion for Research Study" For all future subjects enrolled, ensure this progress note is made for all research subjects.
9.	Did each subject sign and date the consent form for him/herself? (excluding IRB approved surrogate/parental consent)		<ul style="list-style-type: none"> • Report this violation to the IRB. • Write a signed and dated note to file explaining any missing signature/date; or explaining who signed and dated for subject..
10.	Did an IRB-approved study representative obtain consent for all subjects?		<ul style="list-style-type: none"> • Report this violation to the IRB. • Check the current "Report of Research Staff Members" on file in the IRB Office to verify who is IRB-approved to obtain consent.
11.	Did a witness (not part of the Investigator's research group) sign the consents?		<ul style="list-style-type: none"> • Report this violation to the IRB.
12.	Did the IRB-approved study representative obtaining consent sign and date for him/herself?		Write a signed and dated note to file explaining who signed/dated for the study representative or if it was an omission, explain how and when consent was obtained.
13.	Are there any discrepancies between the dates the subject and the study representative signed the consent form?		<ul style="list-style-type: none"> • Write a signed and dated note to file clarifying how and when consent was obtained.

14.	Are there any changes/handwritten corrections (e.g. contact telephone number) to any of the consent forms used?	<ul style="list-style-type: none"> • Report this violation to the IRB. • Submit an amendment to the IRB updating the consent form.
15.	Has there been a CPRS progress note entered using the template entitled “T— Research Study: Documentation of Informed Consent Discussion for Research Study”	<ul style="list-style-type: none"> • Write a signed and dated progress note using the named template for any subject for which this progress note has not been made. • Make sure the Research IRB Office is notified of this (these) subject’s participation in the study.
16.	When applicable, was a copy of the consent document and approved Drug Information Record (VA Form 10-9012) provided to the Research Pharmacy together with the prescription?	<ul style="list-style-type: none"> • Report this violation to the IRB.
17.	Were copies of all executed consent documents (including a copy of the Drug Information Record – VA Form 10-9012, when applicable) submitted to: <ul style="list-style-type: none"> • the Research IRB Office? • the Research Pharmacist? (when applicable) 	<ul style="list-style-type: none"> • Report this violation to the IRB. • Provide the Research IRB Office with copies of all missing consent documents. • Provide the Research Pharmacist with appropriate documentation.
18.	Are original copies of all IRB-approved consent forms (previous versions as well as the current version) in your files?	Obtain missing versions of the IRB-approved consent forms from the protocol administrator.
19.	Was a valid (most recent version with an IRB-approval stamp on the bottom) consent form used to consent each subject?	<ul style="list-style-type: none"> • Report this violation to the IRB. • If possible, re-consent the subject on a valid consent form.
20.	Are yes/no or similar options on the consent form (if applicable) complete for all subjects?	Assume the subject “does not” agree to the option unless the subject can complete the information at a later time.
21.	Is the number of subjects who have signed the consent form less than or equal to the target enrollment goal approved by the IRB?	<p>Report this over-enrollment to the IRB.</p> <ul style="list-style-type: none"> • Submit an amendment to the IRB requesting an increase in the enrollment goal.
22.	Have all subjects enrolled on or after April 14, 2003 signed a HIPAA-compliant version of the consent document?	<ul style="list-style-type: none"> • Re-consent these patients and report this violation to the IRB. • Ask each subject to indicate that the consent (authorization) is retroactive to the time of enrollment. • Provide the Research IRB Office with copies of these consents as soon as they are available.