

# UNIVERSITY OF IOWA IRB03 RESEARCHER GUIDE

The University and the VAHCS are responsible for the advancement of science through their individual research activities. Each institution has unique resources that are of high quality, and when these resources are combined the potential for scientific enhancement is exponentially increased. Therefore, the University and VAHCS have established collaborations under several Institutional Agreements allowing maximization of resources available at their respective institutions.

An integral part of scientific research is its translation to human application and public health. A critical step in this translation involves studies being performed with human subjects. It is essential that studies performed on human subjects be conducted in a safe and informed manner. The VAHCS and its investigators are committed to these principles. The VAHCS offers expertise in certain areas, allowing for maximization of scientific expertise into such projects, but has not established either an IRB for the review of human subjects research or a Privacy Board for the VAHCS's compliance with HIPAA in the context of human subjects research. Due to the institutions' proximity, the collaboration allows for enhancement of mutual research interests of both institutions by sharing staff and resources, including the University Institutional Review Board (IRB-03) hereinafter referred to as the IRB-03. (Excerpted from ***IRB Memorandum of Understanding Between*** The University of Iowa And Iowa City Veterans Affairs (VA) Health Care System). Standard Operating Procedures across all University of Iowa IRBs are applied as outlined in the first part of the [UNIVERSITY OF IOWA IRB STANDARD OPERATING PROCEDURES \(SOP\) AND RESEARCHER GUIDE](#).

The following document describes the process that VAHCS Investigators are to follow in presenting research to The University of Iowa IRB 03 for IRB approval.

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## Part 1: Human Subjects Research Process

VA Investigators are required to submit an application for IRB review prior to initiating a research project. The Human Subjects Office requires all new project applications be submitted using HawkIRB. HawkIRB is an online application submission tool that uses “smart form” technology to guide VA investigators through the application process. Instructions for completing the new project application are contained within each section of the HawkIRB system. HSO staff are available for consultation and help using the system. Please refer to the [HawkIRB FAQ](#) for additional information.

### 2018 Human Subjects Research Regulatory Changes

Human Subjects Research (Common Rule) under [45 CFR 46 regulatory framework](#) has undergone significant revisions. These revisions go into effect on January 21, 2019 and will apply to all common rule agencies with the exception of the Food and Drug Administration (FDA) and Department of Justice (DOJ). Communications within this guidance document will be utilizing the following terms when referring to the regulatory changes:

- **Pre-2018 Regulations** – regulations current IRB approved research will continue to follow
- **2018 (Revised Common Rule) Regulations**– regulatory changes that go into effect 1/21/19 for research approved on or after this date.

### Transition plans

Research subject to the DOJ will follow the pre-2018 regulations. Per guidance issued by the FDA in October 2018, research subject to the FDA cannot be inconsistent with FDA’s current policies and guidance found under 21 CFR parts 50 and 56. Only two of the Revised Common Rule regulations will be applied to University of Iowa IRB-03 approved research under FDA purview:

- Key information 45 CFR 46.116(a)(4), (a)(5)(i), and (a)(5)(ii)
- New required\additional elements of consent 45 CFR 46.116

<ul style="list-style-type: none"><li>• All research projects approved prior to 1/21/19 will remain under the Pre-2018 Common Rule regulations. No changes required.</li></ul>
<ul style="list-style-type: none"><li>• All new project applications (either pending with the PI or HSO\IRB not approved on or after 1/21/19 will follow the Revised Common Rule (2018 regulations.)</li></ul>

### 1.A Beginning the IRB New Project Application

HawkIRB requires the investigator to respond to all applicable items on the New Project Application in order to submit the project to the HSO. The most common problem with New Project applications is that not enough detail is provided for the IRB Chair or members to evaluate the study's purpose and/or procedures.

In particular, VA investigators are required to provide detailed information regarding how potential subjects are initially identified, and how consent is obtained. The Principal Investigator

must accurately and completely describe the study procedures in the HawkIRB application. The more complete the initial description is, the less likely that time will be spent with correspondence back and forth between the investigator and Human Subjects Office staff and/or IRB chairs to fill in the details. The New Project application in HawkIRB will indicate what is required with regard to supporting documentation.

In general, a complete submission for IRB-03 review includes the following items as applicable:

- 1) HawkIRB application
- 2) Separate, written protocol (an existing written protocol)
- 3) Informed Consent Document(s) (or other applicable consenting materials):
- 4) If children are involved, an assent document may be required
- 5) Letter or information sheet containing the elements of consent
- 6) Exempt Information sheet
- 7) Letters of Agreement (when either of the following applies):
- 8) Study activities will be conducted off-campus at an agency, school or other non-UI site
- 9) Data will be obtained from an outside agency or organization
- 10) Sample Informed Consent Document(s) (for example, the DHHS or other sponsor sample consent, if available).
- 11) Recruitment materials
- 12) Posters, flyers, brochures
- 13) E-mail messages
- 14) Scripts and/or presentation materials
- 15) Letters
- 16) Data collection instruments
- 17) Surveys or questionnaires
- 18) Written assessments
- 19) Interview questions
- 20) Grant application, statement of work, or other materials used to acquire support/funding
- 21) Investigator's Brochure (Clinical Investigator's Brochure)
- 22) Other materials specific to the proposed study (e.g. sponsor correspondence with a regulatory agency such as the FDA regarding test article risk, etc.)

There are detailed instructions within the HawkIRB application regarding how to attach supporting documentation. HSO staff are available to respond to questions by e-mail or phone. Staff members are also available to consult individually with VA investigators on how to use HawkIRB. VA Investigators are encouraged to contact the Human Subjects Office with their questions.

#### **1.B. Use of the NCI CIRB for research occurring at the Iowa City VAHCS.**

The [NCI CIRB](#) is an institutional review board (IRB) that reviews federally funded oncology research under the purview of the [National Cancer Institute \(NCI\)](#). NCI mandated clinical trials are listed on the [Clinical Trials Support Unit \(CTSU\) website](#). If the NCI clinical trial will be conducted at the Iowa City VAHCS, the NCI CIRB review process is initiated by contacting the

VA Research Office. Neither the University of Iowa Human Subjects Office nor IRB-03 will be involved in the review of these projects.

### **1.C Are researchers required to complete Human Subjects Protections Certification prior to submitting a research study to the IRB for review?**

All VA investigators conducting human subjects research at the Iowa City Veteran Affairs Health Care System (VAHCS) are required to complete an education program and become "certified" in human subject protections. This educational requirement applies to:

All members of the research team, including the principal investigator and all other individuals (faculty, staff, or student) who have contact or interactions with research subjects or with their private, identifiable information.

The option available for becoming certified is by completing the VAHCS modules of the on-line tutorial called the Collaborative Institutional Training Initiative program (CITI). Instructions can be found on the HSO Website on how to complete CITI training. In addition to completion of all applicable human subjects certification(s), VA credentialing is also required. If credentialing has not been completed, the application will be returned to the VA investigator with instructions that the credentialing must be completed prior to the application moving forward. For more information on credentialing, contact Lori Fisher at VA ext. 637645 or [Lori.Fisher4@va.gov](mailto:Lori.Fisher4@va.gov)

### **1.D Conflict of Interest**

Conflicts of Interest must be disclosed to the Conflict of Interest Officer (COIO). Researchers with questions about conflicts of interest should contact Sommarani Chan in the VA Research Office at [Sommarani.Chan@va.gov](mailto:Sommarani.Chan@va.gov) or 637667 for further information about this process.

### **1.E Assurances and Responsibilities**

#### **1.E.i Principal Investigator**

The Principal Investigator (PI) must sign the assurance document and attach it to the HawkIRB new project application. If the PI changes over the course of an IRB approved research protocol, a new signed assurance document with all applicable signatures will be required via a modification form. This signed page should be attached to the HawkIRB application in the Assurance section on the attachments page of the application prior to initial submission. This page assures that the PI is in compliance with all federal, state, and VA policies as they apply to the study. In signing the final page of the application form, the VA investigator assures that:

- 1) S/he is ultimately responsible for the conduct of the study
- 2) S/he agrees to comply with all applicable VA policies and procedures, and applicable federal, state and local laws
- 3) The application is consistent with proposal(s) submitted to external funding agencies
- 4) The research will only be performed by qualified personnel

- 5) all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions
- 6) S/he will not implement any changes in the approved IRB application, study protocol, or informed consent process without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of a human participant)
- 7) If unavailable to conduct this research personally, as when on developmental leave, or permanently leaves the institution s/he will arrange for another VA investigator to assume direct responsibility for the study
- 8) S/he will obtain Continuing Review approval prior to 12:01AM on the date the approval for the study expires. S/he understands if s/he fails to apply for continuing review, approval for the study will automatically expire. All study activity must cease until IRB approval is granted
- 9) If protected health information is used or created as part of this research project, the research team agrees NOT to reuse or disclose the information to any other person or entity (beyond the named research team) except as required by law, for authorized oversight of the research project, or unless subsequent IRB approval is obtained for such reuse or disclosure.
- 10) If members of the research team access protected health information from a covered component in order to seek consent/authorization for research, such access is necessary for the research, is solely for that purpose, and the information will not be removed from the covered component.
- 11) Neither the principal investigator nor any member of the research team has entered into a financial arrangement with a sponsor of this study whereby the value of the compensation to the principal investigator or any member of the research team for conducting the study could be influenced by the outcome of the study. For further information about Conflict of Interest in Research, see section 4.F “Conflict of Interest”.
- 12) S/he further assures that the proposed research is not currently being conducted and will not begin until IRB approval has been obtained.

The VA investigator is expected to be familiar with the policies contained in 1200.05 VHA Directive and the VA Investigator’s Guide. Additional information on [Principal Investigator oversight and responsibilities](#) can be found on the Human Subjects Office website.

### **1.E.i.a Student PI**

Trainees or students are **not** permitted to be listed as PI on IRB 03 (VA) research applications. The PI for these applications must be conducting the research as a faculty or staff member.

Trainees (e.g., students, residents, or fellows of any profession) may serve as participants, but not PIs within a VA facility, use VA human subjects data, or use human biological specimens that have been collected within VA for clinical, administrative, or research purposes only when: (1) The study has been approved by the local VA medical facility and IRB, if appropriate; and (2) Either they are:

- (a) Enrolled in an institution with an educational affiliation agreement with that VA facility; or
- (b) Directly appointed to a VA training program that has no external institutional sponsorship (e.g. VA Advanced Fellowship). **NOTE:** *A waiver may be obtained from the CRADO under*

*special circumstances. See 1200.05 VHA Directive, Notes under Paragraph 3. Definitions, (t)(3) VA Investigator and 1200.02 VHA Directive, Paragraph 10. Trainee Research.*

### **1.E.iii Department Chair**

The signature of the departmental executive officer (department chair) also is required on the signature page of the New Project Application. If the departmental executive officer is the principal investigator, s/he may sign as both the VA investigator and the DEO. This signature of the DEO is an assurance that the PI:

- 1) Is qualified to conduct the research as described in the application
- 2) Has adequate resources, facilities, and numbers of qualified staff to conduct the research as described in this application
- 3) Has used sound study design consistent with the standards of the VA investigator's area of research
- 4) Has available time to oversee and conduct the project

### **1.E.iv Research Team Members**

Research team members include all VAHCS employees (this includes paid employees, Without Compensation employees, or those on Intergovernmental Personnel Agreements (IPA)) who have direct contact (by phone or in person) with research subjects or access subjects' private identifiable information collected for research purposes. Research team members must have the appropriate experience and expertise to conduct the study. For example, if your project involves medical procedures or interventions, the research team should include a member who is qualified to conduct the procedures.

## **Part 2: HawkIRB Section I Project Introduction**

In Section I of the HawkIRB New Project Application, VA investigators:

- 1) Select the IRB the project will be reviewed by (IRB-03)
- 2) Provide the project title that will also appear on the Consent Document
- 3) Provide an optional short title for the project. If provided, the short title is used in the automated e-mail messages sent from HawkIRB
- 4) Provide an overview of the study
- 5) Provide the research questions, study aims, or hypotheses
- 6) Provide background information for the research and the scientific rationale for the proposed study
- 7) Provide a list of the top 10-20 most relevant literature citations

### **2.A Research Purpose, Aims, & Hypothesis**

The IRB reviews the research purpose, study aims, and hypothesis of each project. This information must be provided in Section I of the HawkIRB application.



## **Part 3: HawkIRB Section II Research Team**

### **3.A CITI Certifications**

For VA research team members, the VA investigator will be asked to provide the person's HawkID and whether or not the individual will be a contact person for the project. If a Hawk ID is not assigned to a VA faculty, staff, or student contact Lori Fisher in the VA research office. If the person has completed human subjects protections training and is entered into the HSO database, his/her certification date will show up automatically in HawkIRB. VA Investigators will not be able to submit their application until all members of the research team have met this requirement. Information about how to obtain the required human subjects protections training can be found on the HSO website. All team members must have a paid, WOC or IPA appointment at the Iowa City VAHCS to be considered VA research team members.

### **3.B VA Team Members**

As part of the New Project Application, VA investigators are asked to list all members of the research team for the project. The HawkIRB application should list all individuals who have contact or interactions with research subjects or their private, identifiable information as research team members.

HawkIRB will reflect a deactivated status if no formal appointment with the Iowa City VAHCS is in place.

### **3.C Non VA Team Members**

The University of Iowa IRB 03 will only provide oversight to research team members who have an affiliation with the Iowa City VAHCS. In some circumstances the VA Research Office may allow a without compensation (WOC) appointment to the Iowa City VAHCS. This will occur at the discretion of the VA Research Office.

### **3.D Status of PI**

Section II of the HawkIRB application asks for the status of the Principal Investigator. The Principal Investigator may be identified in HawkIRB as one of the following:

- 1) Faculty
- 2) Staff
- 3) Other

If “Other” is selected, the Principal Investigator’s status or position within the VAHCS must be provided.

Trainees or students are **not** permitted to be listed as PI on IRB 03 (VA) research applications. The PI for these applications must be conducting the research as a faculty or staff member.

## **Part 4: HawkIRB Section III Funding/Support**

All original sources of funds that will be used to support the study must be listed in Section III of the HawkIRB application. This includes “pass-through” funding, in which the Principal Investigator of the study and identified in the HawkIRB application, is not the Principal Investigator of the funding grant.

### **4.A Federal Funding Sources**

Federal funding sources include all funds received from a federal agency (such as the National Institutes of Health (NIH), Department of Defense (DoD), or the National Science Foundation (NSF)). Federal funding sources include those that are passed through another institution, organization, or individual. VA investigators who are recipients of federal funding are expected to comply with all applicable federal regulations.

#### **4.A.i Just in Time Funding**

“Just in time” funding status refers to the stage in federally funded projects which have received a favorable score and the Principal Investigator has been notified to complete just in time procedures (such as obtaining IRB approval).

#### **4.A.ii Department of Defense Funding**

Department of Defense (DoD) supported research involving human subjects for which the DoD is providing at least some of the resources. Resources may include but are not limited to funding, facilities, equipment, personnel (VA investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by a non-DoD institution.

Research conducted or supported by the DoD, including its separate components (i.e., the Army, Navy, Air Force and Marine Corps), requires compliance with additional federal regulations, directives and instructions. The DoD has adopted 32 CFR 219, a version of the Common Rule that mirrors 45 CFR 46. The Department of Defense Instruction 3216.02 (DoDI 3216.02) establishes policy and assigns responsibilities for protection human subjects in DoD-supported research. The Principal Investigator, IRB and institution involved in DoD research must be knowledgeable about these obligations in order to adhere to them.

#### **4.A.iii National Institutes of Justice Funding**

The National Institute of Justice (NIJ) is the research, development and evaluation agency of the U.S. Department of Justice. To ensure that human subjects are adequately protected in research, NIJ and recipients of its funds are required to comply with Department of Justice regulations at 28 CFR Part 46

#### **4.A.iv National Science Foundation Funding**

The IRB reviews studies funded or supported by the National Science Foundation under the regulations contained in [45 CFR 46 Part 690](#).

#### **4.B Corporate or Industry Funded sources**

VA investigators conducting research supported by corporate or industry sources must list each source in Section III of the HawkIRB application and the Consent Document. Corporate or industry contracts are handled by the Iowa City VA Medical Research Foundation.

#### **4.C Departmental Funding**

VA investigators conducting research supported by funds for their academic departments must indicate the use of departmental funding in Section III of the HawkIRB application.

#### **4.D Department of Veterans Affairs Funding**

The VA Office of Research and Development (ORD) provides funding that aspires to discover knowledge, develop VA researchers and health care leaders, and create innovations that advance health care for our Veterans and the nation. Funding is provided through four main programs: Biomedical, Clinical, Rehabilitation and Health Services Research.

#### **4.E Pass Through Funding**

Pass-through funding is funding in which the Principal Investigator of the study and identified in the HawkIRB application is not the Principal Investigator named on the funding grant.

#### **4.F Conflict of Interest**

HawkIRB question III.4 asks if each team member has a personal significant financial interest in the project according to the VA Conflict of Interest Policy. In this question, indicate if any members of the research team have a financial interest in the study if one or more of the following are true:

- INCOME AND COMPENSATION.

- Do you, your spouse, dependent child or general partner receive income or other compensation (including non Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?
- **BUSINESS RELATIONSHIPS.**
  - Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected by this study?
  - Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?
  - Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?
  - Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?
- **INTELLECTUAL PROPERTY.**
  - With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer:
    - listed as the inventor on an invention disclosure or a patent application;
    - the owner of any intellectual property;
    - the holder of a license of a patent, copyright, software or other intellectual property;
    - entitled to earn royalties now or in the future; v. the author of written materials that are, or are going to be, commercialized; vi. otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR
    - holding any other financial relationship not covered elsewhere?
- **NON-PUBLICLY TRADED COMPANIES.**
  - Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?
- **SPECIFIC TYPES OF FINANCIAL INTERESTS.**
  - Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? Note: This does not include stock controlled through a diversified mutual fund or a blind trust.
  - Sector Mutual Funds: Do you, your spouse, or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by

this study? Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States.

Sommarani Chan in the VA Research Office shall serve as the Conflict of Interest Officer (COIO). Any IRB applications in which a significant financial interest has been disclosed will not undergo IRB review until the COIO has reviewed the financial interest and either determined that no conflict exists, or, the IRB is provided with a management strategy for the conflict of interest.

Researchers with questions about conflicts of interest should contact Sommarani Chan for further information about this process. Contact Sommarani Chan at [Sommarani.Chan@va.gov](mailto:Sommarani.Chan@va.gov) or 637667.

## **Part 5 HawkIRB Section IV Project Type**

### **5.A Regular Review (Expedited, Full Board)**

Question IV.1 of the HawkIRB application requests the Investigator to choose the type of review appropriate to the research. The response to this question is primarily based on the research aims and hypothesis, proposed research related intervention(s), and risk level of the proposed research. The research is categorized as Exempt, Expedited, or greater than minimal risk research. Additionally, some types of funding allow for IRB review when there are no current plans to begin enrolling human subjects under that IRB#. These two review types are Concept and Overall approval.

#### **5.A.i Exempt Approval**

Exempt research is under [45 CFR 46.101](#) under Pre-2018 regulations and [45 CFR 46.104](#) under the current 2018 regulations. Research approved prior to 1/21/19 was approved under six exemption categories. For any research compliant with the 2018 Regulations, there are now eight exemption categories. Six of the categories are applied for University of Iowa human subjects research. The University of Iowa IRBs are not applying exemption category 7 and 8. Exempt research is research conducted posing little to no risk to subjects. For research compliant with the 2018 regulations, reflect application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

- (1) Subpart B. Pregnant Women, Fetuses, and Neonates: Each of the exemptions at this section may be applied to research subject to subpart B if the conditions of the exemption are met.
- (2) Subpart C. Prisoners: The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

- (3) Subpart D. Children: The exemptions (1), (4), (5), and (6), may be applied to research subject to subpart D if the conditions of the exemption are met. Exemptions (d)(2)(i) and (ii) only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Exemption (d)(2)(iii) may not be applied to research subject to subpart D.

Research activities under Exempt must follow the requirements of 1200.05 Paragraph 10 and as specified in the applicable exempt category. Exempt determinations are made by an IRB-03 Chair or designee. An exemption tool has been created to assist in determining if a project is eligible for an exemption. Exempt research activities requiring limited IRB review involving researcher interaction(s) with human subjects, or obtaining information by educational tests, survey or interview procedures, or behavioral interventions, the following information must be included in the exempt information sheet given to the prospective human subject in writing or orally:

- The activity is research.
- Participation is voluntary.
- Permission to participate can be withdrawn.
- Permission for use of data can be withdrawn for exempt research activities involving the collection and use of identifiable data.

#### **Contact information for the VA Researcher**

**5.A.ii Expedited Approval**  
Research activities under Expedited category of review must follow the requirements of 1200.05 Paragraph 11 and as specified under [45CFR46.110](#). The [expedited categories](#) of review remain unchanged from the pre-2018 regulations. Research falling under any expedited category would be considered no more than minimal risk. An IRB Chair or designee determine whether the research meets the expedited criteria based on the review of the IRB application. For any studies under IRB-03 review, a VA approval checklist documenting VA specific finding will be completed, when necessary, by the IRB Chair or their designee prior to final IRB approval.

#### **5.A.iii Greater than Minimal Risk Research**

Studies that do not qualify for Exempt or Expedite review are assigned to review by full board at a convened meeting. All projects involving the use of investigational drugs, devices, or biologics for which an IND/IDE is required receive full board review.

#### **5.A.iv Overall Approval**

Overall approval is limited to an IRB application for a training grant, center grant, or program project grant that involves human subjects. This type of approval allows the Principal Investigator to provide a single IRB approval date to the funding agency for the overall award itself. Overall approval is therefore an administrative tool. It does not indicate approval for any of the specific projects described in the grant.

Overall approval is given via the expedited review procedure. Projects which have received only overall approval may not enroll human subjects. To obtain approval for the individual projects described in the training grant, center grant, or program project grant, the principal investigator of each individual project should submit a New Project Application in HawkIRB for each project that involves human subjects. When completing the application form for each individual project in HawkIRB, the investigator should indicate the funding source as the funding agency that provided the overall award.

### **5.A.v Concept Approval**

Concept approval is limited to an IRB application for a funded project where the funding agency has approved an initial period of time for development of the final protocol, questionnaires, data forms, or similar activities. Since the IRB may not approve "draft" protocols or Informed Consent Documents, concept approval shows that the IRB has approved the study in concept only, so that funds may be awarded for the preliminary work. Concept approval is therefore an administrative tool. It does not indicate approval for the enrollment of human subjects. Human subjects may not be enrolled in a project given Concept approval. Concept approval is given via the expedited review procedure. Refer to the section on submitting modifications to the HawkIRB application to learn more about changing a project from Concept to Regular approval once the investigator is ready to enroll human subjects.

### **5.B ICH-GCP**

This option to receive IRB review in compliance with ICH-GCP requirements may only be selected if the sponsor will not accept contract language that states the VAHCS will “comply with ICH-GCP requirements as adopted by FDA.” The VA investigator should select “Regular review” when the contract contains this language. VA Principal Investigators who select ICH-GCP review are required to sign an additional assurance for adherence to ICH-GCP guidelines.

When following the ICH-GCP (E6) (R2) guideline, the following disclosures are required in the informed consent document:

- The alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks.
- That the monitor, the auditor, the IRB, and the regulatory authority will be granted direct access to the participant’s original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant’s legally acceptable representative is authorizing such access.
- The approval of the IRB.

Documentation of the informed consent process includes the following:

- Prior to a participant’s participation in the trial, the written consent document should be signed and personally dated by the participant or by the participant's legally acceptable representative.

- Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion.
- If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.  
(ICH-GCP (E6R2) definition of Impartial Witness)
- After the written consent document and any other written information to be provided to participants is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document.
- By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that consent was freely given by the participant or the participant's legally acceptable representative.
- Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants.

#### **5.B.i What does this mean?**

Additional standards are required under [full ICH-GCP compliance](#).

#### **5.B.ii Expectations**

When the option for ICH-GCP review is selected, the Principal Investigator is held solely responsible for ensuring all study procedures meet ICH-GCP standards.

#### **5.B.iii Process**

If this option is selected, additional questions will require a response and additional documentation will be requested by HawkIRB in order to collect to documentation necessary to meet ICH-GCP requirements.

#### **5.B.iv CVs included as an attachment**

ICH-GCP requires the IRB review the Principal Investigator's CV. The CV should be attached to the HawkIRB application at the time of submission

### **5.C Waiver of Informed Consent**

Federal regulations ([45 CFR 46.116\(d\)](#) under Pre-2018 regulations and [45 CFR 46.116\(f\)](#) under the current 2018 regulations) allow for the IRB to grant a waiver of consent in some cases. The



IRB may approve an informed consent procedure that does not include, or that alters, some or all of the elements of informed consent. This waiver allows the VA investigator to collect and use data without obtaining the information consent of subjects. Subjects do not provide consent for participation and are not given the opportunity to decide whether or not their information will be used for research purposes. A waiver of consent is approved by the IRB if the VA investigator requests the waiver and provides justification for the use of the waiver in the HawkIRB application. The IRB chair may waive informed consent if research is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

### **5.C.i Waiver of Consent Process for Public Demonstration Projects**

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

- 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
- 4) Possible changes in methods or levels of payment for benefits or services under those programs.
- 5) The research cannot practicably be carried out without the waiver or alteration
- 6) The research is not FDA-regulated

#### **5.C.i.a Waiver of Parental Permission – Public Demonstration Project**

Research requiring this type of waiver is not conducted at the Iowa City VAHCS.

#### **5.C.ii Criteria**

The waiver is commonly granted when there will be no contact with subjects, for example a secondary data analysis or use of data that has already been collected as of the date of the HawkIRB application (such as a retrospective medical record review). Secondary analysis of already aggregated data sets (e.g., meta-analysis) does not require IRB review, since the VA investigator does not obtain individual human subject information.

In order to assist the IRB in making the determination for waiver of consent, the VA investigator should provide the inclusive dates of chart/record information that will be used in the study. In addition to describing the purpose or hypothesis being studied, and the types of analyses that will be done, the VA investigator should provide the IRB a list of specific variables that will be used from the original source. This should be provided in the HawkIRB application by including the data collection forms that will be used for compiling the chart/record data.

### **5.C.iii VAHCS requirements to access CPRS, VISTA, or other national VAHCS-maintained record systems**

VA investigators are required to get approval to access CPRS, VISTA, or another national VAHCS-maintained record system. This is handled when they fill out their paperwork for a VA appointment whether it is a Without Compensation or Paid appointment. VA investigators will need to contact Kyle Rossin the Research Office for this process. Please contact Kyle at [Kyle.Ross@va.gov](mailto:Kyle.Ross@va.gov) or VA ext. 637670.

### **5.D HIPAA**

The Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) provides standards for maintaining the privacy of individually identifiable health information. It applies only to individually identifiable health information that is maintained by a covered entity. If the health information is individually identifiable and if it is held by a covered entity, it is likely to be considered “protected health information.”

All identifiable information collected from researchers is considered individually identifiable information based upon the 18 HIPAA identifiers. If the information is not identifiable, it would still be considered federal records. See 1605.1, Appendix B which explains de-identified data within VA and lists all the HIPAA identifiers.

Protected Health Information (PHI) is health information that:

- 1) is transmitted or maintained in any form (electronic, oral, paper) by a covered entity
- 2) identifies the individual or could reasonably be used to identify the individual
- 3) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

#### **5.D.i Privacy Board Responsibilities**

The IRB Memorandum of Understanding between the University of Iowa and Iowa City VAHCS sets forth the responsibilities of IRB-03 in serving as the IRB of record and performing limited Privacy Board services for VAHCS-conducted research involving human subjects IRB-03 will provide limited Privacy Board services to carry out the covered entity’s HIPAA obligations for waivers or alterations of authorization (documentation that an alteration to or waiver, in whole or in part, of the HIPAA authorization requirement has been approved by either a duly established Privacy Board or IRB) in the course of its regular IRB review of VAHCS studies.

#### **5.D.ii HIPAA Identifiers**

Any of the following information for the individual, relative, employer, or household member of the individual are examples of the 18 HIPAA identifiers:

- 1) Names

- 2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
- 3) The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people
- 4) The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000
- 5) 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 over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
- 6) Telephone numbers
- 7) Facsimile numbers
- 8) Electronic mail addresses
- 9) Social security numbers
- 10) Medical record numbers
- 11) Health plan beneficiary numbers
- 12) Account numbers
- 13) Certificate/license numbers
- 14) Vehicle identifiers and serial numbers, including license plate numbers
- 15) Device identifiers and serial numbers
- 16) Web universal resource locators (URLs)
- 17) Internet protocol (IP) addresses numbers
- 18) Biometric identifiers, including fingerprints and voiceprints
- 19) Full-face photographic images and any comparable images
- 20) Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification

## **5.E Full Waiver of Authorization**

Federal regulations permit the use of Protected Health Information (PHI) for research under two conditions:

- 1) the VA investigator obtains a signed authorization from the patient, or
- 2) the VA investigator obtains a waiver of authorization from the IRB

A waiver of HIPAA authorization is a regulatory determination that is made by the board. Federal regulations allow the IRB of a covered entity to waive in full or in part the individual authorization required by HIPAA for use and disclosure of PHI for research purposes. The VAHCS includes the authorization required by HIPAA for use and disclosure of PHI for research purposes as part of the informed consent document.

The waiver of authorization to use PHI for research purposes is different from the waiver of elements of consent allowed under Department of Health and Human Services (DHHS)

regulations at 45 CFR 46. Similar to the DHHS waiver however, the waiver of authorization to use PHI for research must be approved by the IRB.

An example of research that might be eligible for a waiver of HIPAA authorization includes retrospective chart reviews. The New Project Application in HawkIRB includes questions to help the IRB decide whether or not the regulatory criteria for a waiver have been met for a given research project.

These criteria include:

- 1) The research could not practicably be conducted without the waiver AND
- 2) The research could not practicably be conducted without access to and use of the PHI.
- 3) The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
- 4) The PI has an adequate plan to protect identifiers from improper use/disclosure
- 5) The PI has an adequate plan to destroy identifiers at the earliest opportunity
- 6) The PI gives adequate written assurance that the PHI will not be disclosed to others.

VA investigators or members of the research team may look at, use, or create PHI in the following situations:

- 1) Look at a clinic schedule, a medical chart, or an electronic record, to schedule subjects for a study visit or identify a diagnosis for subjects
- 2) Conduct research with an inpatient population
- 3) Conduct medical testing
- 4) Conduct research on a Research Unit (i.e CADRE (Health Services Research), Vision Center)
- 5) Conduct a retrospective or prospective chart review
- 6) Create or add information to an in-house database or registry for research use
- 7) Provide treatment through a research protocol
- 8) Collect medical records from an outside institution
- 9) Look at or use data from a Quality Assurances/Quality Improvement (QA/QI) database
- 10) Compare information collected on a survey to information in the medical record

For more information about the HIPAA Privacy Rule, review the HIPAA page on the HSO website or the following links:

- 1) HIPAA Privacy Rule Office of Civil Rights
- 2) NIH Information for Researchers on the HIPAA Privacy Rule
- 3) Privacy Rule Complete Regulation (45 CFR 160 and 164)
- 4) Privacy Rule Summary
- 5) Privacy and Release of Information (VHA Handbook 1605.1)
- 6) Notice of Privacy Practices (VHA Handbook 1605.04)

For more information, refer to the section on the Partial Waiver in Section VII.D.

### **5.E.i Partial Waiver of HIPAA Authorization and Waiver of Informed Consent - Section VII.D.**

The HIPAA regulations apply to patient/clinic records from the VAHCS. The HIPAA regulations require authorization from the individual to access his/her medical records. VA investigators may request a Partial Waiver of HIPAA Authorization for use of medical or protected health information for recruitment purposes for research. This includes diagnostic and other information that would be used to determine eligibility for a study. With proper justification, the IRB can grant this waiver for limited use of specified medical information for the purposes of identifying potential subjects for a research study. This request and justification for a partial HIPAA waiver must be completed in section VII.D.1-7 of the Hawk IRB application.

### **5.E.ii Screening, recruiting, or determining eligibility prior to a signed informed consent document**

The researcher will not be required to formally request a waiver of informed consent in the HawkIRB application for the purpose of screening, recruiting, or determining eligibility prior to a signed informed consent.

### **5.F Letter of Agreement granting permission to access data**

VA investigators planning to use a restricted data set need to obtain documented permission. The IRB requires documentation of approval to access and use the data from the owner. This permission should be provided in a letter on letterhead or an e-mail signed by an individual with authorization to grant permission for the use of the data for research purposes.

### **5.F.i Ownership of data/medical record system to be accessed**

If collaborating with an outside agency, company or clinic and that non-VA entity is giving the VA investigator access to its clients, files, or premises, a letter of agreement from that agency will need to be attached to the HawkIRB application. This letter should confirm knowledge of the project's purpose and permission for the VA investigator to conduct the study there.

### **5.F.ii Who can provide authorization**

Authorization for access to and use of data for research purposes must be provided by the owner or administrator of the data set or medical record system. Authorization should be documented in a letter on letterhead or an e-mail and signed by an individual who has the authority to grant the permission.

For VA researchers the approval to access CPRS, VISTA, or another national VAHCS-maintained record system is obtained through Kyle Rossin the Research Office. Please contact Kyle at [Kyle.Ross@va.gov](mailto:Kyle.Ross@va.gov) or VA ext. 637670.

## **Part 6: HawkIRB Section V Other HRPP Committee Review**

Section V of the HawkIRB application asks the VA investigator to provide information on ‘Other Committee Reviews’ required for IRB approval. This includes the VA Pharmacy and Therapeutics Committee, Medical Radiation Protection Committee, and Institutional Biosafety Committee review. See also section II for further information on interactions with other HRPP committees.

### **6.A: VAHCS Pharmacy and Therapeutics Investigational Drug Service**

VAHCS Pharmacy and Therapeutics must review a research protocol if it involves the administration of off-label investigational new drugs or drugs. Additionally, if a study involves Food and Drug Administration-approved drugs that are given as a component of a research protocol or any other substance that is ingested, injected, or applied to the body, the study must be reviewed by VAHCS Pharmacy and Therapeutics. Hawk IRB questions V.1-8 address the use of any substance ingested, injected, or applied to the body in a project. It is not a requirement that an investigator have VAHCS Pharmacy and Therapeutics approval prior to IRB review.

### **6.B: VAHCS Research Radiation Review**

VAHCS research radiation review will be conducted by Laura Scholl. This will occur through an agreement with the University of Iowa, Laura Scholl is the VA Radiation Safety Officer. Hawk IRB questions V.9-19 address the use of radiation in a project. Specific information about this process is located on the HSO website at: <http://ehs.research.uiowa.edu/vamc-safety-information-and-training>

Contact Laura Scholl with questions at x6805 or [laura.scholl@va.gov](mailto:laura.scholl@va.gov).

### **6.C: Institutional Biosafety Committee (IBC) Review**

VAHCS Institutional Biosafety Committee (IBC) review will be conducted through the UI IBC. This committee is responsible for ensuring that recombinant DNA (rDNA) activities comply with the National Institutes of Health (NIH) Guidelines. Projects involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules must answer YES to question V.20 in the Hawk IRB application. This will trigger IBC review. The IBC will review IRB-03 using the same process as IRB-01. A description of the [IBC application process](#) is located on the HSO website.

## **Part 7: HawkIRB Section VI Subject Enrollment**

Section VI of the HawkIRB application asks the VA investigator to provide the number of adult and minor subjects that will be enrolled in the study. The number provided in the response is the

maximum number of subject that can be enrolled without submitting a modification to increase the enrollment number. This number cannot be exceeded without prior IRB approval for an increase in the approved number of subjects. VA investigators should consider the potential for screening failures or dropouts and be sure to request an appropriate number of subjects.

## **7.A Who is a Subject?**

2018 DHHS regulations (45 CFR 46.102(e)) and VA Directive 1200.05 (3)(m) define a human subject as a living individual about whom a VA investigator (whether professional or student) conducting research obtains either:

- (i) information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

FDA regulations (21 CFR 50.3(g)) define a human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. For research involving medical devices, a human subject is also an individual on whose specimen an investigational device is used.

Since the definition of a human subject is a "living" individual, research which involves only autopsy materials, cadavers or death records is not considered human subjects research and is not reviewed by the IRB.

Intervention (45 CFR 46.102(f) and VA Directive 1200.05 (3)(s)) includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

An example of an intervention occurring in the conduct of biomedical research includes randomly providing pamphlets to some patient-subjects that provide tips for sticking to medication regimens while not providing that information to a set of other patient-subjects with the intent of testing the effectiveness of such a program on increasing compliance with medication schedules. This type of project involves human subjects because there is an intervention (handing out educational pamphlets) with living individuals.

An example of an intervention occurring in the conduct of social/behavioral research includes administering a paper-and-pencil survey to a group of elementary school student-subjects before and after the research investigator teaches a novel lesson to analyze their ideas and beliefs on a particular topic. This type of project involves human subjects because there is an intervention (a lesson plan the children would not otherwise receive) with living individuals.

Interactions (45 CFR 46.102(f) and VA Directive 1200.05 (3)(r)) include communication or interpersonal contact between a VA investigator and subject.

An example of an interaction with a human subject occurring in the conduct of biomedical research includes a blood draw or finger stick for research purposes. In this case, there is an interaction with a living individual that is being done outside of the realm of regular patient care.

An example of an interaction with a human subject occurring in the conduct of social/behavioral research includes administering surveys, conducting interviews or focus groups for research purposes. In this case, there is an interaction with a living individual that is being done to collect private information.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical record information).

Identifiable private information must be individually identifiable (i.e. the identity of the subject is or may readily be ascertained (easily discovered) by the VA investigator or associated with the private information) in order for obtaining the information to constitute research involving human subjects.

Obtaining a person's identifiable private information means receiving or accessing identifiable private information or identifiable specimens for research purposes. "Obtain" includes a VA investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the VA investigator. In general, private information or specimens are individually identifiable when they can be linked to specific individuals by the VA investigator(s) either directly or indirectly through coding systems.

"Coded" means that:

identifying information (such as name or social security number) that would enable the VA investigators to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (i.e., the code); AND a key to decipher the code exists, linking the identifying information to the private information or specimens

## **7.B Subject Enrollment Requirements**

An enrolled subject is anyone who has signed an Informed Consent Document, whether or not that individual actually completes the study. Thus, someone who signs a consent document but is determined during screening to be ineligible, or chooses not to continue, must still be counted as an enrolled subject. For studies granted a waiver of documentation of consent, a subject is considered enrolled when they have returned information to the research team or have indicated agreement to participate.



### **7.B.i Inclusion Criteria**

All inclusion criteria for each subject population must be described in Section VI of the HawkIRB application. Potential subjects must also be told why they are being asked to participate in the study in the Informed Consent Document.

For all IRB-03 studies enrolling non veterans as a study population, the Principal Investigator must present a compelling argument to the IRB in Section VI for the inclusion of non-Veterans. This justification is reviewed by the VA Research and Development (VA R&D) committee. The justification should provide a detailed compelling argument for consideration by the VA R&D to fulfill regulatory requirements under 38 CFR17.45 and 38 CFR17.92. Reasons may include, but are not limited to, examples such as insufficient number of Veterans; survey of VA employees; study of active duty military; or study involving Veterans' family members, and the research is relevant to the care of Veterans or active duty military personnel. A detailed rationale must also accompany the reason to ensure appropriate VA approvals can be secured.

### **7.B.ii Exclusion Criteria**

All exclusion criteria for each subject population must be described in Section VI of the HawkIRB application. Exclusion criteria which may endanger subject health or safety should also be clearly described in the Informed Consent Document.

### **7.C Vulnerable Population(s) Considerations**

Federal regulations involving human subjects in research include specific protections for children, pregnant women and fetuses, and prisoners. The IRB expects the VA investigator to provide additional information regarding cognitively impaired individuals in research as well as indicate in the application any other populations that the VA investigator might consider to be particularly vulnerable in a research setting. Examples of these additional types of vulnerable populations include those persons who are educationally or economically disadvantaged, students, or other groups that may require special consideration.

The IRB considers certain groups of human subjects to be particularly vulnerable in a research setting. The IRB considers additional protections for research activities involving prisoners, children, and persons with impaired decision-making capacity. The IRB may also consider additional protections for those who are educationally or economically disadvantaged, students, or other groups that require special consideration. In reviewing these research projects, the IRB ascertains that the inclusion of the vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to each population.

Requests for approval of federally funded research that exposes children to risks that do not meet one of the above criteria must be submitted to the United States Secretary of Health and Human Services for review and approval. Determinations of approval by the IRB of federally funded research involving prisoners are reported to the DHHS Office of Human Research Protections

(OHRP). Requests for approval for a clinical investigation under FDA oversight that exposes children to risks that do not meet one of the above criteria must be submitted to the Commissioner of Food and Drugs for review and approval. The IRB must have present at its meeting a designated prisoner advocate in order to review projects involving the use of prisoners in research. The Chair or his/her IRB member designee may approve new studies limited to retrospective review of prisoners' records and minor modifications using expedited review procedures after review and comment by the prisoner advocate.

#### **7.C.i Subjects lacking decision making capacity**

Individuals who lack decision-making capacity may be enrolled in VA research where:

(1) The IRB determines that the proposed research entails: (a) No greater than minimal risk to the subject; or  
(b) Presents a greater probability of direct benefit to the subject than harm to the subject; or  
(c) Greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

(2) In addition to satisfying the conditions above, the IRB determines that: (a) The research cannot be performed solely with persons who possess decision-making capacity and the focus of the research is the disorder leading to the subjects' lack of decision-making capacity, whether or not the lack of decision-making itself is being evaluated (e.g., an individual who lacks decision-making capacity as the result of a stroke can participate in a study of cardiovascular effects of a stroke); **or**

(b) The subject of the research is not directly related to the subjects' lack of decision-making capacity but the VA investigator has presented a compelling argument for including such subjects (e.g., transmission of methicillin-resistant staphylococcus aureus infections in a nursing home where both individuals with and without decision-making capacity are affected).

#### **7.C.iii Surrogate consent**

When the potential subject is determined to lack decision-making capacity, investigators must obtain consent from the LAR of the subject (i.e., surrogate consent). **NOTE:** *Investigators and IRBs have a responsibility to consult with the Office of General Counsel (OGC) regarding state or local requirements for surrogate consent for research that may supersede VA requirements.*

#### **7.C.iv Authorized Person**

The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority in accordance with VA regulations at 38 CFR 17.32(e), (g)(3). **NOTE:** *Consent for research is required in addition to the consent that is obtained for the patient's non-research related treatments and procedures.* (1) Health care agent (i.e., an individual named by the subject in a Durable Power of Attorney for Health Care);  
(2) Legal guardian or special guardian;

(3) Next of kin: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or

**NOTE:** *The persons authorized to consent on behalf of persons who lack decision-making capacity for participation in the research may not necessarily be the same as the persons authorized to provide permission for the use and disclosure of information on a HIPAA authorization on behalf of persons who lack decision-making capacity (see VHA Handbook 1605.1).*

#### **7.C.v Dissent or Assent**

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

#### **7.C.vi Responsibilities of LAR's**

LARs are acting on behalf of the potential subjects, therefore:

- (1) LARs must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision.
- (2) If the potential subjects' wishes cannot be determined, the LARs must be told they are responsible for determining what is in the subjects' best interest.

For VA studies, in order for IRB-03 to approve research involving persons with impaired decision-making capacity, IRB-03 finds and documents in the minutes or IRB records the following:

- 1) Only incompetent persons or persons with impaired decision making capacity are suitable as participants.
- 2) Competent persons are not suitable for the proposed research.
- 3) The VA investigator has demonstrated to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as participants.
- 4) Incompetent persons or persons with impaired decision-making capacity are not being proposed as participants simply because they are readily available.
- 5) The research does not impose a risk of injury, unless that research is intended to benefit that participant and the probability of benefit is greater than the probability of harm.
- 6) Procedures have been devised to ensure that legally authorized representatives are well informed regarding their roles and obligations to protect incompetent participants or persons with impaired decision making capacity.
- 7) Legally authorized representatives will be told that their obligation is to try to determine what the prospective participant would do if competent, or if the prospective participant's wishes cannot be determined, what they think is in the incompetent person's best interest.

For VA studies, in order for IRB-03 to approve research involving adults unable to consent, VA investigators must obtain consent from the LAR of the subject (i.e., surrogate consent).

- 1) Consent by a legally authorized representative must be limited to situations where the prospective subject is incompetent or has impaired decision-making capacity as determined and documented in the person's medical record in a signed and dated progress note.
- 2) The determination that a participant is incompetent or has an impaired decision-making capacity has to be made by a legal determination or a determination by the practitioner, in consultation with the chief of service, after appropriate medical evaluation indicates that the prospective subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

The following restrictions also apply to VA studies (IRB-03) with respect to vulnerable populations:

- 1) Research involving fetuses in which the focus is either a fetus, or human fetal tissue, in-utero or ex-utero (or uses human fetal tissue), can be approved and require VA Medical Facility Director certification. (VHA Directive 1200.05, Paragraph 19)
- 2) Research involving in vitro fertilization can be approved and require VA Medical Facility Director certification. (VHA Directive 1200.05, Paragraph 19)
- 3) Research involving prisoners as subjects cannot be approved unless a waiver has been granted by the Chief Research and Development Officer (CRADO). (VHA Directive 1200.05, Paragraph 20)

Research involving children as subjects cannot be approved unless:

- 1) The VA medical facility Director must approve participation in the proposed research.
- 2) The study presents no greater than minimal risk.
- 3) The study meets all requirements of Subpart D of the DHHS or FDA regulations.
- 4) The Medical Center Director certifies that the facility is able to respond to pediatric emergencies.
- 5) If a contractor or a non-VA employee conducts the research, the individual or entity performing the research has appropriate liability insurance.
- 4) The IRB must have the appropriate expertise to evaluate any VA research involving children. (VHA Directive 1200.05, Paragraph 21)

Research involving pregnant women as subjects cannot be approved unless:

- 1) All of the requirements of 45 CFR 46.204 are met including informed consent requirements and the following ethical and scientific criteria:
  - a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have

- been conducted and provide data for assessing potential risks to pregnant women and fetuses;
- b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus. If there is no such prospect of benefit, then the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means;
- c. Any risk is the least possible for achieving the objectives of the research; and
- 5) The VA medical facility Director certifies that the medical facility has sufficient expertise in women's health to conduct the proposed research. (VHA Directive 1200.05, Paragraph 19)
- 2) The research includes adequate provisions to monitor the risks to the subject and the fetus
- 3) Adequate consideration is given to the manner in which prospective subjects are going to be selected.
- 4) Adequate provision is made to monitor the actual consent process by procedures such as:
  - a. Overseeing the process by which individual consents are secured either by:
  - b. Approving enrollment of each individual.
  - c. Verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity were being followed
  - d. Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

Where relevant, the IRB must document why it considers an individual or population to be vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of participants who are likely to be vulnerable.

Individuals or populations that might be temporarily or permanently vulnerable include, but are not limited to, those who:

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

For adults unable to consent:

When researchers are likely to approach adults who lack decision-making capacity, the IRB evaluates whether:

- 1) The proposed plan for the assessment of the capacity to consent is adequate
- 2) Assent of the participants is a requirement, and if so, whether the plan for assent is adequate
- 3) A re-consenting process might be necessary for participants with fluctuating decision-making capacity or those with decreasing capacity to give consent.

## **7.D Children**

By regulatory definition, a child is a person who has 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)). By FDA definition, a child is a person who has not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. For purposes of research conducted in the state of Iowa, the term “child” as used in both the DHHS and FDA definitions is analogous to “minor” under Iowa Code and is viewed as “an unmarried person under the age of eighteen years.” (Iowa Code 600A.2(13))

In cases of human subjects research under the authority of the VA IRB but conducted outside of the state of Iowa, the IRB confers with VA attorneys regarding the applicability of other state, national, or international laws to the particular project. In general, the IRB will apply the law of the state in which the research is being conducted. For example, if a project involves children and one of the recruitment sites is in a bordering state, the laws of the bordering state will be evaluated to which individuals meet the DHHS and FDA definition of “children” at that site.

Federal regulations permit IRBs to approve a research project involving children after determining which of the following categories applies, and only if the project satisfies all of the conditions in the applicable category (45 CFR 46, Subpart D (DHHS) and 21 CFR 50 Subpart D (FDA)):

- 1) Research that does not involve greater than minimal risk may be approved if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. The IRB may determine that permission of one parent or guardian is sufficient.
- 2) Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject, or a monitoring procedure that is likely to contribute to the subject's well-being, may be approved if the IRB finds that:
  - a. the risk is justified by the anticipated benefit to the subject;
  - b. the relationship of anticipated benefit to risk is at least as favorable as that presented by available alternative approaches; and
  - c. adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
- 3) Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, may be approved if the IRB finds that:

- a. the risk represents a minor increase over minimal risk;
  - b. the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
  - c. the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and
  - d. adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.
- 4) Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved if the IRB and the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, find that:
- a. the research satisfies one of the above three conditions; or
  - b. the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
  - c. the research will be conducted in accordance with sound ethical principles; and adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

In compliance with federal regulations, the IRB must determine that permission of both parents is required, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

Federal regulations (45 CFR 46.409(b)) also indicate that children who are wards of the state, or any other agency, institution, or entity can only be included in research in this category if the research is related to their status as wards or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If one of these criteria is met and the research is approved, the IRB must require appointment of an advocate for each child who is a ward in addition to the person acting as guardian or in loco parentis. One person may serve as the advocate for multiple wards, however this advocate must have the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and cannot be associated in any way (except as advocate or member of the IRB) with the research, the VA investigator(s), or the guardian organization.

Research involving children is only permitted at the VA with the approval of the VA Medical Facility Director . This approval must be attached to any research proposals at the VA which propose to involve children. The research participation of children must be no greater than minimal risk.

## **7.E Pregnant Women, Human Fetuses and Neonates**

Federal regulations direct that IRBs require additional safeguards before approving research involving fetuses, pregnant women, or neonates (45 CFR 46, Subpart B).

The IRB may approve research involving pregnant women or fetuses if all of the following conditions are met:

- 1) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
- 2) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means;
- 3) Any risk is the least possible for achieving the objectives of the research;  
If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the woman's consent is obtained OR
- 4) If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
- 5) Each individual providing consent under (d) or (e) is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- 6) For children who are pregnant, assent and permission are obtained in accord with the regulations for children in research (45 CFR 46, Subpart D);
- 7) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- 8) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- 9) Individuals engaged in the research will have no part in determining the viability of the neonate.

When a child is screened in a study or participating in study procedures that require a pregnancy test be administered, additional consent and assent information must be provided in the Informed Consent Document. The IRB has determined that children in research must be afforded the same rights they would normally have in a clinical setting with regard to the privacy of results from pregnancy testing.

Any child or adult who may be brought in or reports to Iowa City VA Health Care System or outpatient clinic site, and abuse is suspected, will receive a prompt examination and evaluation on a humanitarian basis if not entitled to VA medical care. Any health care worker who examines, attends, counsels, or treats a child or dependent adult and suspects abuse or neglect



has occurred must contact the Privacy Officer prior to contacting the appropriate reporting state agency.

Research involving women known to be pregnant is only permitted at the VA with the approval of the Facilities Director. This approval must be attached to any research proposals at the VA which propose to involve women known to be pregnant.

VA investigators can conduct interventions in research that enroll neonates while on official duty, or at VA facilities, or at VA-approved off-site facilities and require VA Medical Facility Director certification. Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted. (VHA Directive 1200.05, Paragraph 19)

### **7.I Non-English speaking Subjects**

A VA investigator should use the Short Form when s/he unexpectedly encounters a non-English speaking, potential research participant but has not had the IRB-approved Informed Consent Document (ICD) translated into a language understandable to the individual. A short form written consent document stating that the elements of informed consent shall be presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said in the oral presentation to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form. **NOTE:** *The IRB cannot waive the requirement for a witness or witness signature when the short form consent is used.* [VHA Directive 1200.05, Paragraph 18 (2)] See the Short Form Consent policy outlined on the HSO Website.

### **7. J Students in Research**

The informed consent process is not an exercise in persuasion. If a VA investigator has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive due to the special relationship between parties. Refer to the section 11.D Coercion and Undue Influence.

### **7.K Students as Subjects**

Consistent with an overall concern that no research subject should be coerced, researchers should take particular precautions to avoid the unintentional or subliminal coercion that may occur when a potential research subject is also a student. For this reason, researchers should avoid using their own students as research subjects. Researchers who wish to use their own students should be able to provide a good scientific reason, rather than convenience, for selecting those students as research subjects. The research project should be relevant to the topic of the class, and participation should be part of the learning experience for the students.

In instances where VA investigators can provide a good reason for using their own students in their research, the IRB generally requires that someone other than the VA investigator (instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor whether or not a student participated in the research project until after final grades have been determined. The students should be informed of what these procedures are in the Informed Consent Document.

#### **7.K.i Departmental Subject Pools**

Some departments or colleges employ "subject pools" where students enrolled in introductory courses are recruited by VA investigators from both within and outside of the department for participation in research projects. Departments or colleges may impose their own standards for the type of research that may be conducted in this setting, and for who may have access to such subjects. VA investigators who recruit from "subject pools" are still required to submit their projects to the IRB for review and approval. Beyond the considerations outlined above, academic units may impose their own additional constraints on using students as research subjects.

#### **7.L VA Staff or research team members as subjects**

Potential subjects must be able to decide whether or not to participate in a study free from coercion or undue influence. Individuals who are subordinates of the PI or a research team member may not feel entirely free to decline or refuse participation because of their relationship with the PI or research team member. The recruitment of VA staff as research subjects should be undertaken with caution. It is important that supervisors in research settings refrain from recruiting or enrolling their own employees and staff to participate in their research. There can be inherent coercion in these situations and so should be avoided.

There are limited instances when it may be appropriate to enroll persons who are subordinates of the PI or research team member. These are primarily treatment studies for which the exclusion of these persons might restrict them from receiving medical treatments that would otherwise be unavailable to them.

In other cases it may be acceptable to enroll subordinates of the PI or a research team member if someone other than the supervisor conducts the recruitment and consent processes and/or if the supervisor is blinded to whether or not the subordinate participates in the study. The enrollment of subordinates should be approved by the IRB and precautions should be described in the HawkIRB application.

#### **7.M Cognitively Impaired Persons**

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur at times of great stress. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be

decisionally impaired. Some research questions may be answered only by research that involves persons with impaired decision making capacity; precluding this research would contribute to needless suffering. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. While this area is controversial, limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual participant but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non-therapeutic approaches may benefit subsequent generations.

While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population. Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired.

### **7.M.i Surrogate consent**

When the potential subject is determined to lack decision-making capacity, VA investigators must obtain consent from the LAR of the subject (i.e., surrogate consent). **NOTE:** *Investigators and IRBs have a responsibility to consult with VA attorneys regarding state or local requirements for surrogate consent for research that may supersede VA requirements.*

### **7.M.ii Authorized Person**

The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority in accordance with VA regulations at 38 CFR 17.32(e), (g)(3). **NOTE:** *Consent for research is required in addition to the consent that is obtained for the patient's non-research related treatments and procedures.*

- (1) Health care agent (i.e., an individual named by the subject in a Durable Power of Attorney for Health Care);
- (2) Legal guardian or special guardian;
- (3) Next of kin: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or

**NOTE:** *The persons authorized to consent on behalf of persons who lack decision-making capacity for participation in the research may not necessarily be the same as the persons authorized to provide permission for the use and disclosure of information on a HIPAA authorization on behalf of persons who lack decision-making capacity (see VHA Handbook 1605.1).*

### **7.M.iii Responsibilities of LARs**

LARs are acting on behalf of the potential subjects, therefore:

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

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

The IRB will consider the following to ensure the protection of the rights and welfare of research subjects who, due to impairments in their capacity to give informed consent, may be vulnerable to coercion or undue influence:

#### **7.M.iv Conflicting Roles and Potential Conflicts of Interest**

Potential and actual research participants, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic and possibly creating confusion among participants and their families. It is essential that the consent process (including consent documents) clearly indicate differences both between individualized treatment and research and between clinician and clinical VA investigator.

#### **7.M.v Assessing Capacity to Consent**

Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. A key factor in participants' decision making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision making capacity covers a broad spectrum. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

The IRB and clinical VA investigators must keep in mind that decision making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may require an outside witness to observe the consent process.

Because no generally accepted criteria for determining competence to consent to research exists for persons whose mental status is uncertain or fluctuating, the role of the IRB in assessing the criteria proposed by the VA investigator is of major importance. The selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without clear guidance from statutes, case law, or regulations.

VA investigators may use a questionnaire to assess an individual's capacity to provide consent. The HSO offers one option, Evaluation to Sign an Informed Consent Document for Research, on the HSO website.

### **7.M.vi Comprehension**

When planning to enter subjects with impaired decision-making capacity, VA investigators must address in the protocol how they will determine when surrogate consent (i.e., a LAR) will be required. In general, the research staff must perform or obtain and document a clinical assessment of decision-making capacity for any subject suspected of lacking decision-making capacity. However, the IRB must review and approve the plan to ensure that it is appropriate given the population and setting of the research. NOTE: Individuals ruled incompetent by a court of law are considered to lack decision-making capacity.

### **7.M.vii Voluntary Agreement**

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

### **7.M.viii Second Signature on the Consent Document**

There are many situations in which a subject should be encouraged to authorize the involvement of family members. However, the permission of another party will be required only when the subject is determined to lack the legal ability to provide an informed consent. This would include children (when research is conducted in the state of Iowa, unmarried persons under the age of 18) and persons legally determined incompetent. This also includes persons who are not capable of understanding the nature of their illness or the risks, benefits, and natural consequences of participation.

Varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be highly advisable in certain circumstances. However, treating all individuals who have cognitive deficits as incapable of understanding research is inaccurate and disrespectful of their autonomy. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

### **7.M.IX Non Therapeutic Clinical Trials following full ICH-GCP (E6)(R2)**

When following full ICH-GCP (E6) (R2) guidelines when enrolling adults who are unable to consent, the IRB requires:

- Non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written consent document.

- Non-therapeutic clinical trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
  - The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally.
- The foreseeable risks to the participants are low.
- The negative impact on the participant's wellbeing is minimized and low.
- The clinical trial is not prohibited by law.
- The opinion of the IRB is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

## **7.N Prisoners**

Research involving prisoners cannot be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities unless a waiver has been granted by the CRADO. Contact Mark Yorek, Associate Chief of Staff for Research, at [Mark.Yorek@va.gov](mailto:Mark.Yorek@va.gov) or 637696 if interested in pursuing a waiver.

If such a waiver is granted, the research must comply with the requirements of 45 CFR 46.301 - 46.306. (VHA Directive 1200.05, Paragraph 20)

Any project that recruits prisoners must be reviewed at a full IRB meeting with a prisoner advocate present. If the project has not already secured approval to enroll prisoners, then the VA investigator may not enroll a prisoner

Federal regulations pertaining to prisoners also apply for a subject who at a later date becomes a prisoner, because it is unlikely that the IRB review of the research project contemplated the constraints imposed by incarceration. Therefore, if a VA investigator determines that a subject has become a prisoner at some later date after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or a modification application must be submitted requesting review for inclusion of prisoners as subjects, and a waiver from CRADO must be secured.

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find that:

- 1) The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);
- 2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

- 3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
- 4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- 5) The information is presented in language which is understandable to the subject population;
- 6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- 7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Four categories of research involving prisoners are permitted under the federal regulations:

- 1) Studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- 2) Studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- 3) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere); and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults; or
- 4) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

The Informed Consent Document must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on the duration of incarceration or terms of parole. For the review of research involving prisoners, a majority of the IRB members (exclusive of prisoner members) has no association with the prison involved, apart from their membership on the IRB.

## **7.O Veterans diagnosed with PTSD**

The Secretary of Veterans Affairs charged a Work Group in October 2008 to provide consensus recommendations to the under Secretary for Health (USH) for the following questions:

1. Is it ever ethically permissible for the Veteran's Health Administration (VHA) to support the conduct of research on veterans with PTSD?
2. Are veterans with a diagnosis of PTSD considered "vulnerable" for the purpose of applying guidelines for the protection of human subjects in research?
3. Should veterans with a diagnosis of PTSD be afforded special consideration and/or extra protections under VHA guidance to protect human subjects in research?
  - a. If yes, what criteria would trigger the application of special consideration and/or extra protections?
  - b. If yes, what special consideration and/or extra protections should be afforded, and what mechanism would be used to implement them?

The Work Group agreed to the following recommendations:

1. It is not only ethically permissible for VHA to support the conduct of research involving veterans with PTSD but VHA has an ethical obligation to do so.
2. As a group, veterans with PTSD are not categorically vulnerable and, therefore, do not require special protections in the form of new regulations, policy or guidance. Under current Federal regulations and VA policy, Institutional Review Boards (IRB) are directed to scrutinize individual protocols to determine whether potential participants may have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. None of these factors applies categorically to veterans with PTSD; however, one or more of these factors might apply to certain veterans with PTSD who are involved in a particular research study. If an IRB determines that this is the case with respect to a particular research study, the IRB should give special consideration to protecting the welfare of those veterans with PTSD who are involved, and consider whether special safeguards are needed to protect them, just as they would for any other study population.
3. Veterans with a diagnosis of PTSD should be afforded special consideration consistent with current regulation and policy if and when an IRB determines that these veterans have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. Because veterans with a diagnosis of PTSD are not categorically vulnerable, no extra protections in the form of additional regulation or policy are needed for this group beyond what is already specified for all participants in research. (Report of a Work Group Convened by the National Center for Ethics in Health Care of the Veterans Health Administration on Behalf of the Secretary of Veterans Affairs October 2008)

Any VAHCS study that involves PTSD undergoes additional review to ensure all safety measures are met for this population. The IRB-03 Supplemental Primary Reviewer Checklist is completed by the Primary Reviewer in the Full Board review of the research protocol. It includes the following information which must be satisfied by the VA investigator. The primary reviewer and the IRB review the research protocol and determine whether the protocol satisfies the following criteria.



1. Any study that involves PTSD will undergo additional review to ensure all safety measures are met for this population. This document will be completed as a supplemental to the Primary Reviewer Checklist and the IRB-03 VA Supplemental Primary Reviewer Checklist in the Full Board review of the research protocol.
  - a. The protocol must reflect consideration of the perspectives of individuals with PTSD and of providers experienced with PTSD. Specifically, does the study evidence adequate sensitivity to needs of individuals with PTSD? Specifically,
    - i. If so, please explain.
    - ii. If not, how should the study be modified?
  - b. The study's design and implementation must incorporate appropriate consideration of relevant FDA or Sponsor advisories, alerts, and warnings. Specifically,
    - i. If so, please explain.
    - ii. If not, how should the study be modified?
  - c. Subjects must have been appropriately notified regarding such advisories, alerts, and warnings. Specifically,
    - i. If so, please explain.
    - ii. If not, how should the study be modified?
  - d. The risks associated with all study drugs must have been adequately evaluated relative to possible interactions with medications likely to be used by the persons in the study population. Specifically,
    - i. If so, please explain.
    - ii. If not, how should the study be modified?
  - e. The study must have received scientific review by the VHA Office of Research and Development (ORD), the Department of Defense (DoD), or an agency of the Department of Health and Human Services (HHS). Specifically,
    - i. If so, is there any indication that additional scientific review is warranted at this time?
    - ii. If not, how was scientific review accomplished? Is there any indication that additional scientific review is warranted at this time?
  - f. The study as presently implemented must satisfy all the criteria for IRB approval under the Federal Policy (Common Rule) for the Protection of Human Subjects at 38 CFR 16.111. Specifically,
    - i. Are risks to subjects minimized and reasonable in relation to anticipated benefits? Specifically,

- Has the most up-to-date information available from the scientific literature, the Sponsor, and the FDA been included in the risk/benefit analysis?
- ii. Is selection of subjects equitable? Specifically,
- Do the burdens of participating in the research fall on those most likely to benefit from the research?
  - Are groups that are particularly vulnerable to research risks included or excluded appropriately?
- iii. Are the informed consent process and documentation of consent appropriate? Specifically,
- Does the consent process ensure that prospective research subjects will understand the nature of the research and its reasonably foreseeable risks and discomforts?
  - Does the consent process include a discussion of alternatives to participation, including (where appropriate) the availability of the study interventions “off protocol”?
  - Is consent information provided in such a way that prospective subjects can knowledgeably and voluntarily decide whether or not to participate?
- iv. Is safety monitoring adequate? Specifically, does the protocol provide a plan for:
- Monitoring adverse events?
  - Conducting a meaningful and systematic evaluation of adverse events?
  - Periodically reviewing the research to determine whether the risk/benefit ratio has shifted, there are unanticipated findings involving risks to subjects, and any new information should be provided to subjects?
  - Determining whether the study should be continued in light of emerging information?
- v. Are privacy and confidentiality provisions adequate? Specifically,
- Does the protocol adhere to ethical and VA standards for privacy and confidentiality?
  - Does the protocol make appropriate provisions for protecting the confidentiality of the data?
  - Are subjects provided with sufficient information about current and future data uses and data disclosures?

- Is an accurate and valid HIPPA Authorization for Research Use and Disclosure of Protected Health Information (PHI) obtained?
- g. Remuneration for participation must be modest, appropriate, and neither coercive nor unduly influential.
  - h. The protocol must reflect consideration and implementation of special safeguards to protect the rights and welfare of research subjects who may be vulnerable to coercion.

## **Part 8: HawkIRB Section VII.A. Collaborative Research**

The IRBs may approve human subjects research activities at locations for which the IRB has an understanding of the local research context or the IRB is assured that there is appropriate oversight for the conduct of human subjects research. The IRB approves collaborative projects within the VA and have mechanisms in place to assure appropriate oversight of collaborative research with non-VA entities.

### **8.A Collaborative Research with VA Personnel**

Collaboration is encouraged when VA investigators have a substantive role in the design, conduct, and/or analysis of the research. VA may also serve as a Coordinating Center for collaborative studies. Research team members can be from any department at the VAHCS. There are some projects that may develop into the sharing of information with other researchers who are not members of the research team. Research team members should not share data or specimens with investigators outside of the research team for the project unless the subject is informed of this possibility in the informed consent document. Refer to the section on Data and/or Specimens for more information.

### **8.B Collaborative Research with non-VAHCS Entities**

In the conduct of cooperative research projects, each institution (entity) is responsible for safeguarding the rights and welfare of human subjects and for complying with any applicable regulations. Federal regulations from DHHS and FDA [45 CFR 46.114 and 21 CFR 56.114] allow for cooperative research projects which involve more than one institution (or entity). To avoid duplication of review efforts by IRBs, institutions can choose to conduct joint reviews, rely upon the review of another qualified IRB, or make other arrangements to establish oversight responsibilities.

Discussion of how to assure the rights and welfare of human subjects in research at each entity involved in the research usually begins with an evaluation of whether or not each entity is “engaged” in human subjects research. An entity becomes “engaged” in human subjects research when its employees or agents (agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility):

- 1) intervene or interact with living individuals for research purposes OR
- 2) obtain individually identifiable private information for research purposes

An entity is automatically considered to be “engaged” in human subjects research whenever it receives a direct DHHS award to support such research. In these cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award.

OHRP has provided guidance and examples for when institutions are considered to be “engaged” in research and examples of when institutions are NOT “engaged” in research. The UI IRB makes a determination about whether or not a cooperating outside institution is engaged in human subjects research. This determination is made by the appropriate UI IRB Chair based on the outside institution’s role and whether or not that role meets any of the criteria for “engaged in research” as defined in the guidance above.

Any questions an IRB chair might have regarding making that determination are posed to OHRP by phone call or e- mail. Please call the HSO for more information if there is any question about the involvement of outside institutions in human subjects research.

Once the determination is made that the outside institution is engaged in human subjects research, the following are the IRB policies with regard to IRB oversight at those institutions.

#### **8.C Research at the VA and UI**

VA investigators or sponsors may want to conduct their research at the VA and UI. For cooperative research projects between the VA and UI, IRB 03 will conduct review of research conducted at the VA while IRB 01/02 will conduct review of research conducted at the UI. Each respective IRB will provide oversight responsibilities for the research conducted at their respective institution.

VA researchers may include conducting research at other institutions or sites. When conducting research at both the VA and UI, this is considered a multi-site study. IRB-03 will conduct review of research conducted at the VA while IRB 01/02 will conduct review of research conducted at the UI. The Hawk IRB application in section VII.A must be completed indicating that the project is also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project) in VII.A.2. The application must indicate what role the Iowa City VAHCS is performing for the study (participating site, coordinating center, central laboratory, statistical/data management center, etc.) Research at the UI will be considered its own site and must have its own IRB approval (IRB 01/02). The IRB-03 application, protocol, and informed consent document(s) must clearly delineate which activities will occur as the VA portion of the collaborative study. In addition, the IRB-03 informed consent document must clearly state when procedures will be conducted at the UI as part of the VA’s portion of the study.

The following describe several scenarios that may arise when collaborating between the Iowa City VAHCS and the University of Iowa, and items to consider when completing the HawkIRB application.

- The PI will be participating in a clinical trial at conducted both the UI and the VA. Study procedures will be performed at both sites, and subjects will be treated at the institution they are recruited from. There are other study sites besides the UI or VA, and neither UI or VA is the coordinating center.
  - The PI will submit an IRB 01 application to describe the study at the UI, and an IRB-03 application to describe the study at the VA. The 01 application will cover research activity at the University of Iowa, and the 03 application will cover research activity at the Iowa City VAMC. The IRB-03 application, protocol, and informed consent document(s) must clearly delineate which activities will occur as the VA portion of the collaborative study. In addition, the IRB-03 informed consent document must clearly state when procedures will be conducted at the UI as part of the VA's portion of the study.
- The PI will be conducting a clinical trial at both the UI and the VA. Study procedures will be conducted at both sites, and subjects will be treated at the Institution they are recruited from. The UI or the VA are the ONLY sites for the research, or there are multiple sites and either the UI or the VA is the coordinating center,
  - The PI will submit an IRB 01 application to describe the study conducted at the UI, and an IRB-03 application to describe the study as conducted at the VA. Either the UI site or the VA site will be named as the coordinating center in VII.A as appropriate, and the other site not acting as a coordinating center will be listed as a participating clinical site. Pay special attention to HawkIRB section X, to accurately describe where data is stored and how it is transferred to other sites. The IRB-03 application, protocol, and informed consent document(s) must clearly delineate which activities will occur as the VA portion of the collaborative study. In addition, the IRB-03 informed consent document must clearly state when procedures will be conducted at the UI as part of the VA's portion of the study.
- Study procedures are conducted almost entirely at the University of Iowa, and all subject activity takes place at the University of Iowa. However, because a resource of the of the VA is needed for the study (either lab space, equipment, or a VA personnel), both the VA and the UI are engaged in research, and both an 01 and an 03 application will be submitted.
  - The 01 application will describe all study procedures as they are conducted at the University of Iowa. In section VII.A.2, indicate that this is a multi-site study. In question VII.A., indicate the University of Iowa is the coordinating site. Provide reasonable responses to the following questions regarding communications with other study sites. Indicate that the Iowa City VA is a participating site.
  - The 03 application will indicate that this study is performed primarily at the University of Iowa, however, this IRB application is to allow to the research oversight of a VA employee. Request a waiver of consent in HawkIRB question IV.3. Chose "other" for the type of study, and in the response box, indicate what particular recourse or personnel

- The study procedures will occur at both the University of Iowa and the Iowa City VAHCS. Subjects may be identified at both sites, and all subjects will have procedures as both sites. For example, a study enrolls subjects at either site, the subjects will have a procedure conducted at UIHC, and then attend a workshop at the VA.
  - Two IRB applications must be created, IRB 01 to cover activities at UIHC, and IRB 03 to cover activities at the VA. The IRB-03 application, protocol, and informed consent document(s) must clearly delineate which activities will occur as the VA portion of the collaborative study. In addition, the IRB-03 informed consent document must clearly state when procedures will be conducted at the UI as part of the VA's portion of the study.
  - Subjects must be enrolled using a consent and HIPAA authorization specific to the institution they were recruited from, PRIOR to any PHI leaving that institution.
  - If the subject travels from one institution to the other, they must be consented using the receiving institution's consent in addition. Consider if a waiver of documentation of consent is allowable for this, to minimize the burden of an additional consent process on the subject.
- VAHCS Researchers who have an 8/8ths appointment as well as an appointment at the University of Iowa and want to do research at the University of Iowa.
  - An 8/8 appointment is based on a 40 hour work week. It is possible that if an investigator is 8/8ths VAHCS and has a UI appointment, that their work can be done on their UI only time. If no research activity occurs at the VAHCS, and the investigator has a UI appointment, and the work is being done on their UI time, then this research activity can be reviewed under IRB 01. For further information on how to verify compliance with your VAHCS appointment while conducting research at the University of Iowa, consult with Kari Points (IOW) Kari.Points@va.gov
- Research conducted at both the University of Iowa and the Iowa City VAMC, with funding from the Veterans Administration, requires a subcontract to the University of Iowa. . Indicate in the IRB 03 application that the research funding will be processed through the Iowa City VAMC. To describe the subcontract to the University of Iowa, in the IRB 01/02 application, enter the funding information as is accurate, in HawkIRB question III.1..

#### **8.D International Research**

Human subjects research conducted by VAHCS investigators in foreign countries typically remains under the VA purview and guidelines. Procedures normally followed outside the United States for research involving human subjects may differ from those set forth in federal and VA policies. These may result from differences in language, cultural and social history, and social mores. In addition, national policies such as the availability of national health insurance, philosophically different legal systems, and social policies may make forms and procedures inappropriate. While the IRB cannot impose our standards for written documentation on other

cultures, we do not relax our standards for ethical conduct of research or for a meaningful consent process.

VA international research is defined as any VA-approved research conducted at international sites (i.e., not within the United States (US), its territories, or Commonwealths), any VA-approved research using either human biological specimens or human data originating from international sites, or any VA-approved research that entails sending such specimens or data out of the US. *NOTE: Research conducted at U.S. military bases, ships, or embassies is not considered international research.*

International research includes multi-site trials involving non-US sites where VA is the study sponsor, a VA investigator is the overall study-wide PI, VA holds the IND, or the VA manages the data collection and the data analyses. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator (i.e., the PI for the study as a whole is not a VA investigator).

International research can be approved at the VA Under the following circumstances.

- The research should be relevant to VA's mission and the care of Veterans, or
  - is directly relevant to VA's role as a health care provider in a period of local or national emergency, or
  - supports the mission of another Federal agency (e.g. DoD or NIH) through an interagency agreement or similar mechanism.
- There should be adequate protection of human subjects (including privacy and confidentiality), and the implementation of adequate safety measures for research subjects and personnel.
- There should be appropriate security of VA data and VA sensitive information and storage of data and specimens in accordance with all applicable VA requirements.
- The investigators should comply with the applicable VA policies related to the identification and resolution of conflicts of interest of research personnel.
- All data should be obtained in accordance with international ethics rules and regulations pertaining to human research subjects and consistent with FR Vol. 70, No. 57, pp15322-15327, March 25, 2005 "Protection of Human Subjects, Proposed Criteria for Determinations of Equivalent Protections".
- All international sites should hold an international Federal Wide Assurance (FWA).
- The research should be approved by the IRB or Research Ethics Board of the participating site(s) that are listed on the international FWA. [ORD Guidance on Approval of International Research (<http://www.research.va.gov/resources/policies/guidance/intl-research.pdf>)]
- International Research must have the approval of the VA Medical Center Director.

Special attention should be given to local customs and to local cultural and religious norms in drafting written consent documents or proposing alternative consent procedures. Protections afforded subjects must be equivalent to those provided to subjects in the United States.

For some research proposals, it may be appropriate to request a waiver of consent or the elements of consent. Such proposals should include explanations of cultural norms or conditions

requiring such a waiver. For example, societies where no written language is used or societies where signatures might represent something quite different than what they represent in the United States.

The first step in the review process is to make a determination about whether or not the project meets the definition of human subjects research. If unsure about whether the project constitutes human subjects research, the VA investigator should submit a Human Subjects Research Determination (HSRD) form in HawkIRB to receive a documented determination from the IRB Chair.

If the project does involve human subjects research, the VA investigator will be required to submit a New Project application in HawkIRB for IRB review and approval prior to the conduct of the research. In federally funded research, research activities in a foreign country may be approved if the procedures proscribed by a foreign institution are equivalent to those in the U.S. Research projects must have been approved by the local equivalent of an IRB before they are given final approval by the IRB. OHRP provides a listing of the laws, regulations, and guidelines that govern human subjects research in many countries around the world. Where there is no equivalent board or group, VA investigators must rely on local experts or community leaders to provide approval of the project. The IRB will require documentation of this “local approval” using the International Research Local Context Review Form before it gives final approval of the project. This form is available on the attachments page in the HawkIRB application.

## **8.E Multi Center Studies**

Section VII.A of the HawkIRB application asks if investigators at other institutions or sites are conducting the research study, including some or all of the study procedures or receiving identified study data (identified with a study ID number for which there is a link to the subject identifiers). All studies being conducted at both the Iowa City VAHCS and UI shall be considered multi-center studies and need IRB approval at each institution. IRB 03 will conduct review of research conducted at the VA while IRB 01/02 will conduct review of research conducted at the UI.

Examples include:

- Sending data or samples with identifying information (name, date of birth, study ID code, etc.) to a non-Iowa City VA researcher or location
- A researcher at another institution that is conducting study procedures in conjunction with this study
- Studies that involve collaboration with a contract research organization, coordinating center, central laboratory or statistical/data management center or some other organization or entity
- Community-Based Research in which a VA investigator collaborates with research affiliates outside of the UI

The IC VAHCS research team conducting study procedures at an outside organization or institution does not constitute “collaboration.” The conduct of the research study at an outside



organization or institution should be indicated in Section VII.A.1 and described in Section VII.D and VII.E.

#### **8.E.i Lead Site Responsibilities**

If the VA is the lead institution or coordinating center, additional information must be provided in the HawkIRB application. VA investigators should provide detailed information regarding the procedures requested in Section VII.A of the HawkIRB application including the methods used, communication channels, and the process for responding to serious problems occurring at the participating sites.

One responsibility of the lead institution is to ensure IRB approval for the project and any protocol modifications. The lead institution must also ensure that participating sites maintain continuing approval from their local IRB on an annual basis. The VA investigator should describe plans for tracking documentation of IRB approval for each participating site in Section VII.A of the HawkIRB application.

When research is conducted at the IC VAHCS and UI only (they are the only two sites), one site must be designated the 'Lead Site' or Coordinating Center and take on the responsibilities described above. The IC VAHCS and UI would be considered clinical participating sites when there are multiple sites and another site is taking on the responsibility of the 'lead site' such as in a cooperative group study.

#### **8.E.ii Collaborative Research responsibilities when the Iowa City VAHCS is involved**

When the IC VAHCS is involved in collaborative research, the IRB-03 application or protocol must describe:

- what research data will be disclosed to collaborators,
- the entities to which the data are to be disclosed,
- how the data are to be transmitted, and
- Any applicable collection, use, transfer, and disposition of biospecimens obtained or collected.
- how the transmitted data will be stored, retained, destroyed, and/or further disclosed and to whom.

This includes data from individual participants as well as other data developed during the research such as the analytic data and the aggregate data. All disclosures and data transmission must meet privacy and security requirements per VHA Directive 1605.01 and VA Handbook 6500. The VA Privacy and Information Security Officer will require this documentation be included in the VA Privacy Officer and VA Information Security Officer Checklists.

#### **8.F Community Based Research**

Community based research conducted by researchers of the Iowa City VAHCS is permitted, however all persons engaged in research under the study must have an Iowa City VAHCS appointment, which may be a paid appointment or without compensation (WOC). See section 3C

## Part 9: HawkIRB Section VII.B. Study Design

### 9.A Clinical Trial

In a clinical trial (also called an interventional study), participants receive specific interventions according to the research plan or protocol created by the VA investigators. The definition of a **clinical trial** under the 2018 regulations 45 CFR 46.102(b) is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, for example, diet. Clinical trials may compare a new medical approach to a standard one that is already available or to a placebo that contains no active ingredients or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The VA investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. For example, VA investigators may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases.

Clinical trials used in drug development are sometimes described by phase. These phases are defined by the FDA. Research, **with a federal funding source**, meeting the 2018 Regulatory definition of a clinical trial will be required to publicly posted an IRB approved version of the informed consent document. There are two locations available for posting the informed consent document.

- For those clinical trials that meet the FDAAA definition of an Applicable Clinical Trial (ACT), the informed consent document can be uploaded to the relevant [clinicaltrials.gov](https://clinicaltrials.gov) record.
- For clinical trials that are not an ACT, the informed consent document can be uploaded to a docket folder on Regulations.gov (Docket ID: HHS-OPHS-2018-0021).

The informed consent form must be posted on one of the Federal Website options after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol. To better track the timing of the posting requirement, a new question for federally funded clinical trials has been added in HawkIRB under VII.B.1.c to document the estimated date of the last subject visit.

#### 9.A.i Phases of Clinical Trials

Refer to The FDA's Drug Review Process [here](#).

#### 9.A.ii ClinicalTrial.gov reporting

Studies where the VA is the coordinating center of a study (listed in VII.A of the IRB application), the study must be registered under the VA per their registration policy. For studies

funded by the VA Office of Research and Development (ORD), the registration will be processed through the VA Annual Report (ART) system and not directly into clinicaltrials.gov. For all other funded studies, the VA is requiring investigators who need to register at ClinicalTrials.gov under their institution to create and maintain their own institutional account in the Protocol Registration and Results System (PRS) for any records where the VA is the lead site. Accounts can be created by emailing a request to [register@clinicaltrials.gov](mailto:register@clinicaltrials.gov) (link sends e-mail). Any study with both an IRB 01 and an IRB 03 application for the same study should look to VII.A.10 to identify which institution, the VA or UI, is the coordinating center of the study. Questions can be directed to [Kari.Points@va.gov](mailto:Kari.Points@va.gov). Review information about clinical trials requirements for registration with ClinicalTrials.gov [here](#).

### **9.A.iii FDA Clinical Trials and Human Subject Protection**

### **9.B Repositories**

Refer to the Specimen or Data Repository Procedures at the VA [here](#).

There are specific requirements established by the Veterans Health Administration for the use of data and data repositories in VA research. These requirements are outlined in VHA Handbook 1200.12 (USE OF DATA AND DATA REPOSITORIES IN VHA RESEARCH). This guidance can be located on the Office of Research & Development website at:

[http://www.research.va.gov/resources/policies/by\\_topic.cfm](http://www.research.va.gov/resources/policies/by_topic.cfm).

### **9.B.i Data/Specimen Use Agreements**

If a VA researcher stores human specimens for the specific purpose of providing specimens and/or associated data to others who are not members of the original “specimen collection” research team, the IRB may require that the researcher provide additional information to the IRB for establishing a formal repository. The IRB has developed these procedures based on guidance from the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (DHHS) as well as the VHA Handbook 1200.12. The VA researcher will need to work with the VA ISO and VA PO (Michele Myrvik at VA ext. 636092 or [michele.myrvik@va.gov](mailto:michele.myrvik@va.gov) and Merle Kelley at VA ext. 636265 or [merle.kelley@va.gov](mailto:merle.kelley@va.gov)) to determine what is needed for data repositories. The VA researcher will need to work with Kari Points if the repository is for tissue banking. (Contact Kari at VA ext. 637678 or [kari.points@va.gov](mailto:kari.points@va.gov)).

Purpose for Establishing a Formal Repository:

- 1) To give the “collector investigator” authority and responsibility for distributing specimens or data from the repository if certain pre-determined guidelines are met
- 2) To minimize the paperwork burden on “recipient investigators” (those individuals with whom the PI intends to share the specimens or data)
- 3) Features of a Formalized Repository:

- 4) Repository PI (“collector”) obtains IRB approval for establishing and maintaining the repository
- 5) Repository PI determines the conditions under which s/he will share specimens or data from the repository with Recipient Investigators
- 6) Repository PI develops a “Usage Agreement” that describes those conditions
- 7) Repository PI is responsible for maintaining a copy of the signed Usage Agreements

If Recipient Investigator agrees to those conditions, and the Repository PI and Recipient Investigator both sign the Usage Agreement, the Recipient Investigator does NOT need IRB approval – the Repository PI may provide the specimens or data based on the signed Usage Agreement alone.

The Recipient Investigator DOES need IRB approval in the following circumstances:

- 1) If the Recipient Investigator wants to use the specimens or data in a manner that goes beyond what is described in the Usage Agreement (e.g., get subject identifiers so that additional data items can be obtained from medical records), the Recipient Investigator must submit an IRB application for review and approval. The IRB application should specifically describe why the Recipient Investigator cannot do his/her study without going beyond the terms of use in the Usage Agreement.
- 1) If the Recipient Investigator is being funded by a funding source that requires evidence of IRB approval (e.g., NIH), the Recipient Investigator should submit an IRB application for review and approval. The Recipient Investigator should include with his/her IRB application a copy of the funding agency grant, and a copy of the signed Usage Agreement so that the IRB knows that the terms of the Usage Agreement will be followed. IRB approval of the Recipient’s use of the specimens or data will be classified as exempt from the federal regulations. The funding agency will be notified by the Iowa City VA Medical Research Foundation (via the DHHS 310 form) that the PI has obtained IRB approval for an exempt project.

Further information about establishing a formal specimen repository, along with sample usage agreements and additional information required by the IRB, may be found in a document called "Specimen/Data Repository Procedures at UI" on the HSO website. VA investigators are encouraged to contact the Human Subjects Office for assistance before submitting an application to establish a formal registry.

## **9.C Registries**

A research registry is defined as the collection and maintenance of data in which:

- 1) the individuals in the registry have a common condition,
- 2) the individuals in the registry may be contacted for future studies, and
- 3) the names/data of the individuals may be used by investigators other than the original research team.

If a registry is being created, the VA investigator should include the name of the registry, the method of data storage, how subjects are informed of their inclusion in the registry, and how subject identity and information is protected in the New Project Application. The Informed Consent Document should inform a potential subject that if s/he decides to participate, his/her name will be stored in a registry and s/he may be contacted in the future by investigators other than the current research team.

Not all compilations of individuals' names and associated data constitute a research registry.

A database is not necessarily a registry. The key element in a registry is that names and other identifying information are being stored so that people other than the original research team may access the registry information in the future to contact individuals for other studies. For further guidance, please contact the Human Subjects Office.

## **9.D Investigational Drugs or Biologics**

### **9.D.i IND – Investigational New Drug**

Federal law requires that a drug be the subject of an approved marketing application (i.e. an application for Food and Drug Administration (FDA) approval to market or sell the drug) before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical VA investigators in many states, it must seek an exemption from that legal requirement. The Investigational New Drug (IND) application is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

The FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) has screened the pharmacological activity and acute toxicity potential of the drug in animals and wants to test its diagnostic or therapeutic potential in humans.

There are three IND types:

- 1) A VA investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying

an unapproved drug, or an approved product for a new indication or in a new patient population.

- 2) Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- 3) Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

#### **9.D.i.a Determination of Need for an IND**

Studies that involve FDA-regulated products that are submitted without a valid IND number will be reviewed with respect to determining the need for an IND, based on the VA investigator's response to questions contained in the New Project application form.

If the UI IRB determines that the study is exempt from an IND and approves the study, the study may begin without submission of an IND application to FDA. If the UI IRB determines that an IND is needed, the VA investigator/sponsor must submit an IND application to the FDA and provide documentation of the outcome of the FDA determination to the UI IRB before the UI IRB approves the study.

The UI IRB may consider a study using a drug product that is lawfully marketed in the United States to be exempt from the requirements for obtaining an IND if all the following apply:

- 1) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- 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 and with the requirements for informed consent; and
- 5) The investigation is conducted in compliance with the requirements with regard to promotion and charging for investigational drugs in 21CFR312.7

A clinical investigation involving an in vitro diagnostic biological product that is a blood grouping serum, reagent red blood cells, or anti-human globulin is exempt from the requirements for an IND if:

- 1) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and
- 2) it is shipped in compliance with 21 CFR 312.160.
- 3) A drug intended solely for tests in vitro is exempt from the requirements of an IND if it is shipped in accordance with 21 CFR 312.160.
- 4) A clinical investigation involving use of a placebo is exempt from the requirements of an IND if the investigation does not otherwise require submission of an IND
- 5) Once the IND is submitted to FDA, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk. For more information on IND's, refer to the following link: FDA (CDER) website. VAHCS investigators conducting studies with an IND are required to submit documentation from the sponsor (either a letter or email from the FDA or sponsor, or indication on the commercial sponsor's protocol) of the IND number assigned by the FDA. If the IND is a VA investigator held IND, the entire IND application and the FDA Form 1571 (IND application cover page) are required. This documentation must be attached to the New Project application in HawkIRB.

#### Promotion and Charging for Investigational New Drugs (21 CFR 312.7)

A sponsor or VA investigator, or any person acting on behalf of a sponsor or VA investigator, shall not represent in a promotional context (e.g. in advertisements, brochures or any recruitment media) that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including the dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

A sponsor or VA investigator shall not commercially distribute or test market an investigational new drug. In addition, a VA investigator should be aware that a sponsor cannot unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

Charging for an investigational drug in a clinical trial under an IND is NOT permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered by the sponsor to be part of the normal cost of doing business.

VA investigators should include a statement in the "Will it Cost Me Anything to be in this Study?" template section of the Informed Consent Document that there will be no charges for the investigational new drug(s) used in the study. If this statement is not included in the informed consent document, the IRB will only allow its absence if the VA investigator attaches the prior written approval of the FDA to the sponsor to allow for test subject charges. This authorization to charge for an investigational drug under this section may be withdrawn by the FDA if the

agency finds that the conditions underlying the authorization are no longer satisfied. In this instance, it is the responsibility of the VA investigator to submit a modification to the HawkIRB application to include the required statement the informed consent document. In such cases where charges are allowed, sponsors are not allowed to commercialize the investigational new drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug. The VA investigator must be cognizant of this rule when participating in a clinical trial of an investigational new drug.

A sponsor or VA investigator may charge for an investigational drug for a treatment used under a treatment protocol or treatment IND provided:

- 1) There is adequate enrollment in the ongoing clinical investigations under the authorized IND;
- 2) Charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
- 3) The drug is not being commercially promoted or advertised; AND
- 4) The sponsor of the drug is actively pursuing marketing approval with due diligence.

The FDA must be notified in writing in advance of commencing any such charges, in an information amendment. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

#### **9.D.ii Expanded Access**

Refer to the [FDA's Access to Investigational Drugs Outside of a Clinical Trial \(Expanded Access\)](#).

#### **9.D.iii Investigational Use of FDA-approved Drugs or Biologics**

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see [21 CFR 312.3\(b\)](#)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, according to [21 CFR 312.2\(b\)\(1\)](#), the clinical investigation of a marketed drug or biologic does not require submission of an IND if certain conditions are met. In its review of the project, the IRB will determine if all six of the following conditions are met:

- 1) It 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;
- 2) It is not intended to support a significant change in the advertising for the product;
- 3) It 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;
- 4) It is conducted in compliance with the requirements for IRB review and informed consent;



- 5) It is conducted in compliance with the requirements concerning the promotion and sale of drugs; and
- 6) It does not intend to invoke the exception for informed consent requirements ([21 CFR 50.24](#)).

#### **9.D.iv Investigator-Initiated Research with Drugs or Biologics**

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IND. The federal regulations for INDs are found under [21 CFR 312](#). Responsibilities of sponsors and VA investigators are also contained in the International Conference on Harmonisation (ICH) Guidance for Industry, [E6 Good Clinical Practice](#). For more information, review the FDA’s Center for Drug Evaluation and Research (CDER) web site [www.fda.gov/cder](http://www.fda.gov/cder).

This text is a synopsis of requirements specific to sponsor-investigators who hold INDs. It is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks for the corresponding regulations are included throughout the section. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and University of Iowa policies and guidance for Human Subjects research, and VAHCS requirements as applicable.

When a VA investigator holds an IND for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a “Sponsor-Investigator.” The FDA defines a Sponsor-Investigator as “means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.” [[21 CFR 312.3](#)]

#### **9.D.iv.a Sponsor-Investigator Reporting Requirements**

##### **9.D.iv.a.i New Protocol [21 CFR 312.30\(a\)](#)**

Once the IND has been approved by the FDA, the sponsor-investigator must submit a new protocol for any study not contained in the IND application. The protocol can be submitted before or after IRB approval. The study may not begin until the protocol has been reviewed by the FDA and approved by the IRB

##### **9.D.iv.a.ii Changes in the protocol [21 CFR 312.30\(b\)](#)**

The following protocol changes must be submitted to the FDA:

1. For Phase 1 studies, any change that significantly affects the safety of subjects.
2. For Phase 2 and 3 studies, any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

#### **9.D.iv.a.iii New investigator** *21 CFR 312.30(c)*

The addition of a new VA investigator must be reported to the FDA within 30 days of the VA investigator being added. The IND may not be shipped to the new VA investigator until the FDA has been notified.

#### **9.D.iv.a.iv Information amendments** *21 CFR 312.31*

Any essential information that is not included in a protocol amendment, IND safety report, or annual report must be submitted to the FDA. Examples of essential information include new toxicology, chemistry, or other technical information. Information amendments should be submitted as necessary, but not more than every 30 days.

#### **9.D.iv.a.v IND safety/adverse events reports** *21 CFR 312.32*

A VA investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the VA investigator shall report the adverse effect immediately (*21 CFR 312.64*). Guides to adverse event reporting are indicated below:

- 1) Unexpected fatal or life-threatening suspected adverse reactions that are associated with the investigational drug must be reported to the FDA by fax or telephone as soon as possible, but no later than 7 calendar days after the sponsor-investigator initially receives the information.
- 2) Serious and unexpected suspected adverse reactions associated with the use of the drug that are not fatal or life-threatening only if there is evidence to suggest a causal relationship between the drug and the adverse event. These must be submitted to the FDA as soon as possible, but no later than 15 days after the sponsor-investigator initially receives the information.
- 3) Findings from other studies that suggests a significant risk in humans exposed to the drug whether or not conducted under an IND or not conducted by the sponsor-investigator. This includes any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies.
- 4) Findings from animal or in vitro testing that suggests a significant risk in humans exposed to the drug whether or not conducted by the sponsor-investigator. This includes reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.
- 5) Increased rate of occurrence of serious suspected adverse reactions that are a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor should consider a variety of factors (study population, nature and seriousness of the reaction and the magnitude of the observed increase in rate).

- 6) Additional information that must be included in each IND safety report including all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

#### **9.D.iv.a.vi Annual reports** [21 CFR 312.33](#)

The sponsor-investigator must submit a progress report to the FDA within 60 days of the anniversary date that the IND went into effect. The sponsor is also required under [21 CFR 312.33](#) to submit annual reports to the FDA on the progress of the clinical investigations. ([21 CFR 312.64](#)). The expected contents of the progress report are included in [21 CFR 312.33](#).

#### **9.D.iv.a.vii Withdrawal of an IND** [21 CFR 312.38](#)

Sponsor-investigators must inform the FDA of desire to withdraw an IND.

#### **9.D.iv.a.viii Discontinuation of an investigation** [21 CFR 312.31\(a\)2](#)

If the sponsor-investigator determines that an investigation drug presents an unreasonable and significant risk to subjects, she/he must discontinue the investigation within 5 working days after determining that the investigation should be discontinued. A report of the discontinuation of the investigation should be submitted to the FDA within 5 working days of the discontinuance.

#### **9.D.iv.a.ix Financial disclosure reports** [21 CFR 312.57d](#)

Any changes to financial disclosure information must be promptly reported to the FDA during the investigation and for 1 year following completion of the study.

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such an indication, the sponsor-investigator is responsible for maintaining the following records until 2 years after the investigation is discontinued and FDA is notified [[21 CFR 312.62](#)]. The sponsor-investigator must make these available to FDA inspectors at their request.

#### **9.D.iv.a.x Drug accountability** [21 CFR 312.57a](#)

The sponsor-investigator must maintain records showing receipt, shipment, or other disposition of the investigational drug.

#### **9.D.iv.a.xi Financial interest** *21 CFR 312.57b*

The sponsor-investigator must maintain records showing any financial interests of any of the clinical investigators involved in the study (see also *21 CFR 54*). The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study [*21 CFR 312.64*].

#### **9.D.iv.a.xii Case Histories** *21 CFR 312.62b*

The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject who received the investigational drug and each subject who was employed as a control in the investigation. [*21 CFR 312.62*]. Case histories include the case report forms and supporting data such as signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

#### **9.D.iv.b General responsibilities of sponsors** *21 CFR 312.50*

The sponsor-investigator is responsible for:

1. Selecting qualified VA investigators and providing them with the information they need to conduct an investigation properly.
2. Ensuring proper monitoring of the investigation.
3. Ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND.
4. Maintaining an effective IND with respect to the investigations.
5. Complying with FDA regulations with regard to the promotion and charging for investigational new drugs.
6. Ensuring that FDA and all participating VA investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

#### **9.D.iv.b.i Selection and monitoring of investigators** *21 CFR 312.53 – 312.56*

The sponsor-investigator is responsible for:

- 1) Selecting qualified VA investigators and monitors.
- 2) Ensuring that the study drug is shipped only to participating VA investigators.
- 3) Informing co-investigators of new observations with regard to the investigational drug and progress of the study.

- 4) Reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational drug, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

#### **9.D.iv.b.ii Recordkeeping and record retention** [21 CFR 312.57](#)

The sponsor-investigator is responsible for maintaining study records, as described above.

Inspection of sponsor's records and reports [21 CFR 312.58](#)

The sponsor-investigator must allow FDA employees access to all records and reports at their request. Drug Enforcement Administration and Department of Justice employees must be given access to records and reports involving controlled substances at their request.

#### **9.D.iv.b.iii Disposition of unused supply of investigational drug** [21 CFR 312.59](#)

If the investigation is terminated, suspended, discontinued, or completed, the sponsor- investigator is responsible for assuring that all co-investigators return any unused supplies of the investigational drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under [21 CFR 312.59](#) [[21 CFR 312.62](#)]. The sponsor- investigator must maintain records of the disposition of the drug as described above. As a VA investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

#### **9.D.iv.c General responsibilities of VA investigators** [21 CFR 312.60](#)

The sponsor-investigator is responsible for:

- 1) Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.
- 2) Protecting the rights, safety, and welfare of subjects under the VA investigator's care
- 3) Ensuring the control of drugs under investigation.

#### **9.D.iv.c.i Control of the investigational drug** [21 CFR 312.61](#)

The sponsor-investigator must administer the investigational drug only to subjects under his/her direct supervision, or under the supervision of a sub-investigator responsible to the VA investigator. The sponsor-investigator must also ensure that the investigational drug is not given to any person not authorized to receive it.

#### **9.D.iv.c.ii Investigator recordkeeping and record retention** [21 CFR 312.62](#)

The sponsor-investigator is responsible for maintaining adequate records of the disposition of the drug, including dates, quantity, and use by subjects. This is described above.

#### **9.D.iv.c.iii Investigator reports** [21 CFR 312.64](#)

The sponsor-investigator must provide reports to the FDA as described above.

#### **9.D.iv.c.iv Assurance of IRB review** [21 CFR 312.66](#)

The sponsor-investigator is responsible for:

- 1) Assuring that a qualified IRB will be responsible for initial and continuing review and approval of the investigation.
- 2) Providing a letter or email from the FDA (as an attachment to the HawkIRB new project application) giving the IND number assigned by the FDA.
- 3) Assuring that he/she will report to the IRB all changes and unanticipated problems involving risk to human subjects or others.
- 4) Assuring that he/she will not make any changes in the investigation without prior IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

#### **9.D.iv.c.v Inspection of investigator's records and reports** [21 CFR 312.68](#)

The sponsor-investigator must allow FDA employees access to all records and reports at their request. A VA investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the VA investigator pursuant to [21 CFR 312.62](#) [[21 CFR 312.68](#)]. The VA investigator is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

#### **9.D.iv.c.vi Handling of controlled substances** [21 CFR 312.69](#)

The sponsor-investigator must take adequate precautions to ensure the safe and secure handling of controlled substances. The VA investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

#### **9.D.v Emergency Settings: Research in Emergency Setting (Planned Emergency Research)**

See 9.D.i above. VAHCS does not conduct planned emergency research (see 21 CFR 50.24) research involving human subjects (See VHA Directive 1200.05).

#### **9.D.vi Emergency Use of an Investigational Drug or Device**

##### **9.D.vi.a Exemption from Prospective IRB Approval**

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [[21 CFR 56.102\(d\)](#)]. The emergency use provision in the FDA regulations [[21 CFR 56.104\(c\)](#)] is an exemption from prior review and approval by the IRB.

The exemption, which may not be used unless the subject is in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available, allows for one emergency use of a test article without prospective IRB review. Life threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life threatening do not require the condition to be immediately life threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Not all emergency use requires an exemption from prospective IRB review. When there is time for prospective IRB approval, the University of Iowa IRB expects the VA investigator to complete a New Project application describing the emergency use. The application will be scheduled for review at the next IRB meeting. The FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. [21 CFR 56.104(c)] Therefore, if the first use does not have prospective review, the IRB notifies the VA investigator that if it is possible subsequent use of the agent will occur, a New Project application should be submitted for IRB review immediately following the first emergency use. The FDA defines emergency use as the use of a test article on a human subject in a life- threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). However, it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

The VA investigator should notify the [IRB Chair](#) prior to the emergency use. However, this notification should not be construed as IRB approval. The VA investigator is required to file a written report within five working days, and notifying the chair is used to initiate tracking to ensure that the VA investigator files this report as required by [21 CFR 56.104\(c\)](#). The FDA regulations do not provide for expedited IRB approval in emergency situations. An IRB must convene and give "full board" approval of the emergency use or, if the conditions of [21 CFR 56.102\(d\)](#) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB Chair will send the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of [21 CFR 56.104\(c\)](#). Any emergency use of a test article does not require R&D committee approval.

#### **9.D.vi.b Obtaining an Emergency IND**

The emergency use of an unapproved investigational drug or biologic requires an [Investigation New Drug \(IND\)](#) application. If the intended subject does not meet the criteria of an existing study protocol, or if an



approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

#### **9.D.vi.c Exception From Informed Consent Requirement (21 CFR 50.24(a)(1))**

Even for an emergency use, the VA investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the VA investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- 1) The subject is confronted by a life-threatening situation necessitating the use of the test article.
- 2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- 3) Time is not sufficient to obtain consent from the subject's legal representative.
- 4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
- 5) If, in the VA investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical VA investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The VA investigator must notify the IRB within 5 working days after the use of the test article.

#### **9.D.vii Placebo-Controlled Trials**

If a VA investigator proposes a study in which a placebo is given for any length of time in lieu of an approved FDA indicated drug, the VA investigator must include risk management procedures in the research plan for the IRB for review. To the extent that the VA investigator demonstrates that the subjects' safety is monitored at all times and provisions are made for immediate rescue if needed, the IRB will consider approval of the study. Once an approval is granted, the VA investigator is bound to follow the risk management procedures as with any other provision of the approved protocol.

Use of placebos may be appropriate where the VA investigator demonstrates that:

- 1) standard therapy is unavailable or is of unproved efficacy, or
- 2) standard therapy possesses unacceptable side effects, or
- 3) minimal harm may result from the use of placebo (e.g., ongoing disease has little adverse effect on the patient during the course of the trial and is reversible), or
- 4) placebo itself may be an effective therapy, or the disease process is characterized by exacerbation and remission.



- 5) The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:
- 6) the frequency of monitoring,
- 7) whether monitoring is in person or by telephone,
- 8) the criteria for managing a subject in the event of worsening, and
- 9) how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or withdrawal from the protocol.

The IRB may make its decision based upon the extent to which the above factors are demonstrated and upon a relative weighing of these and other factors. In discussing potential harm from the use of placebos, the VA investigators must provide a procedure for adequate monitoring of subjects to ensure their safety.

#### **9.D.viii Washout Issues in Drug Treatment Studies**

When a subject is asked to stop taking some or all medications prior to beginning a drug treatment study, this is called a drug washout. Washouts are appropriate depending upon the disease to be studied and the nature of the proposed protocol. Washout studies require balancing the likelihood of harm, the effectiveness of monitoring, and the potential severity of the risk(s) to be avoided. When subjects are being washed out from a FDA approved and indicated drug, the individual VA investigator should clearly define the nature and degree of risk to the subjects and include risk management procedures in the research plan. To the extent that the VA investigator demonstrates that the subjects' safety is monitored at all times and provisions are made for immediate rescue if needed, the IRB will consider approval of the study.

Once an approval is granted, the VA investigator is bound to follow the risk management procedures as with any other provision of the approved protocol. The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:

- 1) careful definition as to when a subject would be withdrawn from the study,
- 2) the frequency of monitoring,
- 3) whether monitoring is in person or by telephone,
- 4) the criteria for managing a subject in the event of worsening, and
- 5) how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or withdrawal from the protocol.

#### **9.E Physiology intervention studies**

Physical procedures by which data are gathered (e.g. drawing blood).

#### **9.F Behavioral intervention studies**

Manipulations of the subject or the subject's environment that are performed for research purposes.

## 9.G Diagnostic trial

A protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition ([ClinicalTrials.gov](https://clinicaltrials.gov))

## 9.H Investigational Medical Devices

When research is conducted to determine the safety or effectiveness of a device: The device fulfills one of the IDE exemption categories:

- 1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- 2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
- 3) A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a participant, is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure, 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 participants at risk. 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.H.i Investigational Device Exemption (21 CFR 812)

An [investigational device](#) is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the Investigational Device Exemption (IDE) regulations. An IDE study may not necessarily commence 30 days after an IDE submission to FDA. Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations.

If the sponsor has an IDE number or the IRB requires an IDE, the VA investigator must submit to the IRB documentation of the assignment of an IDE number using the HawkIRB system. If the IDE is a VA investigator held IDE, the entire IDE application is required. This documentation must be attached to the new project application in HawkIRB. IRB staff will check for this documentation and return protocols with inadequate or incomplete documentation of the IDE.

## Significant and Nonsignificant Risk Medical Device Studies

The Investigational Device Exemption (IDE) regulations describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and:

- 1) is intended as an implant; or
- 2) is used in supporting or sustaining human life; or
- 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
- 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

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

Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR). The determination that a device presents a nonsignificant or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).

SR device studies must be conducted in accordance with the full IDE requirements, and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether the study should be approved. In considering whether a study should be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product (21 CFR 56.111). FDA considers all SR studies to present more than minimal risk, and thus, full IRB

review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Distinguishing between SR and NSR Device Studies ([21 CFR part 812](#))

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

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

#### **9.H.ii The IRB and the NSR/SR Decision**

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion regarding its NSR/SR determination.

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

For nonsignificant risk devices, the VA investigator must maintain the following:

- 1) The name and intended use of the device (type and quantity of the device, the dates of its receipt, and the batch number or code mark).

- 2) A brief explanation of why the device is not a significant risk.
- 3) The name and address of each VA investigator and the names of all persons who received, used, or disposed of each device.
- 4) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- 5) A statement of the extent to which Good Manufacturing Practice (GMP) regulations will be followed in manufacturing the device (see also [21 CFR 820](#)).

### **9.H.iii Investigator-Initiated Research with Medical Devices**

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IDE. The federal regulations for IDEs are found under [21 CFR 812](#). For more information, review the FDA's Center for Devices and Radiologic Health (CDRH) web site [here](#).

This is a synopsis of requirements specific to sponsor-investigators who hold IDEs. It is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks for the corresponding regulations are included throughout this section. Sponsor- investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and University of Iowa policies and guidance for Human Subjects research, and VAHCS requirements as applicable.

A [Sponsor-Investigator](#) is a VA investigator who holds an IDE for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a "Sponsor-Investigator." The FDA defines a Sponsor-Investigator as "an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used . . . . The obligations of a sponsor-investigator under this part include those of an investigator and a sponsor."

#### **9.H.iii.a Sponsor-investigators Reporting Requirements**

##### **9.H.iii.a.i Changes in the protocol [21 CFR 812.35](#)**

Changes to the investigational plan or manufacturing process must be submitted to the FDA for approval if they significantly affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects. These changes should be submitted to the FDA as a supplement to the IDE protocol and must be approved by the FDA before being implemented. Changes that do not meet the above criteria (e.g., adding follow-up visits, changing secondary endpoints, etc.) should be submitted to the FDA within 5 working days of implementation of the change. Minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect the validity of study data, risk-benefit ratio, scientific

soundness of the study, or the rights, safety, or welfare of subjects can be submitted with the annual report.

A VA investigator shall notify the sponsor and the reviewing IRB (21 CFR 56.108(a) (3) and (4) of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with (21 CFR 812.35(a)). For more information, see [Changes or Modifications during the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff](#).

#### **9.H.iii.a.ii IDE safety/adverse device effects** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must report all unanticipated adverse device effects to the FDA within 10 working days of receiving the first notice of the event. VA regulations require reporting to the IRB within five working days of becoming aware of the event.

#### **9.H.iii.a.iii Withdrawal of IRB approval** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must inform the FDA, all reviewing IRBs, and participating investigators of withdrawal of approval of an investigation or any part of an investigation by any reviewing IRB. This notification must occur within 5 working days after receipt of the withdrawal of approval.

#### **9.H.iii.a.iv Withdrawal of FDA approval** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval. This notification must occur within 5 working days after receipt of the withdrawal of approval.

#### **9.H.iii.a.v Current investigator list** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must provide the FDA with a current list of investigators participating in the investigation. This list must be provided to the FDA every 6 months.

#### **9.H.iii.a.vi Annual reports** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must submit a progress report to all reviewing IRBs at regular intervals, at least yearly. The first report must be within 60 days of the anniversary date that the IDE went into effect. For IDEs that have been determined to be significant risk, these reports must also be submitted to the FDA.

#### **9.H.iii.a.vii Recall and device disposition** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must notify the FDA and all reviewing IRBs of any request that a VA investigator return, repair, or otherwise dispose of any units of a device. The notification must occur within 30 working days after the request is made.

#### **9.H.iii.a.viii Discontinuation of an investigation** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must report the completion or termination of an investigation. These reports should be made by submitting a final report. For significant risk devices, the sponsor-investigator must notify the FDA within 30 working days and all reviewing IRBs within 6 months of the completion of the investigation. For non-significant risk devices, the sponsor must notify all reviewing IRBs within 6 months of completion of the study.

#### **9.H.iii.a.ix Informed consent** [21 CFR 812.150\(b\)](#)

The sponsor-investigator must report to the FDA any use of the IDE without informed consent. This report must be submitted within 5 working days of receipt of notice of this use.

#### **9.H.iii.a.x Financial disclosure reports** [21 CFR 812.43](#)

A clinical VA investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements. The VA investigator shall promptly update any changes to financial disclosure information and report it to the FDA during the investigation and for 1 year following completion of the study.

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after completion or termination of the investigation or 2 years after the records are no longer needed to support a premarket approval application or a notice of completion of a product development protocol. [21 CFR 812.140d](#). The sponsor-investigator must make these available to FDA inspectors at their request.

#### **9.H.iii.a.xi Correspondence** [21 CFR 812.140](#)

The sponsor-investigator must maintain copies of all correspondence with other investigators, reviewing IRBs, monitors, and the FDA including required reports.

#### **9.H.iii.a.xii Financial interest** [21 CFR 812.140](#)

The sponsor-investigator must maintain records showing any financial interests of any of the clinical VA investigators involved in the study (see also [21 CFR 54](#)).

#### **9.H.iii.a.xiii Device records** 21 CFR 812.140

A participating VA investigator shall maintain the following accurate, complete and current records relating to the VA investigator's participation in an investigation. The sponsor-investigator must maintain records relating to the shipment, receipt, use (including adverse effects), and disposition of the device.

A VA investigator or sponsor may withdraw from the responsibility to maintain records for the period required in 21 CFR 812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under 21 CFR 812.140, including the requirements of 21 CFR 812.145 (21 CFR 812.140(e)). Notice of this transfer shall be given to the FDA not later than 10 working days after transfer occurs.

#### **9.H.iii.a.xiv Case Histories** 21 CFR 812.140

The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject exposed to the investigational device. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

#### **9.H.iii.b General responsibilities of sponsors** 21 CFR 812.40

The sponsor-investigator is responsible for:

- 1) Selecting qualified VA investigators and providing them with the information they need to conduct an investigation properly.
- 2) Ensuring proper monitoring of the investigation.
- 3) Ensuring that IRB review and approval are obtained.
- 4) Submitting an IDE application to the FDA.
- 5) Ensuring that any reviewing IRB, FDA, and participating investigators are promptly informed of significant new information about an investigation.

#### **9.H.iii.b.i Selecting and monitoring investigators** 21 CFR 812.43 – 812.46

The sponsor-investigator is responsible for:

- 1) Selecting qualified VA investigators and monitors.
- 2) Ensuring that the investigational device is shipped only to participating VA investigators.



- 3) Obtaining investigator agreements.
- 4) Obtaining statements from participating VA investigators attesting to their commitment to the proper conduct of the investigation.
- 5) Obtaining accurate financial disclosure statements from participating VA investigators.
- 6) Providing participating VA investigators with the investigational plan.
- 7) Informing co-investigators of new observations with regard to the investigational device and progress of the study.
- 8) Reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational device, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

#### **9.H.iii.b.ii Adverse device effects and study termination** [21 CFR 812.46](#)

The sponsor-investigator must immediately evaluate any unanticipated adverse device effect. If the sponsor-investigator determines that the device presents an unreasonable risk to the safety of subjects, the sponsor-investigator must terminate the study within 5 working days after making this determination, but not later than 15 working days after first receiving notice of the adverse effect.

If the device is significant risk, the sponsor-investigator may not resume a terminated investigation without IRB and FDA approval. If the device is nonsignificant risk, the sponsor-investigator may not resume a terminated investigation without IRB approval.

#### **9.H.iii.b.iii Recordkeeping and record retention** [21 CFR 812.140](#)

The sponsor-investigator is responsible for maintaining study records, as described above.

#### **9.H.iii.b.iv Inspection of sponsor's records and reports** [21 CFR 812.145](#)

The sponsor-investigator must allow FDA employees access to all records and reports at their request. A VA investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept). [\[21 CFR 812.145\(a\)\]](#).

A VA investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. [\[21 CFR 812.145\(b\)\]](#).

A VA investigator shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the VA investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [\[21 CFR 812.145\(c\)\]](#).

As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

#### **9.H.iii.c General responsibilities of VA investigators** [21 CFR 812.100](#)

A VA investigator may determine whether potential participants would be interested in participating in an investigation, but shall not request the written informed consent of any participant to participate, and shall not allow any participant to participate before obtaining IRB and FDA approval. [\[21 CFR 812.110\]](#).

The VA investigator is responsible for providing a letter or an e-mail from the FDA giving the IDE number, if applicable, as assigned by the FDA. The sponsor-investigator is responsible for:

- 1) Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable FDA regulations.
- 2) Protecting the rights, safety, and welfare of subjects under the investigator's care
- 3) Ensuring the control of devices under investigation.

#### **9.H.iii.c.i Compliance with protocol** [21 CFR 812.110b](#)

The sponsor-investigator must conduct the investigation in accordance with the signed agreement, the investigational plan, FDA regulations, and IRB conditions. [\[21 CFR 812.110\]](#)

#### **9.H.iii.c.ii Device use and disposition** [21 CFR 812.110c](#)

The sponsor-investigator must permit the use of an investigational device only with subjects under the VA investigator's supervision. Upon completion or termination of a clinical investigation or the VA investigator's part of an investigation, or at the sponsor's request, a VA investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs. [\[21 CFR 812.110\]](#)

#### **9.H.iii.c.iii Investigator recordkeeping and record retention** [21 CFR 812.140a](#)

The sponsor-investigator is responsible for maintaining study records, as described above.

#### **9.H.iii.c. iv Investigator reports** [21 CFR 812.150](#)

The sponsor-investigator must provide reports to the FDA as described above.

#### **9.H.iii.c.v Inspection of investigator's records and reports** [21 CFR 812.145](#)

The sponsor-investigator must allow FDA employees access to all records and reports at their request.

## **Part 10: HawkIRB Section VII.C. Genetic Research**

DNA projects, by nature of their subject matter, are reviewed for the following information in addition to the standard required review. Genetic information is uniquely personal information and has the potential to influence employment, insurance, finance, education and possibly self-perception. Therefore, genetic information must be carefully maintained in order to protect against stigmatization, discrimination, or significant psychological harm to the subject.

The IRB considers the following issues in its review of the application and the Informed Consent Document:

- 1) Information that can be obtained from DNA samples in general, and the specific questions to be addressed in this study.
- 2) The extent of subject and sample confidentiality if the sample and subsequent information will be part of a registry or database (required for all studies, regardless of being a registry or database).
- 3) The rights and limitations of subjects to require destruction of their sample and/or associated data at a future date. The rights and limitations of subjects to require that their sample and or associated data be stripped of any identifying information.
- 4) Identifying information available to other researchers if their sample and/or associated data are part of a registry or database (required for all studies, regardless of being a registry or database)
- 5) Mechanisms for maintaining confidentiality in long-term studies, registries, or databases.
- 6) Potential for commercial profit by the institution, VA investigator or sponsor from information gathered in this study.
- 7) The availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on).
- 8) Subjects must have the right to decline receiving genetic information (required for all studies).
- 9) In the absence of a specific authorization to maintain a DNA sample beyond the initial project, DNA samples collected, stored, and/or analyzed in connection with a research project must be destroyed upon completion of the project or withdrawal of the individual from the project. This information must be clearly stated in the Informed Consent Document.

Before involving children in DNA research, the parent(s) or legal guardian(s) must review and sign the Informed Consent Document. The Informed Consent Document must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them. Whenever appropriate, the child's assent should be solicited. Upon reaching the age of majority, if the subject may request his or her information be disclosed, this should be described in the Consent Document. VA investigators must follow the appropriate measures with regard to releasing such information (e.g., counseling, etc.). In some cases it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (paternity or maternity, as could be hidden by adoption or donor fertilization) and other incidental information should not be revealed. The standard Informed Consent Document template contains suggested language for genetic research and for storing tissue or specimens for future use.

## **10.A Genome-Wide Association Studies (GWAS)**

Refer to the [NIH Policy](#) for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS). The IRB must review and approve data submission plans for institutional certifications under NIH's GWAS Policy.

## **10.B Database of Genotypes and Phenotypes (dbGaP)**

Refer to information about the [National Center for Biotechnology Information's \(NCBI\) database of Genotypes and Phenotypes \(dbGaP\)](#). VA researchers will need to work with the VA ISO and VA PO (Michele Myrviki at VA ext. 636092. [michele.myrvik@va.gov](mailto:michele.myrvik@va.gov) and Merle Kelley at VA ext. 636265 or [merle.kelley@va.gov](mailto:merle.kelley@va.gov)) to determine if sharing with these national databases is permissible.

Refer to the NIH Points to Consider for IRBs and Institutions in their Review of Data Submission Plans for Institutional Certifications under [NIH's Policy](#) for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS).

## **10.C Storage of genetic samples for future use**

VA investigators must describe how requests for genetic samples will be received, reviewed and approved. Plans for data/specimen sharing should also be described in the Consent Document. If the samples have been stripped of identifiers, subjects will not be able to request at a later time that they be destroyed. Samples must be destroyed when the study is closed in HawkIRB unless the study is approved by the IRB to store samples for future research.

### **10.C.i Incidental findings**

The IRB considers availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on). Subjects must have the right to decline receiving genetic information.

## **10.D HIPAA Compound Authorization**

An institution providing health care must notify patients regarding how it will use and disclose the patients' health information for treatment, payment, and health care operations.

When an authorization for the use or disclosure of protected health information is combined with another authorization, such as an Informed Consent Document for research, it is called a compound authorization. The VAHCS does not allow the use of a compound authorization, all HIPAA authorizations are collected on a separate document from the informed consent.

## **10.E Genetic Information Nondiscrimination Act (GINA)**

The Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against individuals based on

genetic information. GINA prohibits health insurance companies and group health plans from requesting genetic information collected for research purposes. Health insurance companies and group health plans may not use genetic information when making decisions regarding eligibility for insurance coverage or the amount of insurance premiums. GINA does not protect individuals from genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. The law also does not prohibit discrimination if the individuals already have a manifest genetic disease or disorder.

The Informed Consent Document template available in HawkIRB includes template language describing GINA. All studies that involve research on genes or genetic testing/research are required to include this template language in the Consent Document.

## **Part 11: HawkIRB Section VII.D. Recruitment & Consent Process**

### **11.A IRB Expectations for a successful Research Recruitment portfolio**

The IRB must review and approve all recruitment methods and materials used to describe a research study to potential subjects. All recruitment materials must have IRB approval prior to their use. VA investigators should select all items that may be used for recruiting subjects in Section VII.D and attach all related materials to be used for recruitment to the HawkIRB application.

#### **11.A.i Partial Waiver of HIPAA Authorization for recruitment purposes**

The full board or IRB Chair can determine that a study qualifies for a partial waiver or a full waiver of HIPAA authorization. The IRB can grant a partial waiver to allow for limited information to be collected from the medical record. For example, a partial waiver must be granted in order to collect eligibility information about potential subjects from the medical record such as whether a person or persons have a specific disease. One situation in which the IRB might grant a full waiver of HIPAA authorization is for a medical record review study that has a waiver of consent.

Any study for which the Principal Investigator or research team plans to access or use protected health information about persons prior to their consent to participate in the research study should request the partial waiver. The access to protected health information can come from electronic or paper file medical record access or by way of the healthcare provider's personal knowledge of the patients' health information.

The request for a partial waiver of HIPAA authorization opens up in the application based on the PI's response to Section VII, Question D.1, "Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application)". In order for the waiver justification questions to open up, the PI must select the option, "Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records, Describe source of records". Selecting this option opens up questions VII.D.2-VII.D.7 which address the waiver criteria listed above. However, it may be necessary to 'read between the lines'. Researchers often describe access to PHI in the "describe" comment boxes for the options "Existing Registry/database", "Referral

from colleague”, and “Other”. The waiver justification questions will not open up if the use of PHI is described under any of these options.

VA researchers must request a waiver of informed consent prior to the use of medical health records to screen and recruit subjects. VHA Directive 1200.05 (23.a and 23.b) grants the IRB the authority to waive HIPAA providing all requirements listed in this section are met. The requirement that the PI give the IRB sufficient information to make the required determination should be met through completion of the Hawk IRB application section VII.D (VII.D.2-VII.D.7). The IRB requirement to document its findings is met through the completion of the waiver of HIPAA authorization letter signed by the IRB Chair.

### **11.A.ii Recruitment materials & methods**

Recruitment strategies in any form must be reviewed by the IRB PRIOR to their implementation. There are some recruitment strategies that are either not allowed or allowed in very limited circumstances at the UI. They include the use of finder’s fees or recruitment incentives and the use of “cold calling” potential research subjects.

Only the currently approved recruitment materials and methods should be used to recruit subjects. No changes can be made to the approved materials without IRB approval via a Modification application.

All recruitment strategies, which include but are not limited to; the mode, method, means, and content of all such recruitment strategies must be reviewed and approved by the IRB prior to their use. Recruitment letters, posters and brochures reviewed by the IRB must contain all information, text, and graphic design elements for the final product. IRB approval is required prior to implementation of any changes in content or graphic design of recruitment materials. Color and graphic design may make the document more attractive and appealing to potential subjects. However, design of recruitment materials must not include graphics, text, fonts, or design effects that emphasize compensation or could be coercive to potential subjects. Certain recruitment strategies (such as Noon News, press releases, mass e-mail) have guidelines for format, content and documentation of IRB approval. For example, an IRB approval stamp is required on Noon News announcements, Campus posters and press releases distributed through UI channels. It is important to consult the guidelines for each office or department prior to the IRB-submission of the advertisement, poster or message.

Any material aimed at recruiting potential subjects into a study (including the final copy of the printed advertisement, audio or video tapes or websites) must be reviewed and approved by the IRB prior to being used. Recruitment messages in any form should not be coercive or perceived as “marketing” of the study.

Advertisements or recruitment letters should:

- 1) Include the purpose of the project and/or briefly state what is expected of the subject
- 2) Include the time commitment required of the subject.
- 3) Include the VA investigator's department affiliation and where the research will take place
- 4) List a contact name and phone number.

- 5) Include in summary form, the criteria that will be used to determine eligibility for the study.
- 6) Include a brief list of benefits, if any

Advertisements or recruitment letters should not:

- 1) Emphasize (for example, in large or bold type) the payment amount.
- 2) Include the name of commercial sponsors or products.
- 3) Use phrases such as "help needed" or "subjects wanted." Instead use "you are invited" or "participants invited."
- 4) State or imply a certainty of a favorable outcome or other benefits beyond what is outlined in the consent document and protocol.
- 5) Emphasize how "important" the study is or include exculpatory language (language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the VA investigator, the sponsor, the institution or its agents from liability for negligence).
- 6) Make exaggerated marketing claims or sales pitches
- 7) Make claims that the drug, biologic or device is safe or effective for the purposes under investigation.
- 8) Make claims, that are inconsistent with FDA labeling, that either explicitly or implicitly that the drug, biologic or device is known to be equal or superior to any other drug, biologic, or device
- 9) Use terms such as "new treatment," "new medication," or "new drug" without explaining that it is investigational.
- 10) Promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation.
- 11) Allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

The following are suggestions for creating effective recruitment messages for IRB review and approval:

- 1) Invite subjects to participate
- 2) The title or invitation to participate should be brief and informative for potential subjects. The title should state that this is a research study. Avoid phrases such as "help needed" or "research subjects wanted." The recommended wording is "you are invited" or "participants invited."
- 3) Identify who is conducting study
- 4) State that the research study is a VA study and give the name of the department or college in which the study is conducted.
- 5) State the purpose of the study:
  - a. Use lay terms to address briefly why the study is being done.
- 6) Describe what subjects will be asked to do:
  - a. Provide a brief description of the study procedures subjects will be asked to do for participation in the study.
- 7) Describe the primary inclusion / exclusion criteria:
  - a. Potential subjects need to know whether or not they would be eligible to participate. Only include the criteria that subjects would know about themselves. Limit the exclusion

criteria to the most common reasons a person would be ineligible to participate. If there are a lot of inclusion/exclusion criteria, it is not necessary to list all of them.

- 8) Include the time commitment:
  - a. Provide a general statement about the overall time commitment for the subject.
- 9) Describe the primary study procedures:
- 10) Provide a brief overview of the main study procedures. If the study protocol includes many study activities for the subject, it is not necessary to list them all in the recruitment poster or brochure.
- 11) State whether subjects will be paid for participation:
  - a. Do not emphasize (large font or bold type) that payment is offered.
- 12) Provide contact information:
  - a. Provide the name and/or contact information for a member of the research team that the potential subject can call to find out more information about the study or to volunteer to participate. The contact information does not have to be the name and contact information for the Principal Investigator.

#### **11.A.ii.a Use of Research subject compensation in recruitment materials**

It is acceptable to include the compensation amount in recruitment materials. However, study materials should not over emphasize the amount of compensation for participation. This policy applies to recruitment materials such as posters or flyers, mass mail or e-mail messages, or newspaper, radio or television advertisements, etc. that provide information about a research study.

#### **11.A.ii.b Use of mass email at the VAHCS**

The IRB allows VA researchers to use targeted or mass e-mail when if it involves VA staff. No mass e-mail can be used when recruiting veterans.

1. E-mail is listed as a recruitment method in Section VII.D of the HawkIRB application
2. Mass e-mail is described as a recruitment method in VII.D.29 (and VII.D.30, if applicable)
3. The email script is attached to the application

#### **11.A.iii Cold Calling**

The VAHCS prohibits the use of cold calls to recruit subjects to research studies (See VHA Directive 1200.05, Paragraph 5. Responsibilities(g)(8)). During the recruitment process, members of the research team must make initial contact with potential subjects 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 as outlined in the study. **NOTE:** *If a research repository from a previous study is used to identify subjects, there must be an IRB approved HIPAA waiver for this activity in the new protocol.*

#### **Finder's Fees and Recruitment Incentives**

UI policy strictly prohibits the acceptance or use of finder's fees, recruitment incentives, or bonuses of any type to enroll study subjects. A finder's fee or recruitment incentive may include bonuses given by sponsors to VA investigators or research team members (coordinators) to boost enrollment or referral fees



given to physicians for referring his/her patients to another investigator's study. Payments to VA investigators, research team members, or subjects for recruitment that are provided to the individual outside of the UI system are not allowed.

Acceptable strategies for recruitment of subjects for research can be varied and may include:

- 1) Advertising to promote the study
- 2) Direct communication with identified groups (patients, students, personnel)
- 3) Referrals from other sources such as other physicians or disease registries
- 4) Accessing listings such as listservs, mailing lists (with permission) and in some cases, medical records (see Partial HIPAA waiver below.)

#### **11.A.iv ResearchMatch**

ResearchMatch is the product of the Clinical and Translational Science Awards (CTSA) Consortium, which is led by the National Center for Research Resources, a part of the National Institutes of Health (NIH). The University of Iowa participates in the CTSA Consortium through its Institute for Clinical and Translational Science. Researchers at the Iowa City VAHCS may use this resource, if the researcher is able to show that appropriate approvals have been obtained via an attachment to the HawkIRB proposal.

ResearchMatch.Org is a national volunteer recruitment registry to connect online with potential research study volunteers. To recruit volunteers using ResearchMatch the VA investigator must be the primary Principal Investigator on an active IRB-approved study. The IRB approved project must be approved to use Research Match as a recruitment method in Section VII.D.

The PI is required to register the study on ResearchMatch.org. The VA investigator will be asked to submit contact and study information and sign a Researcher Acknowledgment Form (RAF), agreeing to treat volunteers' personally identifiable data obtained from ResearchMatch as confidential information. The information may only be used to recruit patients to participate in the study. This RAF must be attachment to the HawkIRB application.

Any communications with volunteers via ResearchMatch will utilize content and/or recruitment language, with the removal of direct study contact information. The VA investigator is also required to attach a copy of the e-mail notification ResearchMatch sends to potential subjects. This email should provide enough information about the study that potential subjects can make an informed decision about participation.

#### **11.B The Full Informed Consent Process**

Obtaining informed consent is a basic ethical obligation for researchers. The process of consent should ensure that potential subjects are provided with information about the research project that is understandable and permits the subject to make an informed and voluntary decision about whether or not

to participate. The amount of information and the manner of presentation is generally related to the complexity and risk involved in the research study. While the initial process is prospective and takes place prior to any research activity, consent should also be an ongoing educational interaction between the VA investigator and the research subject that continues throughout the study. For VA studies, if someone other than the VA investigator conducts the discussion and obtains consent, the VA investigator must first formally delegate this responsibility to a person who is a member of the research team and who has received appropriate training to conduct this process.

If the VA investigator contracts with a firm (e.g., a survey research firm) to obtain consent from participants, collect private individually identifiable information from human participants, or be involved in activities that would institutionally engage the firm in human participants research, the firm must have its own IRB oversight of the activity. IRB-03 will not oversee the private entity's research related activities. The HawkIRB application should adequately describe all research related activities the firm will be completing as the VA PI remains responsible for the conduct of the research. This would also include updates to section VII.A of the HawkIRB application to reflect the study is a multisite collaborative project. The VA Privacy Officer Checklist should reflect also their involvement as the Iowa City VAHCS Privacy Officer (PO) will determine whether or not there is appropriate authority to allow the disclosure of individual names and other information to the contracted firm.

The informed consent process is not an exercise in persuasion. If a VA investigator has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive due to the special relationship between parties.

Consent is a legal concept. Only legally competent adults can give legally effective informed consent. Children and those individuals who are not competent to provide consent should be given the opportunity to assent to participate in the research project. Assent is a knowledgeable agreement to participate in the project. Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively impaired persons who are capable of a knowledgeable agreement.

If the person from whom assent is sought refuses, the person should not be enrolled, even if the parent or legally authorized representative gives permission. (The IRB may make an exception to this guideline in studies of children with life-threatening illnesses who are eligible for research treatment protocols.) Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or legally authorized representative does not give permission. In rare circumstances, depending on the nature of the study and the age and circumstances of the child, the IRB may waive the requirement for parental or legally authorized representative permission.

Signed informed consent is required on all human subjects research that is not exempt from IRB review (Section IV.C) except as provided in this section.

In addition, for VA studies the following documentation is required in a progress note placed in the subject's medical record at the time of consent:

- 1) The name of the study

- 2) The person obtaining the subject's consent.
- 3) A statement that the subject or the subject's legally authorized representative is capable of understanding the consent process.
- 4) A statement that the study was explained to the subject.
- 5) A statement that the subject was given the opportunity to ask questions.
- 6) The VA investigator must enter a progress note in the subject's medical record when:
- 7) The subject is entered into the study.
- 8) The subject's participation is terminated
- 9) The HSO has developed Informed Consent Document templates that provide VA investigators with guidance in developing this information. The templates are initially composed by the HawkIRB system based on information provided in the study application. The templates then provide prompts to the VA investigator to add details about the study, levels of risk, and other issues as indicated.

When participants withdraw from a clinical trial, the IRB determines that:

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

## **11.B.i Consent and Assent**

### ***11.B.i.a Standard Informed Consent Document***

The purpose of an Informed Consent Document is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred

prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the written Informed Consent Document approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The subject or the Legally Authorized Representative (LAR) must always be provided adequate opportunity to read the consent document, consider their participation, and ask questions before the consent document is signed. A copy of the Informed Consent Document should be given to the subject. Unless the VA investigator has requested and been granted a waiver of documentation of consent, the subject's signature on an Informed Consent Document is required prior to beginning any study procedures.

Although the research study and Informed Consent Document must be reviewed and approved by the IRB at least once per year, subjects enrolled in the study generally sign the Informed Consent Document only once, when initially enrolled. The exception to this is when the IRB or study sponsor requires subjects to sign a revised Consent Document due to a modification in the protocol or adding new information that may affect the subject's willingness to participate further in the study. Fre

### ***11.B.i.b. General Requirements and Key Information***

Except as provided in the 1200.05 VHA Directive, no VA investigator may involve a human being as a subject in research covered by this policy unless the VA investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. A VA investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

- (1) The information that is given to the subject or the representative must be in language understandable to the subject or the representative.
- (2) No informed consent process, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive, or appear to waive, any of the subject's legal rights, or releases or appears to release, the VA investigator, the sponsor, the institution or its agents from liability for negligence.

For research subject to the 2018 Requirements, informed consent must begin with a concise and focused presentation of the key information (45 CFR 46.116(a)(5)(i) ) that is most likely to assist a prospective subject or LAR in:

- understanding the reasons why one might or might not want to participate in the research.
- This part of the informed consent must be organized and presented in a way that facilitates comprehension.
- Informed consent as a whole must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one

might or might not want to participate.

A Consent Summary template is available on the HawkIRB attachments page to complete as part of the IRB application to fulfill this 2018 Regulatory requirements. If the informed consent document is four or fewer pages, a consent summary is not required.

### ***11.B.i.c. Basic Elements of Informed Consent***

The basic elements of informed consent, as described in [45 CFR 46.116](#) (DHHS) and [21 CFR 50.25](#)(FDA), are as follows:

- 1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- 2) A description of any reasonably foreseeable risks or discomforts to the subject.
- 3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- 5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. For studies regulated by the FDA, note the possibility that the Food and Drug Administration may inspect the records. [[21 CFR 50.25\(a\)\(5\)](#)]
- 6) For research involving more than minimal risk, an explanation as to whether payments or medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- 7) An explanation of who to contact for answers to pertinent questions about the research and research subjects' rights, and who to contact in the event of a research-related injury to the subject.
- 8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 9) For any research compliant with the 2018 Requirements, a statement about any research that involves the collection of identifiable private information or identifiable biospecimens:
  - a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the LAR, if this might be a possibility; or
  - b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

### ***11.B.i.d. Additional Elements of Informed Consent***

The federal regulations stipulate that additional elements of informed consent should be provided to the potential subject or LAR when appropriate. The additional elements include:

- 1) A statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant which are currently unforeseeable.
- 2) Anticipated circumstances under which the subject's participation may be terminated by the VA investigator without regard to the subject's or LAR consent.
- 3) Any additional costs to the subject that may result from participation in the research.
- 4) Adverse consequences (physical, social, economic, legal or psychological), if any, of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- 6) The approximate number of subjects involved in the study.
- 7) For studies subject to the 2018 Requirements, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- 8) For studies subject to the 2018 Requirements, a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
- 9) For studies subject to the 2018 Requirements and involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen); and
- 10) When appropriate, a statement that informs VA research subjects that they or their insurance will not be charged for any costs related to the research. **NOTE:** *Some Veterans are required to pay copayments for medical care and services specifically related to their medical care provided by VA. These co-payment requirements will continue to apply to medical care and services that are not part of the research procedures or interventions.*

### ***11.B.i.e. Additional Elements Required by VA***

The following additional elements of informed consent are required for VA research:

- (1) Any payments the subject is to receive for participating in the study;
- (2) Any real or apparent conflict of interest by VA investigators where the research will be performed; and
- (3) A statement that VA will provide treatment for research related injury in accordance with 38 CFR 17.85. NOTE: VA's statutory requirements in 38 CFR 17.85 apply regardless of inclusion of the information as part of the informed consent process. (See VHA Directive 1200.05, 17.d.10).

### ***11.B.i.f. Consent Template and HawkIRB***

The Informed Consent Document template is available via HawkIRB and contains the required text for preparing an Informed Consent Document. At the end of the template, there is an Appendix containing suggested language for specific situations. By following the template, the VA investigator ensures that the basic and additional elements of consent as required by the federal regulations are included.

For all New Project applications, VA investigators must begin with the consent template that is available at the end of the HawkIRB application. In HawkIRB, the consent document is populated with template language based on responses to various questions within the application. Thus, when downloaded, many of the pertinent sections of the consent template are already included.

The IRB expects the PI of the study and a contact person who is a member of the research team be listed at the top of the Informed Consent Document. The PI may be listed as both the PI and the contact person for the study. All other members of the research team may be listed at the discretion of the PI, or may be provided in a separate listing to subjects. If a separate listing of research team members is provided, it does not need to be reviewed by the IRB unless other study information is also included on the document. All members of the research team must continue to be listed in the HawkIRB application and IRB approved, even if they are not listed on the consent document. It is the PI's responsibility to keep the listing of research team members in HawkIRB current (and on the consent as applicable.) Only members of the research team which are indicated as involved in the informed consent process in the HawkIRB application can review the informed consent document with a potential subject. This individual will also sign as the person who obtained consent in the appropriate section of the informed consent document.

The Informed Consent Document must include all of the basic elements of consent as outlined in the prior section. Based on the study design and in consideration of the subject's safety and welfare, as well as the relevance of the information in allowing the prospective subject to make an informed decision about participation, the IRB may require the additional elements of informed consent as identified in the prior section in the Informed Consent Document

### ***11.B.i.g. Teenage Subjects and How to Handle Wording on the Consent Document***

If VA investigators receive Medical Center Director approval to recruit teenage subjects (in this instance, teenage means a child older than 12 but less than 18 years of age), and the Informed Consent Document is written at an appropriate reading level, both the teenager and the parent/guardian should sign the Informed Consent. The teenager's signature on the Informed Consent Document indicates knowledgeable agreement to participate (assent), and the parent/guardian's signature indicates legal consent.

In this situation, rather than using "you/your child," use the word "you" throughout, and insert the following statements at the very beginning of the Consent:

- 1) If you are the parent/guardian of a child who is being invited to be in this study, the word "you" in this document refers to your child. You will be asked to read and sign this document to give permission for your child to participate.

- 2) If you are a teenager reading this document because you are being invited to be in this study, the word “you” in this document refers to you. You will be asked to read and sign this document to indicate your willingness to participate.

### ***11.B.i.h. Signature Lines***

In general, the Informed Consent Document must include signature lines for:

- 1) the subject AND [See Example #1 and Exception #1]
- 2) the person who obtained consent AND [See Exception #2]
- 3) for studies involving children, a parent or legal guardian; for studies involving cognitively impaired individuals, a legally authorized representative.

Exceptions:

In some types of studies (e.g., mail-out surveys), the VA investigator may request a waiver of the subject’s signature when submitting the New Project Application. In such cases, the conclusion of the Informed Consent Document (which could be formatted as a letter to the subject) should inform the subject that returning the survey will be considered evidence of consent.

The HIPAA Privacy Rule does not permit a waiver of documentation of authorization if the study data include protected health information. Thus, studies which utilize mailed surveys and wish to obtain HIPAA authorization to access medical record information must include a process for obtaining a signed HIPAA authorization.

When there is no verbal communication with potential subjects (e.g., mail-out surveys), the signature of the person who obtained consent may also be deleted

An auditor/witness signature line is needed only if specifically required by the IRB or the funding agency/company. However, if this line is included on the consent, the consent must always be witnessed and this line signed.

Except in certain minimal risk studies, the Informed Consent Document:

- (1) is typically signed after the VA investigator has verbally explained the purpose and procedures involved in the study, answered questions, and otherwise provided information that permits the subject to make a prospective, informed decision.
- (2) must be signed and dated before any study data collection procedures begin.
- (3) must be obtained using only the methods described and IRB approved within the HawkIRB application
- (4) serves as a written source of information for the subject and documents the fact that the process of consent occurred.



### ***11.C.i. Plain language***

Some common problems with the Informed Consent Document include the use of technical and scientific terms or jargon that a lay person would not understand, and units of measure given in metric rather than in imperial units (the unit system used in the U.S.). Ordinary language should replace technical terms (e.g., upper extremities are better referred to as arms, hematoma as a bruise, venipuncture as taking blood from your arm with a needle, and so forth.) A website that is helpful for converting medical terminology to lay language can be found by clicking on the following link, [Medical Terminology](#) in Lay Language.

Perhaps the most common problem with Informed Consent Documents is that they are written at a reading level several grades higher than the average subject would understand.

Informed Consent Documents should be written at a reading level that potential subjects would understand. For most projects, an eighth grade reading level is suggested. Most word processing programs can determine a document's reading level.

Tips for writing a "user-friendly" Informed Consent Document include the following:

- 1) Write the Consent as though you were speaking to the person who will read it, using “you” and “your,” “we” and “our,” rather than third person.
- 2) Use language that could be understood by a junior high student.
- 3) Put technical jargon into lay terms (e.g., describe the amount of a blood draw in teaspoons rather than milliliters; use “cancer” rather than “carcinoma”).
- 4) Clearly define complicated terms (e.g., randomization means the study treatment you’ll receive will be decided by chance, like flipping a coin).
- 5) Don’t give a lot of technical information that participants don’t need to know (e.g., complicated methods of determining drug doses, exhaustive lists of specific lab tests).
- 6) Use bulleted lists rather than long sentences.
- 7) Use headings and subheadings as appropriate with logical and consistent formatting.
- 8) Use tables and charts to explain when/where each procedure will take place.
- 9) Use pictures and diagrams to help describe devices.
- 10) Number each page of the document.
- 11) Use hard page breaks to eliminate “widow” and “orphan” lines of text.
- 12) Use consistent and reasonable font size (e.g., 12 point).
- 13) Do not “right justify” the text.

### ***11.D. VA requirements***

Use of VA Form 10-1086 to document consent is not required but strongly recommended. The consent document must include all required elements but does not need to be on a specific template.

For VA studies, the following is included in the consent and regulations pertaining to the participation of veterans including requirements for indemnification in cases of research-related injury pertains to both veterans and non-veteran subjects enrolled in VA-approved research:

- 1) A statement that in the event of a research-related injury the VA has to provide necessary medical treatment to a subject injured by participation.
- 2) A statement that except in limited circumstances, the necessary care is provided in VA medical facilities. Exceptions include:
  - a. Treatment for injuries due to non-compliance by a subject with study procedures; or
  - b. Research conducted for VA under a contract with an individual or a non-VA institution.
- 3) An explanation of the VA's authority to provide medical treatment to subjects injured by participation in a VA research project.
- 4) A statement that a veteran-subject will not be required to pay for care received as a subject in a VA research project except in accordance with Title 38 United States Code (U.S.C.) 1710(f) and 1710(g) certain veterans are required to pay co-payments for medical care and services provided by the VA.

The signature and date for a witness to the subject's or legally authorized representative's signature and a note placed under the witness' signature line if the sponsor or IRB requires a witness to the consenting process in addition to the witness to the subject's signature and if the same person needs to serve both purposes. In addition, a statement indicating that a copy of the signed and dated consent document is given to the person signing the consent document.

#### **11.B.1.a.iii IRB Stamp**

The PI and research staff is required to use the currently approved, stamped consent document when enrolling research subjects unless a documented exception has been granted by the IRB.

Only the current, approved Consent Document may be used for documenting informed consent. Documenting consent on a Consent Document on or after the expiration date stamped on that document is not permitted and may not constitute valid consent. With each Continuing Review, the VA investigator receives newly stamped versions with the approval notification. Even if the content is identical, the research team is expected to use the current, stamped version of all stamped materials.

#### **ii.B.1.a.iv Sponsor template Consent**

When a template consent document is available from the study sponsor, the VA investigator should attach it in the Miscellaneous attachments category of the HawkIRB application. The template should be attached even if the VA investigator is not proposing to use the template consent to enroll subjects.

A complete submission for IRB review includes sample Informed Consent Document(s). When federally funded and available from the industry or federal (DHHS, NIH, FDA, etc.) sponsor, the IRB must be provided with the template consent document to review any deviations.

#### **11.B.1.a.v What additional data\info can be added to the consent?**

The Informed Consent Document should not be used as a data collection tool. For example, collection of address, e-mail, screening information, phone numbers, SSN, hospital number, appointment scheduling, or other study data must not be collected on this document. Such information should be collected on a separate document. The use, storage and disposal (as applicable) of this information must be described in the HawkIRB application for review and approval by the IRB.

#### **11.B.1.a.vi Where are consent documents stored? (Section X Privacy & Confidentiality)**

The VA investigator must adhere to the confidentiality protections for paper records, including signed consent documents, paper data collection forms, etc. described in the HawkIRB application, VA checklist, and approved by the IRB and VA ISO.

#### **11.B.i.b Assent**

Children and those individuals who are not competent to provide consent should be given the opportunity to assent to participate in the research project. Assent is a knowledgeable agreement to participate in the project. Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively impaired persons who are capable of a knowledgeable agreement.

If the person from whom assent is sought refuses, the person should not be enrolled, even if the parent or legally authorized representative gives permission. Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or legally authorized representative does not give permission. In rare circumstances, depending on the nature of the study and the age and circumstances of the child, the IRB may waive the requirement for parental or legally authorized representative permission.

An Assent Document is used when the VA investigator recruits subjects who, by age or circumstance, are not able to give legally effective informed consent. When legally effective informed consent cannot be obtained, the VA investigator should obtain the "assent" of the child or cognitively impaired subject. This form documents the child's or cognitively impaired subject's knowledgeable agreement, or assent, to participate in a research project. The VA investigator should respect the decision of a child or cognitively impaired subject not to participate, even when the parent or legally authorized representative gives permission, unless specifically instructed otherwise by the IRB.

The regulations do not specify a certain age at which assent must be sought, but for most studies, the IRB suggests obtaining assent beginning at about age seven. In certain studies involving treatment for an illness or condition that is available only in the context of research study, the IRB may determine that the assent of the child is not necessary.

The IRB must determine and document whether assent is required of all children in the research, some of the children in the research or that assent is not required of any of the children in the research.

For studies involving children, the IRB may recommend that this form be used with children, but it may also be used when teenagers are being recruited to enhance their comprehension if the study involves complicated procedures. VA investigators are asked to select and describe plans for the assent process for children/minors in the HawkIRB application.

Options for assent procedures include the following:

- 1) Children/minors will sign an assent or consent document
- 2) Children/minors will be given an assent or consent document to read, but will provide only verbal assent
- 3) Children/minors will be given only a verbal description of the study and asked to assent verbally
- 4) No assent procedure because some or all of the children/minors do not have the capability to assent or their capability is so limited that they cannot reasonably be consulted to provide assent
- 5) No assent procedure because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children/minors and is available only in the context of the research
- 6) No assent procedure because although children are capable of assenting, we are requesting a waiver of assent (NOTE: must be minimal risk study for children and request must be justified in writing by answering questions to follow)

When using an Assent form, the child or cognitively impaired adult should sign the Assent to indicate knowledgeable agreement (assent) to participate. In addition, the parent/guardian or legally authorized representative should sign the full Informed Consent Document to document his/her permission for the child or cognitively impaired adult to participate.

A template Assent Document is available as a choice on the Consent/Assent attachments page of HawkIRB.

#### **11.B.i.b.i Waiver of Assent**

The IRB may waive assent of children with life-threatening illnesses who are eligible for research treatment protocols.

#### **11.B.ii Legally Authorized Representative**

A legal guardian in the state of Iowa is defined as a person who is not the parent of a child, but who has been appointed by a court or juvenile court having jurisdiction over the child, to have a permanent self-sustaining relationship with the child and to make important decisions which have a permanent effect on the life and development of that child and to promote the general welfare of that child. A guardian may be a court (a district court) or a juvenile court, rather than an individual ([Iowa Code 600A.2](#))

Unless otherwise expanded or restricted by a court or juvenile court having jurisdiction over the child or by operation of law, the rights and duties of a guardian with respect to a child shall be as follows:

- 1) To consent to marriage, enlistment in the armed forces of the United States, or medical, psychiatric, or surgical treatment.
- 2) To serve as a [guardian ad litem](#) (a person appointed by a court or juvenile court having jurisdiction over the minor child to represent that child in a legal action. A guardian ad litem appointed under Iowa code must be a practicing attorney) unless the interests of the guardian conflict with the interests of the child or unless another person has been appointed guardian ad litem.
- 3) To serve as custodian, unless another person has been appointed custodian
- 4) To make periodic visitations if the guardian does not have physical possession or custody of the child.
- 5) To consent to adoption and to make any other decision that the parents could have made when the parent-child relationship existed.
- 6) To make other decisions involving protection, education, and care and control of the child.

In studies involving children in the state of Iowa, the legally authorize representative is:

- 1) the parent, OR
- 2) the court-appointed guardian

In studies conducted in the state of Iowa involving cognitively impaired adults (adults who may be incompetent or have limited decision-making capacity), the legally authorized representative is:

- 1) The designated proxy (such as a Durable Power of Attorney for Health Care)
- 2) Court-appointed guardian
- 3) Spouse (This does NOT include “common law” spouses)
- 4) Adult child
- 5) Parent
- 6) Adult sibling

In studies involving cognitively impaired adults, permission must be sought from the first existing person reasonably available in the above list, even if another relative is more conveniently available. Not reasonably available means the person is deceased, unknown, incompetent, or unable to provide permission due to inability to communicate with the research team (e.g. the individual is stationed outside the United States in the armed services and does not have access to phone, email, or fax).

### **11.B.iii Non-English Speaking Subjects & Consent**

#### **11.B.iii.a Short Form Consent process**

Federal regulations at [45 CFR 46.116 and 117](#) and [21 CFR 50.20 & 27](#), require the presentation of information about the study in a language that potential subjects [or their legally authorized representative

(LAR)] understand. The regulations also require documentation of informed consent in a written consent form, except in specific circumstances (see waivers of consent). If the study population includes non-English speaking individuals, the informed consent document must be translated into a language understandable to those subjects. If an investigator unexpectedly encounters a potential subject who does not speak English, the regulations at [45 CFR 46.117\(b\)\(2\)](#) permit the use of a short form consent document (Short Form) to obtain written consent.

A Short Form is a document written in a language understandable to the potential subject (or their LAR). It documents that the required elements of informed consent were presented to the subject (or their LAR), outlined in the federal regulations. But the Short Form does not contain study-specific information. The research team uses the Short Form in conjunction with an oral presentation of the IRB-approved English version of the Informed Consent Document (ICD).

In accordance with the regulations, the University of Iowa IRB allows the use of a Short Form when **ALL** the following apply:

1. The research team encounters a potential research participant who does not speak English
2. The IRB has not approved an ICD translated into the language spoken by the potential subject
3. The research team does not have adequate time to translate the IRB-approved ICD and obtain IRB approval before enrolling the subject
4. The research team has identified someone to verbally translate the IRB-approved ICD during the consent process and assist with communications throughout the study

As outlined in the [Belmont Report](#), to exclude such individuals from participating in a research study solely because they are unable to read, speak or understand English may not be an ethical practice in all cases. The IRB allows the use of a Short Form for up to 5 subjects. Beyond that, the research team must obtain IRB approval to enroll non-English speaking subjects and use an IRB-approved, translated ICD.

The Short Form consent process must be witnessed by someone over 18 years of age who is fluent in both languages but not affiliated with the study. The translator may serve as the witness. A bilingual member of the subjects' family or significant other may also serve as the witness.

If a study requires multiple visits or the subject's participation lasts more than 60 days, the research team must provide the subject with a translated version of the full IRB-approved ICD within 30 days of enrollment. This document does not need to be signed. Additional information on the process can be found on the [Human Subjects Office website](#).

#### **11.B.iv Documenting Informed Consent in the Medical Record**

Any research studies that occur under IRB-03 or at the VAHCS will be required to place the informed consent document in the medical record.

#### **11.B.v Screening procedures**

All screening procedures conducted before and after the subject gives consent to participate in the study must be described in the HawkIRB application and approved by the IRB. This includes questions asked directly of the subject (or his/her Parent/Legal Guardian/Legally Authorized Representative) prior to consent and any additional questions asked or procedures conducted to determine whether or not the subject qualifies to continue in the study after consent is obtained.

Sensitive and/or medical-related questions and procedures should be asked and/or conducted after consent has been obtained.

To speak with persons by phone or in person about their eligibility prior to consent requires a waiver of documentation of consent if that conversation is going to include PHI or other sensitive information.

### **11.C Waiver of Documentation of Consent**

In some situations, the IRB may waive the requirement for obtaining a signed Informed Consent Document. The DHHS regulations ([45 CFR 46.117\(c\)](#)) state that a signed consent form may be waived if the IRB determines one of the following are true:

- 1) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;
  - a. Example: Some types of studies that fall into this category are survey or interview studies that contain highly sensitive (e.g., criminal behavior, sexual behavior) questions.
- 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 OR, for studies subject to the 2018 Requirements, if the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.
  - i. Example: Studies that may meet these criteria include mail out surveys about topics that could not reasonably damage a participant's reputation or employability or be otherwise stigmatizing.

The FDA regulations ([21 CFR 56.109\(c\)](#)) state that a signed consent form may be waived if the IRB determines that:

- 1) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; OR
- 2) the requirements in [21 CFR 50.24](#) for an exception from informed consent for emergency research are met.

Waiver of documentation of consent may mean that no written document is provided to the subject at all, for example:

The waiver of documentation of consent may also mean only that the subject's signature does not have to be obtained. The regulations stipulate that the IRB may still require that the VA investigator provide the subject with a written statement about the research when granting a waiver of documentation. For example:

In a mailed-out survey study, the IRB may determine that it is reasonable for the VA investigator to provide the subjects with a cover letter containing all of the basic elements of consent. The letter would simply conclude with a statement that returning the survey or questionnaire would be considered agreement to participate.

A template of an Informed Consent as a Letter to the Subject is available as a choice on the Consent/Assent attachments page of HawkIRB.

### **11.C.i Consent by mail**

For minimal risk mail-out or web-based surveys or questionnaires, it may be appropriate to request a waiver of documentation of consent. When the subject's signature requirement is waived, generally the VA investigator provides all of the required elements of consent in a cover letter, with a statement that returning the survey or questionnaire will be considered voluntary agreement to participate.

### **11.C.ii Consent via online**

In some cases, a waiver of documentation of consent may be granted by the UI IRB for research conducted online (i.e. a web-based survey). VA investigators may use a consent letter or information sheet containing the elements of consent (template provided in the attachments section of HawkIRB) to provide consent information to participants. For studies with a waiver of documentation of consent collecting data online, a web portal or screen may be used to present the consent information to the participant, allowing for the individual to indicate consent by selecting a button to proceed with their participation.

If the research is greater than minimal risk, written consent will be required. Currently, the UI IRB does not allow for the collection of electronic signatures to document informed consent over the Internet. VA investigators will need to have subjects submit a signed consent document in order to access the web site to participate in the study.

Survey instruments should be designed in such a way that allows participants to skip questions or provide a response such as "I choose not to answer."

### **11.D Coercion & Undue Influence**

In order to be voluntary, consent must be given under conditions that are free of coercion and undue influence. Consent is valid only if the agreement to participate in the research is given voluntarily.

### **11.E. Use of Deception in Research**

There are certain types of studies in which some of the elements of consent can be waived. These include, but are not limited to, certain types of ethnographic research, and studies that require deception. For example:

In a minimal risk study involving playing a computer game to test subjects' responses to differential pay-offs or reinforcements, the VA investigator might indicate in the Informed Consent Document that the



purpose of the study is to test reaction time. This deception may be necessary because the study would be compromised if subjects were told the true purpose. In this scenario, one of the basic elements of consent -- the purpose of the study -- could be waived by the IRB chair, and not included in the Informed Consent Document.

### **11.E.i Waiver of Informed Consent**

#### **11.E.ii Rationale**

Some research projects would not be possible if informed consent from participants were required. The IRB may consider waiving the requirement for some or all of the elements of informed consent ([45 CFR 46.116\(d\)](#) under Pre-2018 regulations and [45 CFR 46.116\(f\)](#) under the current 2018 regulations) only if the study is not under the authority of the FDA. The regulations state that informed consent may be waived in full or in part if the IRB determines that:

1. The research involves no more than minimal risk to the subjects;
2. The research could not practicably be carried out without the requested waiver or alteration;
3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

#### **11.E.iii Debriefing**

When requesting a waiver of the elements of consent for the use of deception, the IRB will require that participants be debriefed as soon as possible after the conclusion of the experiment. The HawkIRB application should include a description of the debriefing process and who will conduct it. The debriefing statement or information sheet provided to subjects should be attached to the HawkIRB application. The individual conducting the debriefing should not be in a position of authority over the participant.

The IRB may also approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirement to obtain informed consent, provided the UI IRB finds the research is not FDA-regulated and documents that:

1. the research involves no more than minimal 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 will be provided with additional pertinent information after participation.

## **Part 12: HawkIRB Section VII.E. Study Procedures – What will happen during the course of the study?**

### **12.A Randomization**

Randomization refers to different conditions or study procedures. It does not refer to the random selection of subjects to be involved in the study. The randomization of subjects to different conditions or study procedures should be described in the HawkIRB application and the Informed Consent Document.

### **12.B Surveys, Questionnaires, and Interview Studies**

Not all survey, questionnaire, or interview research is minimal risk. For example, a survey or interview that asks questions about sensitive topics (e.g., childhood abuse, sexual functioning) likely to cause emotional stress or discomfort may require full IRB review. Some survey research may be classified as exempt from the regulations if the information obtained is recorded in a way that the subject cannot be identified (either directly or through a code numbers or link); in other words, if the research data are anonymous.

A survey or interview study may also be considered exempt from the regulations even when the data are not anonymous if the information being gathered could not reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. The most common classification for survey, questionnaire, or interview research is expedited approval. If the study is not anonymous and contains information that, if known, could be damaging as described above, but it does not rise to the level of more than minimal risk, it may be given expedited approval. Although the New Project application gives the VA investigator the opportunity to indicate a classification, the chairs or his/her IRB member designee make the final determination as to the classification of exempt or expedited.

#### **12.B.i Distribution\storage by use of VA Redcap**

VA REDCap is a free, secure Web application that facilitates the collection and entry of research data. User-friendly electronic data capture (EDC) tools enable users to quickly develop surveys and databases from conception to production on the Web without additional software requirements. This tool helps VA researchers enter, store, and manage their project data in a systematic manner. The system must be configured to use the FIPS 140-2 encryption available in the underlying infrastructure to protect sensitive data at rest.

While VA REDCap meets VA security requirements for data collection and storage, all users are expected to abide by the regulatory, ethical, privacy and confidentiality responsibilities appropriate to their projects. Responsibilities of the Project Owner/Principal Investigator include, but are not limited to:

- Abiding by regulatory requirements for conducting surveys
- Complying with IRB requirements as appropriate
- Creating project forms and design
- Protecting all PHI identifiable or sensitive data fields

- Maintaining roles and authorizations for project team members
- Testing project prior to moving to production status
- Requesting project be moved to production status and requesting subsequent design changes
- Moving completed project to “Inactive” or “Archive” status

VA Researchers using VA REDCap are responsible for obtaining necessary study approvals and meeting IRB requirements.

Research falling under the FDA using REDCAP are subject to ensuring 21 CFR 11 requirements are met.

Each VA REDCap project must have a designated PO or PI who owns the project and meets the key responsibilities.

#### Project Team Roles

- **Project Owner (PO):** A person responsible for assigning roles and granting authorization to specific forms and functions in VA REDCap to project members. The PO is also responsible for collecting data using VA REDCap once the project is moved to production status. In the absence of a PI (e.g., non-research use of REDCAP), the PO is also responsible for ensuring that all regulatory issues are addressed.
- **Principal Investigator (PI):** A person responsible for the research project, including assigning roles and granting authorization to specific forms and functions in REDCap to project members.
- **POs/PIs create and define additional roles for their project team members, for example:**
- **Project Coordinator:** A person responsible for the day-to-day management of the project, VA REDCap data instruments, and overall management of enrollment or data collection.
- **Statistician:** A person responsible for the development of the study design and the review and analysis of collected data.

The PI is also responsible for ensuring that all regulatory issues are addressed.

- Consulting and advance planning to create well-designed data collection instruments.
- Obtaining proper approvals for study.
- Managing study roles and permissions of team members within the REDCap project.

When using VA REDCap as the data collection instrument that may result in publication, the following VA REDCap boilerplate language and citation for IRB (Section X of the HawkIRB application), any other approval boards or review panels:

- Study data were collected and managed using VA REDCap electronic data capture tools hosted at the (your location) Department of Veterans Affairs. VA REDCap (Research Electronic Data Capture) is a secure, Web application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

VA REDCap is available through the (internal) VA Intranet only.

<http://vaww.virec.research.va.gov/REDCap/FAQs.htm>

Contact [virec@va.gov](mailto:virec@va.gov) for more information about using VA REDCap in VA research.

**NOTE: Only de-identified information should be stored at a Non-VA site with consent from the VA ISO.**

#### **12.B.ii Distribution\storage by use of Internet**

[Reserved for forthcoming Internet Research and Use of Social Media Policy]

#### **12.C Audio\Video Taping\Photographs**

Study procedures may require the videotaping, audio recording, or photographing of subjects. Use of VA Form 10-3203 is no longer required. However, the consent form must include information describing any photographs, video, and/or audio recordings that will be taken or obtained for research purposes.

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

(1) An informed consent to take a photograph, video and/or audio recording cannot be waived by the IRB.

2) The consent for research does not give legal authority to disclose the photographs, video, and/or audio recordings outside VA. A HIPAA authorization is needed to make such disclosures. (See VHA Directive 1200.05, 16.f)

#### **12.D Pregnancy screening**

Pregnancy screening must be described in the Informed Consent Document and HawkIRB application, and must be done after the subject signs the Consent Document.

##### **12.D.i Pregnancy Screening In Minors**

When a minor is required to have a pregnancy test as part of a screening visit (or study procedure), the Informed Consent Document or Assent Document must describe this information. Minors in research must be given the same rights to privacy pertaining to their pregnancy that they would be given in a clinical setting. The research team is required to inform proper authorities if a child of any age has a positive pregnancy test *and* if abuse is expected. The Appendix section of the Informed Consent Document in HawkIRB provides the template language that is to be included in the Informed Consent Document.

## **12.D.ii Drug Studies Requiring Consent of Subject's Spouse or Significant Other**

In certain instances, it may be advisable to have a consent for a Subject's Spouse or Significant Other. A sponsor may request this, or the IRB may decide it is necessary. For additional information contact the Human Subjects Office.

## **12.E Use of Social Media\Internet**

### **12.E.i Use of Social Media such as Facebook or Twitter for Recruiting VA Subjects**

Many VHA facilities and program offices now have Facebook pages and Twitter accounts. These Facebook pages and Twitter accounts may be used to advertise VA-approved studies and recruit potential participants in accordance with applicable policies regarding use of social media tools. Recruitment ads should only be posted on the Facebook page or Twitter account of the Investigator's VA Facility. VA sponsored sites are monitored by the facility, typically by the Public Affairs Office, to insure that inappropriate information, such as Protected Health Information is not posted. If posting to a program office's Facebook or Twitter account is proposed, ORD recommends contacting the applicable VHA program office regarding the program office's policies and procedures for posting prior to seeking approval of the recruitment strategy by the IRB of Record and VA R&D Committee. Non-VA-sponsored Facebook pages or Twitter accounts should not be used for recruitment to VA studies since these sites are not monitored by the VA.

### **12.E.i Use of Facebook, Twitter, e-Mail or Other Social Media for Prospective Subjects to Contact the Study Team**

Communication of sensitive information from or to VA by non-encrypted email is not permitted. Non-encrypted email is not secure and cannot ensure confidentiality of the information communicated to or from the individual. If social media such as Facebook or Twitter are used and allows the potential subject to communicate by email, there is no mechanism to prevent communicating sensitive information, including Personally Identifiable Information (PI I) or Protected Health Information (PHI). Therefore, recruitment ads for VA research placed on Facebook or Twitter cannot invite communication with prospective subjects except by phone, mail, or other methods that do not involve personal e-mail or social media messaging. The text of the recruitment script and the context in which the recruitment takes place must be reviewed and approved by the IRB of Record for the applicable study prior to initiation of the recruitment strategy following R&D Committee approval of the study.

My HealtheVet is a VA approved method for VHA providers to communicate by e-mail with Veterans for clinical care purposes, but my HealtheVet cannot be used in VA research to communicate with the prospective VA subjects. My HealtheVet currently does not have research functionalities and is not authorized for use to recruit or contact prospective VA subjects.

### **12.E.iii Use of Craigslist to Recruit VA Subjects**

Craigslist can be used as a tool for recruitment in VA research if the use is consistent with applicable laws, regulations, and policies regarding privacy, information security, and human subjects protections. The proper mechanisms must be utilized to prevent sensitive information, such as PHI, from being sent

electronically by the prospective subjects in response to the advertisement. Similar to Facebook posts and Twitter messages, Craigslist recruitment ads cannot invite communication with prospective subjects except by phone, mail, or other methods that do not involve personal email or social media messaging. The text of the recruitment script and the context in which the recruitment takes place must be reviewed and approved by the IRB of Record for the applicable study prior to initiation of the recruitment strategy following R&D Committee approval of the study.

#### **12.E.iv Referral of Prospective Subjects to Other Websites in a VA Facebook, Twitter, or Craigslist Ad**

Facebook posts, Twitter messages, or Craigslist ads used in VA research may refer prospective subjects to other webpages for additional information. Referenced webpages should be on the VA Facility's website, VA program office's website, or other appropriate website (e.g., National Institute of Health, ClinTrials.gov). Referring prospective VA subjects to personal webpages is not an acceptable recruitment strategy.

#### **12.F Lost to Follow up**

Lost to follow up refers to the research team's inability to locate enrolled subjects during the study using the contact information the subject provided (i.e. if the subject changed address or phone number). This does not refer to planned follow-up phone calls outlined in the study procedures. This also does not refer to attempts to contact subjects after the completion of this study (i.e. about participation in future research studies). The VA investigator should describe all efforts that will be made to locate subjects that they are unable to reach during the study (for example, use of on-line databases, web-based searches, commercial services, etc.).

#### **12.G Subject Compensation**

Payment for participation in research should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Payments should be based on the research subject's time and/or reimbursement for reasonable expenses incurred during his/her participation in the research study. This could include payment for parking, lodging or transportation. Payment should not be excessive to the nature of the project or be offered to the subject as a means of coercive persuasion or undue influence.

Subjects may be compensated for blood donation as part of their participation in a research study. The compensation amount should not be reflective of the amount of blood donated but rather one set amount that will be compensated to subjects regardless of the amount of blood donated.

Compensation may not be withheld contingent on the subject's completion of the study. In most cases involving continued participation, compensation should be given on a reasonable prorated basis to avoid the impression that the VA investigator is coercing the subject to continue in a study or is punishing the subject for non-compliance. If compensation is pro-rated when a subject withdraws prior to completing the study, explain in the consent process how it is pro-rated. Documentation of compensation amounts

and the complete schedule of the payment plan is required within the HawkIRB application and Informed Consent Document.

The policy covering inclusion of compensation amounts in recruitment materials can be found [here](#).

### **12.G.i Cash Handling Policy**

The VAHCS does not allow VA researchers to handle cash and there is no cash handling policy. Subjects are paid research compensation through direct deposit. Subjects are not issued checks for payment. VA researchers complete additional forms to set up direct deposit for subject compensation. In the event, a subject owes money to the VHA, there is a possibility compensation may be withheld and applied to the outstanding amount owed to the VHA or VA. Research subject compensation forms are obtained from the VA Research Office.

## **Part 13: Section VIII Risks to Subjects**

### **13.A What are the risks?**

Section VIII of the HawkIRB application must describe all known and potential risks and indicate whether the study has any of the following types of risks:

1. Emotional or psychological
2. Financial
3. Legal or social
4. Physical

If there are no known risks, the VA investigator may state that there are “no foreseeable risks” to participating. Depending on the type of study, risks may be described as discomforts or something that might make the subject “uncomfortable,” such as fatigue or embarrassment. The Consent Document must also describe these risks.

Examples of non-physical risks include loss of confidentiality, discomfort from being asked sensitive information, disclosure of illegal activities, disclosure of mental health condition, etc.

### **13.A.i Suicidality and IRB expectations**

In its review of studies, the IRB complies and expects VA investigators to comply with Iowa common law (not statute) which generally requires that one report a demonstration of a current intent to hurt oneself or others.

Based on the nature of study and subject population, the VA investigator may be asked to describe a response plan in the HawkIRB application and Consent Document if subjects may be identified as suicidal or at risk of harming themselves or others.

### **13.B How to minimize risks**

The IRB reviews the risks and considers whether the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, or whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

### **13.C Data Safety Monitoring**

#### **13.C.i Frequency**

Studies that plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data) must describe what data will be summarized and reviewed and how frequently the data will be reviewed in Section VIII of the HawkIRB application.

Refer to [Federal & State Regulations & Guidance Materials](#)

#### **13.C.ii Reporting**

Studies that plan to have an individual or committee review combined data from all subjects on a periodic basis must provide reports from the data safety monitoring committee at the time of Continuing Review.

Refer to [Federal & State Regulations & Guidance Materials](#)

#### **13.C.iii Medical Monitor**

[Reserved]

##### **13.C.iii.a DoD requirements**

Research conducted or supported by the Department of Defense (DoD), including its separate components (i.e., the Army, Navy, Air Force and Marine Corps) requires compliance with additional federal regulations, directives and instructions. The DoD has adopted [32 CFR 219](#), a version of the Common Rule that mirrors 45 CFR 46. The Department of Defense Instruction [3216.02](#) (DoDI 3216.02) establishes policy and assigns responsibilities for implementation of 32 CFR 219 in protecting human subjects in DoD-supported research. The VAHCS, IRBs, and VA investigators involved in DoD research must be knowledgeable about these obligations in order to adhere to them. The Compliance Program has implemented a program to monitor the adherence with the additional requirements for DoD-supported research.



## **Part 14: Section IX Benefits**

### **14.A Direct benefits to Subject**

Direct benefits include benefits that subjects will definitely receive from participating in the research. Often there are no direct benefits to subjects and should be described as such in the HawkIRB application and Consent Document.

Benefits may not promise a cure or a great discovery. Benefits may not include compensation or payment for participation.

### **14.B Benefits to Society**

Potential benefits may include the hypothesized results of the study, benefits to society or the knowledge that the VA investigator hopes to gain from conducting the study. Potential benefits to society may be described in Section IX of the HawkIRB application.

The IRB determines whether risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB does not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

## **Part 15: Section X Privacy & Confidentiality**

An issue of primary importance is the protection of both the privacy of research subjects and maintaining the confidentiality of data. Federal regulations [[45 CFR 46.111\(a\)\(7\)](#) (DHHS) and [21 CFR 56.111\(a\)\(7\)](#) (FDA)] require that the IRB only approve research where there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Although related, the concepts of privacy and confidentiality are distinct from one another. Confidentiality means the ethical or legal right that information is considered private and will be held secret unless consent is provided permitting disclosure.

Privacy is the freedom from unauthorized intrusion or the state of being let alone and able to keep certain personal information to oneself. Research may require the collection, use, or access to identifiable information that would otherwise not be shared with others. When this is required for the purposes of the research, the private information involved should be the minimum necessary to accomplish the goals of the research.

The VA investigator must have sound plans to protect the subject's identity, must collect only the necessary identified information to conduct the study, and must have procedures in place to maintain the confidentiality of the research records. Care should be taken to explain the mechanisms that have been devised, for example, the use of numbering or code systems or safely locked files in private offices.

Furthermore, the VA investigator should describe who has access to the data and under what circumstances a code system may be broken. Without appropriate safeguards, problems may arise from long-term retention of records.

The term anonymous is sometimes confused with the term confidential. In human subjects research, anonymous means that at no time during the data collection could someone determine who provided the information. If a link existed at any time, even if the link is subsequently destroyed, the IRB cannot consider the information anonymous.

### **15.A Certificate of Confidentiality**

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect the privacy of research subjects by protecting VA investigators and institutions from being compelled to release information that could be used to identify subjects with a research project. Certificates of Confidentiality are issued to institutions or universities where the research is conducted automatically if the study meets specified criteria. Research in which identifiable, sensitive information is collected or used, including research that

- Meets the definition of human subjects' research, including exempt research in which subjects can be identified
- Is collecting or using human biospecimens that are identifiable or that have a risk of being identifiable
- Involves the generation of individual level human genomic data
- Involves any other information that might identify a person

A Certificate of Confidentiality allows the VA investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level.

Identifying information in this context is broadly defined as any item or combination of items in the research data that could lead directly or indirectly to the identification of a research subject. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring privacy to subjects. When VA conducts a study that is protected by a Certificate of Confidentiality, the following health record documentation provisions apply:

- (1) For studies that do not involve a medical intervention (e.g., observational studies, including interview and questionnaire studies), no annotation may be made in the health record.
- (2) For studies that involve a medical intervention, a progress note entry should indicate that an individual has been enrolled in a research study, any details that would affect the subject's clinical care, and the name and contact information for the VA investigator conducting the study. Subjects' informed consent forms and HIPAA authorization documents are not to be included in the health record.

VA investigators should work with the research office in their facility to assure that when Veterans are enrolled in a study protected by a Certificate of Confidentiality, they are not simultaneously enrolled in other interventional studies unless it is absolutely clear that this enrollment does not raise safety issues. (See VHA Directive 1200.05, paragraph 22)

### **15.A.i PI requesting the CoC**

The VA investigator may choose to apply a Certificate of Confidentiality on his or her own if they do not have federal funding, or the IRB may require that a VA investigator obtain a Certificate prior to conducting the research. VA investigators without federal funding, who intend to apply for a Certificate of Confidentiality, should contact the Human Subjects Office regarding procedural steps for IRB approval and communicating with NIH. Researchers with a federal funding source are automatically granted a Certificate of Confidentiality if appropriate conditions are met. Complete information regarding the NIH Certificate of Confidentiality is available on the [NIH Office of Extramural Research web site](#).

#### **15.A.i.a Process**

Because NIH requires that the VA investigator submit an IRB-approved Consent Document that includes a description of the Certificate of Confidentiality, the VA investigator must wait until after receiving IRB approval before applying for the Certificate. This means that the VA investigator will have in hand a stamped, approved Informed Consent Document that describes the special protections of a Certificate, but will not yet have the Certificate itself. Therefore, in order to ensure that the Consent is not used before obtaining the Certificate for non federally funded studies applying for a CoC, the HSO places a "watermark" across each page of the stamped Consent that indicates it may not to be used to enroll human subjects.

IRB procedures to ensure appropriate IRB approval of a COC is in place are as follows:

- 1) Submit research project application to the HSO answering X.7 “yes” and in X.8 provide rationale for why the study meets the NIH requirements for a CoC Include the Certificate of Confidentiality Language in the Informed Consent Document.
- 2) For non Federally funded research, apply for the Certificate following the instructions of the [NIH web site](#) (). This involves crafting an application letter to the NIH.
  - a. After finalizing the application letter, bring it to the VA Research Office. VA staff will obtain the VA institutional official’s signature and will return the signed letter to you. If the VA researcher is the lead site, the VA IO will need to sign the application (for studies involving the IC VAHCS and UI).
  - b. Send application to NIH and await Certificate.
  - c. When you receive the Certificate from the NIH, you will need to submit a modification application via HawkIRB. Attach a copy of the certificate.
  - d. The IRB chair will review the application and upon approval the “watermark” will be removed from the approved consent document and it will be released to the PI through HawkIRB.

### **15.A.i.b Requirements**

The PI should apply for a Certificate following the instructions on the [NIH web site](#). For non NIH funded VA research, the CoC application letter must be signed by a VA institutional official so the PI should bring the application letter to the VA Research Office and staff will obtain the institutional official's signature and return the signed letter to the PI.

### **15.A.i.c Expiration**

A Certificate of Confidentiality protects personally identifiable information about subjects in the research project while the Certificate is in effect or as long as federal funding is supporting the research. Generally, Certificates are effective on the date of issuance or upon commencement of the research project if that occurs after the date of issuance. The expiration date should correspond to the completion of the study. The Certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual who participates as a research subject (i.e., about whom the VA investigator maintains identifying information) during any time the Certificate is in effect. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate. However, the protection afforded by the Certificate is permanent. All personally identifiable information maintained about participants in the project while the Certificate is in effect is protected in perpetuity.

## **15.B Data and/or Specimen protections**

Confidentiality protections for data and/or specimens must be described in Section X of the HawkIRB application. The description should include the storage location, who has access to the data and/or specimens, and the individual responsible for maintaining IT security (typically the VA investigator's departmental IT person), as well as the person responsible for the storage of specimens. VA investigators must describe how specimens are labeled (i.e. ID codes, subject's initials, date of collection, etc.). Confidentiality protections must also be described in the Informed Consent Document.

### **15.B.i VAHCS requirements for data and specimen storage outside of the VAHCS**

If the project involves the VAHCS and tissue/sample storage for future use, the VA investigator should check with Kari Points in the VAHCS Research Office (338-0581; from within the University, dial 158, extension 637678 or [Kari.Points@va.gov](mailto:Kari.Points@va.gov)) to determine if this is allowable prior to adding the other site to the tissue storage section of the consent document. VAHCS investigators should include a written statement from the VAHCS research office acknowledging permission to store tissue/samples for future use as an attachment to the HawkIRB application.

## **15.C Use of SSN**

### **15.C.i VA Policy requirements**

Social Security Numbers (SSNs), real or scrambled, are considered identifiers. **NOTE:** *Scrambled SSNs are considered identifiers by the HIPAA Privacy Rule because they are unique to the individual and are*

*derived from the SSN. In addition, this rule prohibits re-identification codes from being based on an identifier such as SSN (in whole or in part), name, or other direct identifier.*

(a) Real SSNs may be obtained only when required to meet the specific aims of the research protocol and their collection and use is approved by the IRB and the R&D Committee. To obtain access to real SSNs, the procedures defined by the VHA Privacy Office must be followed.

(b) When a research protocol calls for use of scrambled SSNs, the SSNs cannot be unscrambled by research staff or other individuals without an amendment to the research protocol and approval by the appropriate review committees. All required approvals from VHA Privacy Officer must also be obtained.

Section X of the HawkIRB application under question X.2 will need to be answered Yes. Section X under question X.3 will need to include ALL intended uses of the Social Security Number.

The collection of a subject's Social Security Number (SSN) may be legally required. For example, IRS regulations require collection of the SSN if the subject is to be paid. When neither of these situations exist, a subject may voluntarily provide his or her SSN. Whether collection is required or voluntary, the researcher is obligated to inform the subject of ALL intended SSN use(s). If collection of the SSN is not legally required or if there is no business necessity for collection of the SSN, the subject must approve all uses of the SSN by initialing his/her choice in the Informed Consent Document.

#### **15.C.ii Privacy Officer and Information Security Officer:**

The PO and the ISO serve in an advisory capacity to the IRB as either non-voting members or as consultants. (See VHA Directive 1200.05, paragraph 7) The facility PO and ISO are responsible for:

- a. Ensuring that the proposed research complies with all applicable local, VA, and other Federal requirements for privacy and confidentiality, and for information security, by identifying and addressing potential concerns about proposed research studies.
- b. Reviewing the proposed study protocol, study specific privacy and security information, and any other relevant materials submitted with the IRB application.
- c. Identifying deficiencies in the provisions for privacy and confidentiality or information security, respectively, of the proposed research, and making recommendations to the VA investigator and/or the IRB of options available to correct the deficiencies.
- d. Following up with the VA investigator and/or the IRB, in a timely manner, to ensure the proposed research is in compliance with relevant privacy and confidentiality and information security requirements, respectively, before the VA investigator initiates the study.
- e. A final review is required only after the IRB has approved the study to ensure no further changes impact the privacy and security requirements of this study.

*NOTE: If a study includes information covered under 38 U.S.C. 7332 that will be disclosed outside of VA, the study must include written assurance from the VA researcher, e.g. within the protocol, that the purpose of the data is to conduct scientific research and that no personnel involved in the study will identify, directly or indirectly, any individual patient or subject in any report of such research, e.g. manuscript or publication.*

### **15.C.iii IRB approved uses of SSN**

Unless the collection of the SSN is legally required or there exists a business necessity for collection, collection of the SSN is strictly optional on the subject's part and is not required for participation in the study. The only exception to this policy is that the VAHCS requires the collection of the SSN for any payment. This action can be completed by adding the new social security template section immediately following the "What Will Happen" section of the consent to inform the subject of the following information:

- 7) The SSN is being retained for use by the research team, PI, etc.
- 8) ALL uses\reasons why the SSN is being retained.
- 9) Who will be provided with or use the SSN#
- 10) For example, is the SSN being sent to a sponsor or coordinating center?
- 11) A statement informing subjects that providing the SSN for the outlined use is strictly optional and not required for participation in the study. The subject is required to initial their choice.

### **15.D Access and/or storage protections for data\specimens (Refer to the section on Privacy & Confidentiality)**

#### **15.D.i Storing research records separate from clinical records**

The Health Insurance Portability and Accountability Act (HIPAA) or Privacy Rule protects the privacy of individually identifiable health information or Protected Health Information (PHI), while at the same time ensuring that researchers continue to have access to medical information necessary to conduct vital research. Whether in healthcare or research, the Privacy Rule requires that PHI be communicated on a "minimum necessary" basis. In other words, research team members should only have access to the individually identifiable information necessary for the research. Therefore, even if members of the research team are the subject's clinicians, only the IRB-approved clinical records, described in the HawkIRB application and the Informed Consent Document, should be stored in research records. Clinical records that are not approved by the IRB for use in the study must be stored separately from the research records.

## **Part 16: Section XI Data Analysis**

### **16.A Analysis methods**

The VA investigator must provide a detailed plan for data analysis in the HawkIRB application. This includes details about the variables that will be analyzed, the comparisons that will be made, the analysis that will be done on the variables and the relationship of these analyses to the indicated study aims, etc. Justification for the number of subjects the VA investigator proposes to enroll in the study should also be provided. A formal power analysis is not necessary. If the project described in the HawkIRB application is a pilot study, this should be indicated that in the response. The VA investigator should also describe how s/he has assessed whether the number of subjects proposed will provide meaningful information to answer the study questions.

## **Part 17: Section XII Future Research**

VA investigators do not need IRB permission to store data collected in this study for future research. However, IRB approval is necessary to conduct research in the future using identified data collected in a previous research study (including data with an ID code for which there is a link between the code number and subject identifiers). In this case, the VA investigator must submit a new HawkIRB application describing the use of the identifiable data, reference the previous IRB ID# and await IRB approval before beginning the study.

### **17.A Contacting subjects for future research**

VA investigators may request to keep subject contact information so members of the research team may contact them about their own future research studies. A statement must be in the Informed Consent Document so subjects are aware they may be contact about other studies.

#### **17.A.i Consent process**

Refer to the section on [Recruitment & Consent Process](#)

#### **17.A.ii Minors aging up process (Minors Reaching the Legal Age of Consent While Enrolled in a Study Policy)**

Informed consent should be viewed as an ongoing process throughout the duration of a research study. Long-term studies may involve subjects who are minors at the time of enrollment but who reach the legal age of consent while study or follow-up procedures are still ongoing. The UI IRB considers on a study-by-study basis whether obtaining new consent from each subject is required or whether a waiver of consent may be granted.

If there is continued interaction with subjects who were first enrolled as minors, obtaining a new consent when a subject reaches the legal age of consent will usually be required. VA investigators enrolling minors who may reach the legal age of consent during the course of the study, and will have interactions with the subject after they turn 18, should describe in Section VII.D.29 of the HawkIRB application how they plan to obtain a new consent from these subjects. Options may include in-person consents, mail out consents, use of email with a pdf. version of the consent form attached, or faxed consent forms.

All materials utilized to obtain the new consent, such as a letter, phone script, or email explaining the requirement, should be attached to the HawkIRB application.

If the VA investigator will not have any interaction with the subject after they turn 18, but would like to continue to analyze the data or specimens collected under the legally effective consent obtained from the parent or guardian, s/he should either describe the plan to obtain a new consent or request a [waiver of consent](#).

For continued collection of new data from record reviews after the subject reaches the legal age of consent, the IRB may approve a waiver of consent under [45 CFR 46.116\(d\)](#) if the required conditions are met.

### **17.B Sharing contact information with researchers outside the research team**

VA investigators who want to share their enrolled subjects' contact information with other researchers who are not on the research team should request IRB approval to do so in Section XII of the HawkIRB application. Template language describing the registry should also be included in the Consent Document.

## **Part 18: Research Related Study Materials**

VA investigators may keep contact information so other researchers can contact subjects for future research. This must be described in Section XII of the HawkIRB application and the Informed Consent Document. However, this does not authorize the PI to share data collected in the current study with researchers outside the research team.

### **18.A What does the IRB expect to see as part of the IRB application**

The New Project Application must be accompanied by some basic materials, when appropriate. HawkIRB will prompt the VA investigator to attach materials based on responses to questions in the application. The VA investigator is required to attach any required materials electronically. If only a hard copy of the supporting documentation is available, the VA investigator will need to convert the document to a single electronic file (for example, scanning the document), so that it can be attached to the HawkIRB application. There are detailed instructions within HawkIRB on how to attach materials. There are also instructions regarding attachments on the [HawkIRB FAQ](#) page. Materials that may need to be attached to the HawkIRB application include the following:

#### **18.A.i Consent materials**

To create any of these documents, the VA investigator or his/her delegate will need to start with the template provided in HawkIRB, download them to a computer, make edits, and re-attach the documents to the HawkIRB application. The IRB application should state if the informed consent materials will be presented in writing or orally.

- 1) Consent document
- 2) Assent document
- 3) Exempt information sheet
- 4) Consent letter

#### **18.A.ii Recruitment materials**

These may include brochures, flyers, newsletters (if they include recruitment announcements or are provided to potential subjects prior to signing the consent), advertisements, audiotapes, videotapes, websites, or other materials used to inform people about the study.



Phone script(s) need to be included for situations that involve screening or providing consenting information to participants via telephone.

#### **18.A.iii Grant application**

The complete grant proposal should be attached. This should include the budget pages and appendices.

#### **18.A.iv Surveys**

This includes questionnaires, surveys, stimuli, etc., that will be used in the study.

##### **18.A.iv.a How to attach if online**

VA investigators using online survey instruments (such as Qualtrics) to collect data from subjects must attach screen shots of the survey as it would be presented to subjects. VA investigators may also provide a survey link in Section VII.E to the HSO/IRB for review.

##### **18.A.iv.b Where to document URL (section VII.E)**

The URL for survey instruments should be provided in Section VII.E.4 of the HawkIRB application for IRB review and approval.

#### **18.A.v Protocol**

If the study involves a clinical or therapeutic intervention, this may include a pharmaceutical company protocol or investigator-initiated study protocol. If available, the DHHS-sponsored or other sponsor sample consent should be included.

#### **18.A.vi Investigator Brochures**

For studies that require review by the Pharmacy & Therapeutics Committee or involve investigational drug interventions, attach a copy of the Investigator's Brochure for the investigational drug under study.

#### **18.A.viii Drug package inserts**

For studies administering drugs within the FDA approved population, indication, dose or route of administration, the drug package insert(s) must be attached to the HawkIRB application for IRB review.

#### **18.A.ix Questionnaires**

All questionnaires administered to subjects (in paper or electronic form) must be attached to the HawkIRB application for IRB review and approval.

### **18.A.x CRFs**

Unless a form is completed by the subject in order to collect data directly from the individual, Case Report Forms (CRFs) should not be attached to the HawkIRB application.

CRFs are paper or electronic forms typically used in clinical trial research. The CRF is a tool used by the sponsor to collect data from each participating site. All data on each subject participating in a clinical trial are documented in the CRF. The IRB does not require VA investigators to attach CRFs as the information collected on these forms should be described in the attached protocol. Additionally, a Modification to the HawkIRB application would have to be submitted each time the attached CRF was revised.

### **18.A.xi Screening logs**

Screening logs that may include subject identifiers (name, date of birth, medical record number, etc.) must be attached to the HawkIRB application for IRB review and approval.

### **18.A.xii Letters of Agreement**

For collaborations with non-VA entities, attach the Individual Investigator's Agreement. See the section on [Collaborative Research](#).

### **18.A.xiii IND documentation**

If the study involves an investigational drug, attach the following documentation:

7. IND application
8. Including documentation of the IND number from the sponsor (if this is not indicated on the Investigator's Brochure or protocol).
9. In the case of investigator-held INDs, attach a copy of the FDA letter that informed the PI of the IND number.

### **18.A.xiv FDA response**

VA investigator/sponsor correspondence with the FDA documenting that an IND is or is not required must be attached to the HawkIRB application.

### **18.A.xv Tracking information**

Detailed procedures for tracking use and disposition of medical devices and the person responsible for maintaining the use and disposition tracking records must be provided in Section VII.B of the HawkIRB application.

## Part 19: PI Responsibilities after initial IRB approval

### 19.A Modifications

Any change in the conduct of a study must be reviewed and approved by the IRB prior to implementing the change. The exception to this is when the change is necessary to eliminate apparent immediate hazards to subjects. The VA investigator is required to notify promptly the IRB of any changes made without IRB approval to eliminate apparent immediate hazards to subjects using the Modification Form. The convened IRB will review these modification forms to determine that any changes made by the VA investigator to eliminate apparent immediate hazards to the subjects were consistent with ensuring the subjects' continued welfare.

Modifications include, but are not limited to:

- 1) Changes to study procedures,
- 2) Adding or removing VA investigators or research team members,
- 3) If a PI is leaving the institution, a new PI must be submitted and approved prior to the current PI's departure. A signed assurance document is required of a newly named PI of a research study. If a PI is on extended leave from the institution, contact the HSO to discuss continued oversight of any open studies.
- 4) Changes to the title of the project,
- 5) Requests for additional subjects beyond the original approved number,
- 6) Change in funding sources,
- 7) Changes in how subjects are being recruited or followed-up,
- 8) New or revised advertisements,
- 9) Changes to Informed Consent Documents, surveys, questionnaires, correspondence with potential or current subjects, or additional new items, protocol changes.
- 10) Modifications to an approved project should be submitted on a Modification/Update Form. A modification may be submitted at the same time as a continuing review. Instructions for the completion of these applications are contained within [HawkIRB](#).

Modifications to an approved project that pose no additional risk to subjects (e.g. changes in title, co-investigator(s), funding sources) are eligible for expedited review. To be eligible for expedited review, the modification must maintain similar or increased safeguards to protect the subject. Expedited modifications are reviewed and approved by the IRB chair or designee. More extensive modifications, or modifications that pose additional risk to subjects, may require full board review. In either case, revisions or clarifications may be required. All modifications must be approved by the IRB prior to implementation (see exception [noted above](#)).

Once a PI has received a protocol amendment from a study sponsor, it is the PI's responsibility to submit the amendment in a timely manner for IRB review and approval. Based on guidance from the FDA, potential subjects who meet eligibility criteria under a pending amendment to the protocol may not be enrolled until after the amendment is approved by the IRB. Further, the FDA will hold the PI responsible

for compliance with this requirement. The sponsor does not have the authority to override this FDA regulation, and therefore, it is inappropriate for the PI to request "special permission" from the sponsor to implement any aspect of the amendment before IRB approval. Rather, the PI should move as quickly as possible towards submitting the amendment for IRB approval.

For projects that have received Concept approval, to obtain approval for enrolling human subjects the VA investigator should submit a Modification/Update Form in HawkIRB. In the Modification/Update Form, the VA investigator should change Question IV.1 to indicate that the project should receive Regular review. This change will open up additional questions for the VA investigator to answer in order to complete the application. An Informed Consent Document and any other materials, such as interview scripts or questionnaires, should be attached to the Modification/Update Form.

## **19.B Reportable Events**

VA investigators are required to report to the IRB if any of the above items occur in a study where IRB-03 is the IRB of record.

### **19.B.i Unanticipated Problems Involving Risks to Subjects or Others**

An unanticipated problem involving risks to subjects or others is any event or problem that:

- 1) was unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied  
AND
- 2) suggests that the research places subjects or others (those not directly involved in the research such as research staff or family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized AND
- 3) is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research).

When a research study includes investigational drugs or devices, some unanticipated problems may also meet the definition of an unexpected adverse drug experience (serious or otherwise), or an unanticipated adverse device effect.

Examples of unanticipated problems involving risks to subjects or others include, but are not limited to:

- 1) A breach of confidentiality
- 2) A subject complaint when the complaint indicates unexpected risks or cannot be resolved by the VA investigators,
- 3) A research team member experiences harm in the conduct of the study

- 4) A new risk of the study drug, device, or study procedure is identified by an outside source (sponsor, federal regulatory agency, outside site, etc.)

VA investigators must report any unanticipated problem involving risk to subjects or others using the Reportable Event Form (REF) in the HawkIRB system. This form includes a description of the event, the date of occurrence, whether it is a local or outside report, how the event affected the rights, safety or welfare of the subject or others, current status of subjects, and any planned changes or modifications to the project as a result of the event. Reports from the VA investigator to the IRB must be submitted via HawkIRB within five working days of the event or within 5 working days of the PI becoming aware of the event.

The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others. If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled under the VA study. If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system. If the event represents more than minimal risk of harm to subjects enrolled under the VA study, the report is referred to the convened IRB for review.

All reports of unanticipated problems involving risks to subjects or others are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. Reports of all such problems for all projects reviewed by the Chair or convened IRB are provided by e-mail to IRB-03 members attending the IRB 03 full board meeting on a monthly basis. Any concerns noted by the membership are documented in the minutes of that review and followed up on as appropriate by HSO staff or the IRB Chair.

#### **19.B.ii Serious adverse drug event (either expected or unexpected) occurring in a UI subject**

If a subject is enrolled by VAHCS investigators, the VA investigator must report to the VA IRB either serious adverse drug events or unexpected adverse drug events. By definition, these events must be associated with the use of the drug.

A serious adverse drug event is any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes:

- 1) Death
- 2) Life-threatening adverse drug experience
- 3) Inpatient hospitalization or prolongation of existing hospitalization
- 4) A persistent or significant disability/incapacity
- 5) A congenital anomaly/birth defect

- 6) Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above (21 CFR 312.32).
- 7) An unexpected adverse drug event is any adverse drug experience (associated with the use of the drug), the frequency, specificity, or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to the subjects and the IRB (21 CFR 312.32) .

VA investigators must report any serious adverse drug event using the Reportable Event Form (REF). This form includes a description of the event, the date of occurrence, the type of risk, whether the event was unexpected, the outcome, and an assessment of degree of relatedness to the research. The form also includes the proposed actions to be taken by the VA investigator with regard to modifying approved study materials (including change in consent documents or other notification procedures) and notifying current subjects. Reports from the VA investigator to the IRB must be submitted via HawkIRB within five working days of the event or within five working days of the PI becoming aware of the event.

Reports of serious and expected adverse drug events occurring in a VAHCS subject are reviewed by an IRB Chair to verify that the event would be considered “expected” based on the information previously reviewed and approved by the IRB. If the Chair verifies that this information is correct, the Chair signs the report through the HawkIRB system.

All reports of serious and unexpected adverse drug events occurring in a VAHCS subject are reviewed by the IRB Chair and/or the IRB in the following manner:

The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others.

If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled under the UI study.

If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system.

If the event represents more than minimal risk of harm to subjects enrolled under the UI\VAHCS study, the report is referred to the convened IRB for review. The full board determines whether subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information.

All reports of serious adverse drug events occurring in a VAHCS subject are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. Reports of all such problems for all projects reviewed by the Chair or convened IRB are provided by e-mail to IRB-03 members attending the IRB 03 full board meeting on a monthly basis. Any concerns noted by the membership are documented in the minutes of that review and followed up on as appropriate by HSO staff or the IRB Chair.

In addition to the above requirements, VA investigators conducting human gene therapy research must submit a written report of serious adverse experiences that are unexpected and associated with the use of the gene transfer product to the NIH Office of Biotechnology Activities (NIH/OBA), the U of I Institutional Biosafety Committee, the IRB, and the FDA or study sponsor within specified timeframes as found in Appendix M-I-C-4 in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). Gene therapy VA investigators must submit annual reports to OBA as set forth in Appendix M-I-C-3 of the NIH Guidelines.

#### **19.B.iii Serious adverse device effects (either anticipated or unanticipated) occurring in a UI subject**

If a subject is enrolled by VAHCS investigator, the VA investigator must report either serious adverse device effects or unanticipated adverse device effects. By definition, these effects must be associated with the use of the device.

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death the frequency, specificity, or severity of which has not previously been identified in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects ([21 CFR 812.3](#)).

VA investigators must report any serious adverse device effect occurring in a VAHCS subject to or IRB-03 using the Reportable Event Form (REF). This form includes a description of the effect, the date of occurrence, the type of risk, whether the effect was unanticipated, the outcome, and an assessment of degree of relatedness to the research. The form also includes the proposed actions to be taken by the VA investigator with regard to modifying approved study materials (including change in consent documents or other notification procedures) and notifying current subjects. Reports from the VA investigator to the IRB must be submitted via HawkIRB within five working days of the event or within five working days of the PI becoming aware of the event.

Reports of serious and anticipated adverse device effects occurring in a VAHCS subject are reviewed by an IRB Chair to verify that the effect would be considered “anticipated” based on the information previously reviewed and approved by the IRB. If the Chair verifies that this information is correct, the Chair signs the report through the HawkIRB system.

Reports of serious and unanticipated adverse device effects occurring in a VAHCS subject are reviewed by the VAHCS IRB Chair and/or IRB in the following manner:

- 1) The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others.
- 2) If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled in the research study.
- 3) If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system.
- 4) If the event represents more than minimal risk of harm to subjects enrolled under the VAHCS study, the report is referred to the convened IRB for review. The full board determines whether subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information.

All reports of serious adverse device effects occurring in a VAHCS subject are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. In addition, reports of all serious adverse device effects for all projects reviewed by the Chair or full board IRB are provided by e-mail to all IRB-03 members on a monthly basis.

Unanticipated serious adverse device effects occurring in a non-UI subject

FDA regulations (21 CFR 150(b)(1)) require the sponsor to report the results of any evaluation of an unanticipated serious adverse device effect to all reviewing IRBs and participating investigators. Any such reports are initially received by the VA investigator who is in turn responsible for reporting this information to the IRB-03. By definition, these effects must be associated with the use of the device.

VA investigators must report any evaluation of unanticipated serious adverse device effects conducted by the sponsor occurring in a non- VAHCS subject to IRB-03 using the Reportable Event Form (REF). This form includes a description of the effect, the date of occurrence, the type of risk, the outcome, and an assessment of degree of relatedness to the research. The form also includes the proposed actions to be taken by the VA investigator with regard to modifying approved study materials (including change in consent documents or other notification procedures) and notifying current subjects. Reports from the VA investigator to the IRB must be submitted via HawkIRB within five working days of the event or within five working days of the PI becoming aware of the event.

All reports of unanticipated serious device effects occurring in a non- VAHCS subject are reviewed in the following manner:

- 1) The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others.



- 2) If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled in the research study.
- 3) If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system.
- 4) If the event represents more than minimal risk of harm to subjects enrolled under the VAHCS study, the report is referred to the convened IRB for review. The full board determines whether subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information.

All reports of unanticipated serious adverse device effects occurring in a non- VAHCS subject are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. In addition, reports of all unanticipated serious adverse device effects for all projects reviewed by the full board are provided to all IRB-03 members on a monthly basis.

#### **19.B.iv Unanticipated Problem Involving Risk to Subjects or Others**

Refer to the section on [Unanticipated Problems Involving Risks to Subjects or Others](#)

#### **19.B.v Receipt of new information**

During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate, or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects, or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

VA investigators must report any new information that may impact the willingness of subjects to participate to IRB-03 using the Reportable Event Form (REF). This form includes a description of the new information and its potential impact on subjects. Reports from the VA investigator to the IRB must be submitted via HawkIRB within five working days of the event or within five working days of the PI becoming aware of the event. In addition, a modification form must be submitted describing the VA investigator's proposed method for providing this information to subjects.

Reports and modifications related to new information are reviewed by an IRB Chair to determine if the method and information provided to subjects is appropriate. If the Chair verifies that this information is correct and notification is appropriate, the Chair signs the report and modification through the HawkIRB system. The Chair refers the review to the full board when s/he believes the information or notification method is not appropriate, or if the new information significantly impacts the safety of current or potential

subjects. When protocol changes are immediately required to eliminate apparent immediate hazards to subjects, the Chair may approve notifications prior to full board review.

#### **19.B.vi Noncompliance**

Noncompliance is a failure to follow the federal regulations (45 CFR 46; 21 CFR 50) with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

VA investigators who are self-reporting noncompliance with federal regulations or the requirements or determinations of the IRB use the Reportable Event Form (REF). This form includes a description of the noncompliance and description of impact on the rights, safety, or welfare of subjects or others. Reports from the VA investigator to the IRB must be submitted via HawkIRB within five working days of the event or within five working days of the PI becoming aware of the event.

Other VA entities may report noncompliance. All reports of noncompliance, regardless of the source are reviewed by the IRB Chair and/or IRB according to the procedures described in Chapter 10 of this Guide.

#### **19.C IRB Determinations Requiring Reporting**

The following policy outlines the procedure for reporting to the appropriate institutional departments and offices, the institutional official, sponsors, and/or the appropriate regulatory agencies of events determined by the IRB to be:

Following an IRB determination of suspension or termination of research, noncompliance investigations, and Unanticipated Problems Involving Risks to Subjects or Others), a full board Human Subjects Office staff member in collaboration with the IRB Chair prepares a letter for signature by the IRB Chair(s) that contains the following information:

- 1) The nature of the event (whether or not the event was an unanticipated problem involving risks to subjects or others, serious or continuing non-compliance, or a suspension or termination of approval of research or a combination of these events),
- 2) The name of the institution conducting the research,
- 3) The title of the research project and/or grant proposal in which the problem occurred,
- 4) The name of the Principal Investigator on the protocol,
- 5) The IRB number assigned to the research project and the number of any applicable federal award(s) such as grants, contracts, or cooperative agreements,
- 6) A short summary of the project,
- 7) A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision,
- 8) Actions the institution is taking or plans to take to address the problem (e.g. revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, increase IRB monitoring of the project, etc.),
- 9) Plans, if any, for any follow-up action

A full board Human Subjects Office staff member sends a copy of this letter no more than one month following the review and final determination by the convened IRB to:

- 1) The University of Iowa Institutional Official (Office of the Vice President for Research and Economic Development),
- 2) Principal Investigator,
- 3) Departmental Executive Officer (Departmental Executive Officer) of the Principal Investigator,
- 4) Research Integrity Officer (RIO) if the event involved research misconduct
- 5) Administrative Officer of the Iowa City VAHCS Office of Research and Development committee
- 6) Regional VA Office of Research Oversight
- 7) VA Privacy Officer, when the report involves unauthorized use, loss, or disclosure of individually identifiable private information
- 8) VHA Information Security Officer when the report involves violations of VA information security requirements.

Either the Associate Chief of Staff or the VA Research Compliance Officer ,ay report to the Regional ORO on behalf of IRB 03.

The letter is also sent to the following federal agencies (as applicable):

- 1) Office for Human Research Protections, if the study is subject to Department of Health and Human Services regulations or subject to a Department of Health and Human Services Federalwide assurance,
- 2) Food and Drug Administration, if the study is subject to Food and Drug Administration regulations (21 CFR 50 and 56)
- 3) If the study is conducted or funded by any Federal Agency other than Department of Health and Human Services that is subject to “The Common Rule”, the report is sent to Office for Human Research Protections or the head of the agency as required by the agency.

Reporting to a regulatory agency does not occur if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms. The Human Subjects Office Assistant Director can provide copies to others as deemed appropriate by the Institutional Official.

## **Part 20: Continuing Review**

The IRB is required to review and approve all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year [pre-2018 regulations [45 CFR 46.109\(e\)](#) (DHHS) and [21 CFR 56.109\(f\)](#) (FDA)]. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

As described above, the Informed Consent Document(s) indicate the project's expiration date. If a project initially received expedited review and risks to subjects remain minimal, the continuing review may be expedited (reviewed by the chair alone). If a project initially received full board review, the project generally requires full board continuing review. The calculation of the approval period for research is based on the date and length of time at which the IRB approved the protocol by either a convened Full Board meeting or through the expedite review process.

For research subject to the 2018 Requirements, unless the IRB determines otherwise, continuing review is not required in the following circumstances:

- a. Research eligible for expedited review; or
- b. Research reviewed by the IRB in accordance with the limited IRB review; or
- c. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
  1. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  2. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.
2. For research subject to the 2018 Requirements, if the IRB requires continuing review for any of the above circumstances, it must document its rationale for requiring continuing review in its communication to the investigator and institution. The R&D Committee is not required to conduct continuing review for studies approved by the IRB for which continuing review by the IRB is not required.
3. Research eligible for the elimination of a continuing review will be required to submit a biennial review every two years to ensure the study is still active.

Due date for submitting an application for continuing review

It is the Principal Investigator's responsibility to submit an application for continuing review in sufficient time to permit the IRB chair or full board to review and approve the application prior to its expiration date. The date by which the continuing review must be approved is available on the project's Summary page on HawkIRB. As a service to VA investigators, the HawkIRB system sends the reminders to the Principal Investigator, and all contact persons listed for a given application. The reminder schedule is based on the Last Possible Submission Date (LPSD) of the project. The LPSD is the date that the VA investigator will need to have the project submitted to the Human Subjects Office to ensure that the project can obtain review and approval PRIOR to the project expiration date. The Principal Investigator, his or her delegates, and contact persons will receive automated reminders on the following schedule: A reminder memo is sent via email 60, 30, 14, 7 and 1 day before the LPSD of the project.

On the day prior to the date of expiration, the Principal Investigator, his or her delegates, and contact persons will receive notice that the project will lapse and that no human subjects activity may take place after 12:01 a.m. on the expiration date.

On the day of the LPSD (if a continuing review application has not yet been received by the HSO) the VA investigator and his/her HawkIRB contacts will receive notice by email that there will not be sufficient time prior to the expiration of the project for review and approval. This notice will state that IRB approval will lapse as of 12:01 a.m. on the expiration date and no further research activity may occur on or after that date. The Principal Investigator will be asked to submit a continuing review application or a project closure form in HawkIRB to close the project.

No human subjects activity (which includes the enrollment and follow-up of subjects and the collection and/or use of research data) may take place on or after the expiration date unless there is an over-riding

safety concern (as determined by an IRB Chair) and until the continuing review application is approved by the IRB and released by the HSO. In the event a Continuing Review lapses for studies greater than minimal risk, the Principal Investigator must immediately submit to the IRB chair a list of research participants who could be harmed by stopping study procedures. The IRB chair, with appropriate consultation with the chief of staff for any studies enrolling VA subjects, determines whether participants on the list may continue participating in the research interventions or interactions. In these situations, IRB approval of a continuing review must be obtained immediately.

If the HSO closes the study due to no response, the HSO sends the Principal Investigator as well as the VA Research Office a notification via email of study closure. The VA investigator's departmental executive officer (DEO) may also receive notification of closure. In cases of on-going externally funded projects, the Division of Sponsored Programs also receives a copy of the closure notice and make an independent determination regarding the need to notify the sponsor. Once the HSO closes a project, the only way for the project to resume is for the VA investigator to submit a New Project Application (via the HawkIRB system) for IRB review and approval.

## **20.A How to submit a continuing review application**

The continuing review information is required to be submitted via HawkIRB. The VA investigator or his/her delegate should log onto the HawkIRB system and choose the open project from the inbox. From there, the VA investigator/delegate can choose to open either of the following forms:

- 1) Continuing review form [Use this form if the VA investigator is not submitting a modification/update in conjunction with the continuing review]
- 2) Modification/Update + Continuing Review Form.

### **20.A.i How to submit a Biennial Review.**

The biennial review information is required to be submitted via HawkIRB every two years as an institutional check in. The VA investigator or his/her delegate should log onto the HawkIRB system and choose the open project from the inbox. From there, the VA investigator/delegate can choose to open a biennial review form to complete and submit to the HSO for an administrative review.

### **20.A.ii Review and Approval Process for Continuing Reviews**

Procedures for expedited or full board review, criteria for approval, and revision prior to approval, are identical to those described above for New Projects. Notification of approval of a Continuing Review form is identical to that described for New Projects. The system notifies the PI and designated members of the research team of the approval and allows access to currently approved documents.

## **Part 21: Reporting Complaints or Concerns**

Refer to [Human Subjects Research Related Complaint or Concern](#)

## Part 22: Project Closure

Projects should NOT be closed unless all of the following are completed:

- 1) Protocol indicated research activities including interaction with subjects and collection of data or specimens
- 2) Collection of data about subjects even when no subject contact is necessary
- 3) “Cleaning” of data
- 4) analysis of identified or linked data for research purposes or during the publication process
- 5) any other research use of the data which involves access to identified or linked (coded) data or specimens collected during the conduct of research

When a study ends, is closed, canceled for any reason, or is prematurely completed, the VA investigator or his/her delegate must complete a Project Closure Form. A Project Closure Form serves as notification to the Human Subjects Office that IRB continuing review of the study is no longer needed.

If no subjects have been enrolled in a study for a period of three or more years, the IRB may require that the project be closed, unless there are extenuating circumstances for keeping the project open (e.g., the study is about a rarely seen condition). If a project is closed and no subjects have been enrolled, study records must be maintained following the VA Record Control Schedule.

Take care not to close the project too soon. Once a Project Closure Form is submitted, no more data may be collected about any of the subjects in the study and no more contact with subjects for research purposes is allowed. There is no mechanism to re-open a closed study. Therefore, if a VA investigator is still collecting follow-up data about subjects (either directly from subjects or indirectly from existing records), the project should remain open until all data have been collected, even if new subjects are no longer being enrolled.

If the project was started in the HawkIRB system or has been transferred to the HawkIRB system, the VA investigator or his/her delegate should use HawkIRB to close the project. Log-on to HawkIRB and select the project that should be closed. Choose the “Project Close Form” and follow the directions to submit the project closure. Take care not to close the project too soon. Once a Project Closure Form is submitted, no more data may be collected about any of the subjects in the study and no more contact with subjects for research purposes is allowed. There is no mechanism to re-open a closed study.

In adherence with federal regulation once a research project is formally closed with the IRB via the HawkIRB electronic system, all research related activity must halt. Research activity includes contact with subjects, review of identifiable subject data, analysis of identifiable subject data, etc. If new information that may affect the safety or medical care of enrolled subjects is discovered or provided to the research team after a project has been closed, notification to the IRB must occur within five working days of the event or notification to the VA investigator of the event. In order to inform subjects of the new information, IRB approval is required prior to subject notification of such information. In order to

provide the appropriate IRB approval to notify subjects of the new information, a HawkIRB new project application submission will be required for a previously closed project.

The project application will require an explanation including the new information that was discovered or provided to the research team and a plan for how the information will be disseminated to the enrolled subjects. If the new information requires action to be taken, or information to be provided to subjects, prior to IRB review in order to avoid immediate harm to the subjects, an IRB chair should be consulted to determine if the action or notification can be undertaken prior to IRB review. In such cases IRB review should be still be carried out eventually as described. All relevant materials in connection with the method of dissemination will need to be included in the HawkIRB application for IRB approval. In most cases, a waiver of informed consent can be obtained in order to provide the new information to the enrolled subjects.

## **Part 23: Record Keeping**

Every principal investigator is required by VAHCS and federal regulations to maintain records relating to the use of human subjects in research. Copies of the Human Subjects application forms, notices of approval, and signed Informed Consent Documents must be maintained in the VA investigator's records. All records of human subject research are subject to inspection by federal authorities and the IRB.

### **23.A How long to keep records**

Copies of all research records for VAHCS studies must be kept for the length of time specified in the VA Records Control Schedule after the close of the study.

Records, including identifiers, must be retained following the disposition instructions that have been approved by the National Archives and Records Administration (NARA) and are published in VHA RCS 10-1. If storage is needed for records after study closure, contact [Sommarani.Chan@va.gov](mailto:Sommarani.Chan@va.gov), Research Records Manager, for storage.

Ultimately, it is the Principal Investigator's responsibility to maintain accurate files of IRB correspondence, approvals, and research records during the life of the study and after completion of the research. All correspondence and IRB documentation related to the project is available electronically through the HawkIRB application. All research related records can be submitted to the VA Research Office for record retention.

## **Part 24: Principal Investigator leaves the Iowa City VAHCS**

The VA owns the primary research results generated from all research conducted under its jurisdiction. Therefore, when a PI plans to leave the VA and wants to take the original data to the new institution, the transfer of the data/samples must proceed according to established guidelines.

If the PI will not have continued access to identifiable research data /samples and is not taking data to the new institution:

- 1) If the study is not complete - submit a Modification form in HawkIRB to change the PI named on the application
- 2) If the study is complete - submit a Project Closure form in HawkIRB

If the PI will take identifiable research data /samples to the new institution, or plans to have continued access, s/he must work with Kari Points (VA ext. 637678 or [kari.points@va.gov](mailto:kari.points@va.gov)) and Merle Kelley, VA PO (VA ext. 636265 or [merle.kelley@va.gov](mailto:merle.kelley@va.gov)) regarding this issue. The VA researcher should:

- 1) Submit a Modification form in HawkIRB requesting IRB approval to take the data/samples or to have continued access
- 2) Obtain a letter from the PI's UI department head that documents awareness/approval of the transfer of the data/samples and outlines the department expectations for the transfer and use of the data/samples

## **Part 25: Other entities of the Iowa City VAHCS program involved in the IRB review process.**

### **25.A Veterans' Affairs Health Care System (VAHCS)**

Under a Memorandum of Understanding (MOU) between the University of Iowa IRB-03 and the Iowa City Veterans' Affairs Healthcare System (VAHCS), the University of Iowa provides IRB review for human subjects research conducted at the VAHCS. The agreement specifies that IRB-03 operates under the conditions of the University of Iowa Federal wide Assurance and obligates IRB-03 to operate under any additional VAHCS-specific regulations or policies. A copy of this document is available upon request from the Human Subjects Office. Projects reviewed on behalf of the VAHCS receive the equivalent IRB review as those conducted at the University of Iowa.

### **25.B VAHCS Pharmacy and Therapeutics Investigational Drug Service**

VAHCS Pharmacy and Therapeutics must review a research protocol if it involves the administration of off-label investigational new drugs or drugs. Additionally, if a study involves Food and Drug Administration-approved drugs that are given as a component of a research protocol or any other substance that is ingested, injected, or applied to the body, the study must be reviewed by VAHCS Pharmacy and Therapeutics. It is not a requirement that an investigator have VAHCS Pharmacy and Therapeutics approval prior to IRB review.

1. VAHCS Pharmacy and Therapeutics Committee (VA P&T) is required when section V.1 of the Hawk IRB application indicates a substance is being ingested, injected or applied to the body. These studies will need to be reviewed by VA P&T.
2. VA P&T will review each project as indicated in Section V.1. Any concerns are discussed and resolved directly with the PI. Once approved, the P&T Committee notifies Lori Fisher.



3. VA investigators need to contact Ryan Weber at [Ryan.Weber@va.gov](mailto:Ryan.Weber@va.gov) with questions about the VA P&T review of their study.
4. The VA P&T approval letter will be added to HAWKIRB application by the VA Research Office.

VAHCS Pharmacy contact information: If a VA investigator needs to request Investigator Drug Service and Pharmacy Service Support for the Initial Review of Drug Studies in Humans, they need to contact [Ryan.Weber@va.gov](mailto:Ryan.Weber@va.gov).

### **25.C VA Research & Development (VA R&D)**

The VAHCS R&D Committee does not share its deliberations with IRB-03 unless there are specific subject protection issues raised by the committee. Should such issues arise, the R&D Committee notifies the IRB in writing following its deliberations. If the IRB agrees that the issue(s) are related to subject protection, the IRB will require the Principal Investigator to revise the application to address the identified issue(s). The Principal Investigator notifies the R&D Committee when any study, including those involving investigational drugs, has been terminated. Once IRB-03 and the VAHCS R&D Committee have reviewed and approved the new research project, the Human Subjects Office releases the project to the Principal Investigator.

1. All new studies have to be reviewed by the R&D Committee.
2. HSO will notify the VA Research Office when IRB-03 approval has been granted. VA R&D review occurs after IRB approval has been issued.
3. VA investigators may contact the VA Research Office with questions.
4. Approval occurs once the R&D Committee has voted for approval. The VA Research Office will add the approval letter to HAWKIRB and upload the approval date.

Research under the direction of the VAHCS, or research that involves VAHCS patients requires review and approval by IRB-03 and the VAHCS Research and Development Committee (R&D Committee). Completion of the University of Iowa IRB-03 review and associated IRB findings and actions is documented on a VA form 10-1223, an IRB approval letter, and IRB minutes for full board studies. This documentation is sent to the VAHCS research office and VA Principal Investigator.

### **25.D Conflict of Interest in Research Committee**

Conflicts of Interest are reviewed by the Iowa City VA Conflict of Interest Committee. Contact [Sommarani.Chan@va.gov](mailto:Sommarani.Chan@va.gov) for information regarding the process.

### **25.E VA Privacy Officer (VA PO)**

The VA Privacy Officer helps to ensure that researchers and the IRB implement the VA's privacy policies at the local level. The VA Privacy Officer reviews all IRB-03 submissions. For additional information about the role of Privacy Officers visit the US Department of Veterans Affairs Privacy Service website.

1. The PO will review all initial submission of human subject research protocols, including exempt protocol submissions, for the use and/or disclosure of individually identifiable information and other privacy considerations. There is one VA checklist that is completed by the PO & ISO. The PI will fill out the information security checklist along with the HIPAA Authorization (if needed)

and upload them to the HAWKIRB application. The Privacy Officer will complete their review and upload signed VA checklist once approved.

2. The checklist is obtained from HAWKIRB on the attachments page. The PI downloads the form(s) and uploads the form(s) to HAWKIRB after completing their portion.
3. The PI contacts the PO, if they have questions. VA investigators may contact Michele Myrvik at VA ext. 636092 or [michele-myrvik@va.gov](mailto:michele-myrvik@va.gov) with questions.
4. Once the VA checklist and HIPAA Authorization (if needed) meet all privacy concerns, the PO will add the approval letter to HAWKIRB and upload the approval date.
5. After IRB-03 approval, the PO will conduct a final review of the study prior to R&D Committee review and approval.

## **25.F VA Information Security Officer (VA ISO)**

The VA Information Security Officer must review all human use protocols to ensure compliance with information security standards as defined by the VA. For additional information about the role of the Information Security Officer visit the Office of Information Security's website.

1. The ISO will review all initial submission of human subjects research protocols, including exempt protocol submissions, for compliance with all applicable federal security requirements. There is one VA checklist that is completed by the PO & ISO. The PI will fill out the information security checklist and upload the form to the HAWKIRB application. The Information Security Officer will complete their review and upload signed VA checklist once approved.
2. The VA checklist is obtained from HAWKIRB on the attachments page. The PI downloads the form and uploads the form to HAWKIRB after completing their portion.
3. The PI contacts the ISO, if they have questions. VA investigators may contact Merle Kelley at VA ext. 636265 or [merle.kelley@va.gov](mailto:merle.kelley@va.gov) with questions.
4. Once the VA checklist is complete and the study meets all security concerns, the ISO will add the approval letter to HAWKIRB and upload the approval date.

## **25.G VA Research Compliance Officer (VA RCO)**

The VA Research Compliance Officer is responsible for monitoring the research conduct and documentation of VA investigators.

1. The RCO is this responsible for monitoring research activity and conducting audits to ensure compliance with all VHA and other Federal requirements for the conduct of research. The Research Compliance Officer is this responsible for providing education to administrative staff, VA investigators, and research staff within the VA facility.
2. The RCO will select studies for audits and notify the PI and/or their designee about the audit. The RCO will provide the PI with the audit tool to be used for the audit. The RCO will then meet with the PI or their designee to conduct the audit. They may review all study documents and records.

3. VA investigators may contact Sara Miller at VA ext. 636217 or [sara.miller@va.gov](mailto:sara.miller@va.gov) with questions.
4. The RCO provides a summary report each month of RCO activity to be reviewed at an IRB 03 meeting.

#### **25.H VAHCS research radiation review**

VAHCS research radiation review will be conducted by Gordon Axt. This will occur through an agreement with the University of Iowa, Laura Scholl is the VA Radiation Safety Officer. Hawk IRB questions V.9-19 address the use of radiation in a project. Specific information about this process is located on the HSO website at: <http://ehs.research.uiowa.edu/vamc-safety-information-and-training>